ORIENTATION DISRUPTOR (*ord*): A RECOMBINATION-DEFECTIVE AND DISJUNCTION-DEFECTIVE MEIOTIC MUTANT IN *DROSOPHILA MELANOGASTER*[1]

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Manuscript received February 9, 1976
Revised copy received June 24, 1976

ABSTRACT

The effects of a semidominant autosomal meiotic mutant, *orientation disruptor* (symbol: *ord*), located at 2–103.5 on the genetic map and in region 59B-D of the salivary map, have been examined genetically and cytologically. The results are as follows. (1) Crossing over in homozygous females is reduced to about seven percent of controls on all chromosomes, with the reduction greatest in distal regions. (2) Crossing over on different chromosomes is independent. (3) Reductional nondisjunction of any given chromosome is increased to about thirty percent of gametes from homozygous females. The probability of such nondisjunction is the same among exchange and nonexchange tetrads with the exception that a very proximal exchange tends to regularize segregation. (4) Equational nondisjunction of each chromosome is increased to about ten percent of gametes in homozygous females; this nondisjunction is independent of exchange. (5) The distributive pairing system is operative in homozygous females. (6) In homozygous males, reductional nondisjunction of each chromosome is increased to about ten percent, and equational nondisjunction to about twenty percent, of all gametes. (7) Cytologically, two distinct meiotic divisions occur in spermatocytes of homozygous males. The first division looks normal although occasional univalents are present at prophase I and a few lagging chromosomes are seen at anaphase I. However, sister chromatids of most chromosomes have precociously separated by metaphase II. Possible functions of the *ord*+ gene are considered.

TO date, all meiotic mutants reported in Drosophila are restricted in their effects to one or the other meiotic division, and all save one, *mei-S332* (DAVIS 1971), are sex-specific in their effect on meiosis. It is possible to divide female-specific meiotic mutants into two categories: recombination-defective mutants that cause a reduction in the rate of crossing over and, as a consequence, a proportional increase in reductional nondisjunction (SANDLER *et al.* 1968; BAKER and CARPENTER 1972; CARPENTER and SANDLER 1974; HALL 1972; PARRY 1973), and disjunction-defective mutants that have normal levels of crossing over but elevated levels of nondisjunction at either the first meiotic division (DAVIS 1969; CARPENTER 1973; WRIGHT 1974), or the second meiotic division (DAVIS 1971). One disjunction-defective mutant, *nod* (CARPENTER 1973), is restricted in its

[1] Research sponsored jointly by grants GM09965 and GM00182, both from the U.S. Public Health Service.
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effect to noncrossover chromosomes, whereas *ca*nd (DAVIS 1969), *l(1)TW-6*^{cs} (WRIGHT 1974), and *mei-S332* (DAVIS 1971) cause nondisjunction of crossover and noncrossover chromosomes alike. Since there is no crossing over during meiosis in males, male meiotic mutants are, of necessity, disjunction-defective. Many male-specific mutants disrupt the segregation of only one chromosome pair at meiosis I (SANDLER *et al.* 1968; BAKER and CARPENTER 1972), while others affect the segregation of more than one, and possibly all, chromosome pairs (SANDLER *et al.* 1968; GETHMAN 1974). For reviews of meiotic mutants, see SANDLER and LINDSLEY (1974) and BAKER and HALL (1976).

This report describes a new meiotic mutant, *orientation disruptor*, that results in abnormal chromosome segregation at both meiotic divisions in both males and females, acts as both a recombination-defective and, independently, as a disjunction-defective mutant.

ISOLATION AND LOCALIZATION

A new second chromosome meiotic mutant has been induced with EMS, treating *Canton-S* males according to the procedure of LEWIS and BACHER (1968), and isolated using the mating scheme described by SANDLER *et al.* (1968). The mutant has been given the name *orientation disruptor* (*ord*).

ord was localized on chromosome-*2* by selecting recombinant chromosomes from *al dp b pr c px sp/ord* females and testing each in homozygous condition. The chromosomes were selected so as to include several crossovers in each of the six marked regions. Females homozygous for each second chromosome were mated and their progeny scored for crossing over on the *X* chromosome and for nondisjunction of the *X* at the first and second meiotic divisions. Males homozygous for each chromosome were tested for reductional nondisjunction of the sex chromosomes. Based on 34 recombinant chromosomes, the following phenotypes are inseparable and map between *px* and *sp* at 103.5 on the standard map: the reduction in crossing over, the increase in reductional and equational nondisjunction in females, and the increase in reductional nondisjunction in males. Subsequently, the factor responsible for inducing equational nondisjunction in males was also mapped to this region. Because of the similarity in phenotype between males and females, and because all of the meiotic manifestations were induced simultaneously and map to the same region of chromosome-*2*, it is concluded that all of the abnormalities associated with *ord* are due to the same mutation. The salivary chromosomes of *ord*/+ larvae were checked for aberrations in the distal half of *2R*; none was found.

The *Y-2* translocations described by LINDSLEY *et al.* (1972) were used to generate terminal duplications of *2R* in order to localize *ord* cytologically. Five translocations were used to construct *C(1)RM, y pn v/0; ord/ord/Dp(2R)* females, where each duplication extends from its breakpoint to the tip of *2R* and is marked with either y^+ or B^s. The presence of ord^+ on each duplication was assayed by monitoring segregation of the attached-*X* from the duplication. If the duplication carries ord^+, the attached-*X* segregates regularly from the duplication. If the duplication does not carry ord^+, meiosis is disrupted by *ord*, and the

attached-*X* and the duplication segregate approximately randomly with respect to each other.

As expected, the attached-*X* and the duplication separate from each other in more than 90% of meiocytes in the *ord/SM1* control. The two largest duplications (*B202* and *P59*) also segregate from the attached-*X* in *ord* females, but the short duplications (*J131*, *H143* and *A160*) nondisjoin from the attached-*X* in about 40% of the ova. Therefore *ord*$^+$ is in the region 59B–59D, between the breakpoints of *P59* and *J131*.

DISJUNCTION IN MALES

Genetics: The effect of *ord* on disjunction of the sex and fourth chromosomes in males was examined in crosses of y/y^+Y males to three types of females: (1) *C(1)RM, y pn v/Y; C(4)RM, ci ey^R/0*, (2) *y pn/y pn;C(4)RM, ci ey^R/0*, or (3)*C(1)RM, y pn v/0*. Taken together, these crosses permit the examination of the effects of *ord* on reductional and equational nondisjunction of the sex and fourth chromosomes in males.

TABLE 1

Disjunction of sex and fourth chromosomes in y/y$^+$Y; spa^{pol}/spa^{pol} *and* spa^{pol}/+ *males crossed to* C(1)RM, y pn v/Y; C(4)RM, ci ey^R/0 *females*

Second chromosome:		+/+				*ord*/+		*ord/ord*	
Fourth chromosome:		*spa^{pol}/spa^{pol}*		*spa^{pol}/+*		*spa^{pol}/spa^{pol}*		*spa^{pol}/spa^{pol}*	*spa^{pol}/+*
Progeny phenotype*									
y male	+	1140	(1140.0)†	1034	(1034.0)	1375	(1375.1)	787 (789.1)	497 (495.9)
	spa^{pol}	3	(3.0)	0	(0.0)	2	(1.9)	398 (384.3)	51 (53.1)
	ci ey^R	1	(1.0)	2	(2.0)	4	(4.0)	96 (107.6)	62 (61.0)
+ male	+	4	(4.0)	2	(2.0)	1	(1.0)	147 (151.5)	138 (139.0)
	spa^{pol}	0	(0.0)	0	(0.0)	0	(0.0)	73 (73.8)	13 (14.9)
	ci ey^R	0	(0.0)	0	(0.0)	0	(0.0)	26 (20.7)	20 (17.1)
y female	+	3	(3.0)	0	(0.0)	1	(1.0)	132 (124.4)	79 (79.7)
	spa^{pol}	0	(0.0)	0	(0.0)	0	(0.0)	48 (60.6)	13 (8.5)
	ci ey^R	0	(0.0)	0	(0.0)	0	(0.0)	22 (17.0)	6 (9.8)
+ female	+	0	(0.0)	0	(0.0)	0	(0.0)	4 (4.3)	3 (2.4)
	spa^{pol}	0	(0.0)	0	(0.0)	0	(0.0)	2 (2.1)	0 (0.3)
	ci ey^R	0	(0.0)	0	(0.0)	0	(0.0)	1 (0.6)	0 (0.3)
Total progeny:		1151		1038		1383		1736	882
Reductional (*XY*) exceptions:		0.0035		0.0019		0.0007		0.1417	0.1939
Equational (*XX*) exceptions:		0.0026		0.0000		0.0007		0.1164	0.1111
Total (*44*) exceptions:		0.0026		——		0.0014		0.3001	——
Equational (*44*) exceptions:		——		0.0000		——		——	0.0873

* Progeny of *spa^{pol}/spa^{pol}* males that are + for fourth chromosome markers are the result of mono-*4* sperm fertilizing *C(4)RM* ova. Some of the progeny of *spa^{pol}/+* males that are + for fourth chromosome markers are the result of mono-*4* sperm fertilizing *C(4)RM* ova, others are produced by diplo-*4* sperm (either *spa^{pol}/+* or +/+) fertilizing nullo-*4* ova.

† Numbers in parentheses are expected based on the hypothesis of independent behavior of the sex and fourth chromosomes.

The results of crosses of y/y^+Y; *ord/ord*; spa^{pol}/spa^{pol} males to *C(1)RM*, *y pn v/Y*; *C(4)RM*, *ci* $ey^R/0$ females are given in Table 1. It is not possible to follow the maternal *Y* chromosome because it does not carry markers. With respect to the attached-*X* and the attached-*4*, four ova types are distinguishable: *XX;44*, *XX;0*, *0;44*, and *0;0*. The ova types are not recovered equally frequently, the deviation from equality owing to nonhomologous segregation of the attached-*X*, *Y* and attached-*4* chromosomes. However, it is possible to score regular progeny, reductional and equational exceptions for the *X* chromosome, and sequential reductional and equational exceptions among progeny arising from nullo-*X* ova. Regular *X*-bearing sperm give rise to *y* males, reductional exceptional *XY* sperm produce wild-type males, and equational exceptional *XX* sperm produce *y* females. Misbehavior of the sex chromosomes at both meiotic divisions yields *XXY* and *XXYY* sperm which are recovered as phenotypically wild-type females.

With respect to chromosome-*4*, regular sperm are mono-*4*; exceptional sperm resulting from nondisjunction at either the reductional or equational division are diplo-*4* or nullo-*4*; sperm resulting from fourth chromosome nondisjunction at both divisions may contain anything from no to four chromosomes *4*. Mono-*4* sperm produce phenotypically wild-type progeny when they fertilize attached-*4* ova or Minute spa^{pol} progeny when they fertilize nullo-*4* ova. Minute individuals have low viability and are excluded from the data. Nullo-*4* sperm are recovered as *ci* ey^R progeny when they fertilize attached-*4* ova. Sperm containing two or three copies of chromosome-*4* are recovered as spa^{pol} progeny when they fertilize nullo-*4* ova. In calculating the frequency of fourth chromosome nondisjunction, it is assumed that progeny with four or more fourth chromosomes are inviable. To the extent that tetra-*4* flies are viable, the calculated frequency of chromosome-*4* nondisjunction will be slightly underestimated (MOORE and GRELL 1972b; BAKER and CARPENTER 1972).

It can be seen that both ord^+/ord^+ and ord/ord^+ males produce only very rare reductional *XY* exceptions and equational *XX* exceptions and no reductional-equational sequential exceptions. Males homozygous for *ord*, on the other hand, produce 137 reductional *XY* and 123 equational *XX* exceptions per 1000 progeny. These values are calculated using only progeny resulting from nullo-*X* ova. The values recorded here are not representative of gametic frequencies of exceptions because several sperm types (most notably nullo-*XY* sperm) are not recovered. Nevertheless, the data in Table 1 make it clear that the sex chromosomes in males frequently nondisjoin at both the reductional and equational divisions under the influence of *ord*.

In a cross of *ord* males to attached-*X*; attached-*4* females, where reductional and equational nondisjunction of sex chromosomes were monitored (Table 1), it can be seen that total fourth-chromosome nondisjunction is independent of sex-chromosome nondisjunction. Based on the hypothesis of independent behavior of the sex and fourth chromosomes, 195 double exceptions were expected, 172 were observed. In addition, fourth-chromosome nondisjunction is independent of reductional sex-chromosome nondisjunction (97 expected double exceptions, 102

observed), and equational X nondisjunction (80 expected double exceptions, 73 observed).

To ask if *ord* induces equational nondisjunction of the Y chromosome, y/y^+Y; *ord/ord* males were crossed to *C(1)RM, y pn v/0* females. The following progeny were recovered: 1618 y ♂♂, 1796 *pn v* ♀♀, 591 + ♂♂, 222 y ♀♀, 1156 *y pn v* ♀♀, and 29 + ♀♀. Some of the *pn v* females and wild-type males were progeny tested to determine the number of y^+Y chromosomes they carried. If a *pn v* female produced a high frequency of XXY ova, or if a wild-type male produced a high frequency of XY sperm, it was classified as a diplo-Y equational exception. Only one of 256 *pn v* females and none of 435 wild-type males tested proved to be diplo-Y exceptions. This suggests either that the Y chromosome does not nondisjoin with any appreciable frequency at the second division in *ord* males, or that diplo-Y gametes are formed but not recovered as fertile individuals. Indeed, some Y chromosomes confer sterility or lethality to XYY males (GRELL 1969) and $XXYY$ females have low viability.

The frequencies of recovered gametes suggest that the latter explanation is the case. The production of a gamete with three or four chromatids of a chromosome pair requires the formation of two or three nullo gametes as reciprocal products. Thus sequential nondisjunction, as well as chromosome loss, yields an excess of nullo over diplo gametes. The frequency of nullo-XY sperm produced by *ord* males is greater than the sum of the frequencies of XY, XX, and 2 times XXY sperm, suggesting that there is chromosome loss. However, 2611 X's are recovered among 5312 sperm, indicating that the X chromosome is not lost. The Y chromosome is recovered in 2316 of the 5312 sperm, suggesting that it is lost in some fraction of meioses. Loss of a Y in an otherwise regular meiosis will convert regular Y sperm to exceptional nullo-XY sperm, but since 1796 regular Y and 1618 regular X sperm are recovered, the Y does not appear to be lost in all gametes equally frequently. If it is assumed that the Y nondisjoins equationally at the same rate as the X and that there is no meiotic loss, 1151 nullo-XY sperm are expected; 1156 are observed. Thus the deficiency in the number of Y chromosomes recovered and the lack of YY and XYY sperm could be explained if diplo-Y sperm are not recovered.

The same analysis can be applied to the behavior of chromosome-*4*. Among regular XY sperm, there were 137 diplo-*4* exceptions and 126 nullo-*4* exceptions per 1000 sperm (Table 2), indicating that chromosome loss and sequential nondisjunction of chromosome-*4* either do not occur or are very infrequent.

It is not possible to distinguish reductional from equational fourth-chromosome exceptions produced by spa^{pol}/spa^{pol} males. In order to estimate the frequency of equational nondisjunction of chromosome-*4* in *ord* males, y/y^+Y; *ord/ord*; $spa^{pol}/+$ males were crossed to *y pn*; *C(4)RM, ci* $ey^R/0$ females (Table 2). In the experimental cross, half of the equational diplo-*4* exceptions are spa^{pol}, while the reductional diplo-*4* exceptions and the other half of the equational diplo-*4* exceptions are phenotypically wild-type and indistinguishable from the regular progeny. Multiple-*4* sperm, resulting from sequential nondisjunction, also yield wild-type progeny. As a control, spa^{pol}/spa^{pol} sibs were used to estimate the frequency

TABLE 2

Disjunction of the sex and fourth chromosomes in y/y+Y; spa^{pol}/+ *and* spa^{pol}/spa^{pol} *male crossed to* y pn; C(4)RM, ci ey^{R}/0 *females*

Cross:		1	2	3	4	5	6
Second chromosome:		+/+		*ord*/+		*ord*/*ord*	
Fourth chromosome:		*spa^{pol}*/*spa^{pol}*	*spa^{pol}*/+	*spa^{pol}*/*spa^{pol}*	*spa^{pol}*/+	*spa^{pol}*/*spa^{pol}*	*spa^{pol}*/+
Progeny phenotype*							
y female	+	2374 (2371.9)	2169 (2168.4)	2735 (2737.0)	1326 (1325.9)	1482 (1481.9)	1444 (1436.7)
	spa^{pol}	1 (2.6)	1 (0.5)	7 (5.6)	0 (0.0)	294 (283.1)	84 (75.9)
	ci ey^{R}	0 (0.5)	0 (1.0)	4 (3.4)	2 (2.1)	240 (250.9)	231 (246.5)
pn male	+	2171 (2171.1)	1980 (1980.6)	2123 (2120.0)	1161 (1160.1)	1431 (1422.4)	1533 (1542.8)
	spa^{pol}	3 (2.4)	0 (0.5)	2 (4.3)	0 (0.0)	248 (271.8)	80 (81.5)
	ci ey^{R}	1 (0.5)	2 (1.0)	2 (2.6)	1 (1.9)	256 (240.9)	276 (264.7)
+ female	+	3 (3.2)	1 (1.0)	5 (6.0)	3 (4.0)	347 (341.1)	349 (347.9)
	spa^{pol}	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	56 (65.2)	22 (18.4)
	ci ey^{R}	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	61 (57.2)	55 (59.7)
y pn male	+	3 (4.1)	4 (4.0)	11 (11.0)	1 (1.0)	791 (805.6)	859 (857.6)
	spa^{pol}	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	176 (153.9)	35 (45.3)
	ci ey^{R}	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	129 (136.4)	156 (147.1)
Total:		4557	4157	4890	2495	5511	5124
XY nondisjunction:		0.0015	0.0012	0.0035	0.0020	0.2831	0.2881
4 nondisjunction†:		0.0013	0.0005	0.0033	0.0000	0.2649	0.1725

* For a description of progeny phenotypes see text and Table 1.

† Total fourth chromosome nondisjunction is calculated by summing *spa^{pol}* and *ci ey^{R}* progeny of *spa^{pol}*/*spa^{pol}* males and dividing by the total. Equational fourth chromosome nondisjunction is calculated by dividing 4 times the *spa^{pol}* progeny by the total progeny from *spa^{pol}*/+ males.

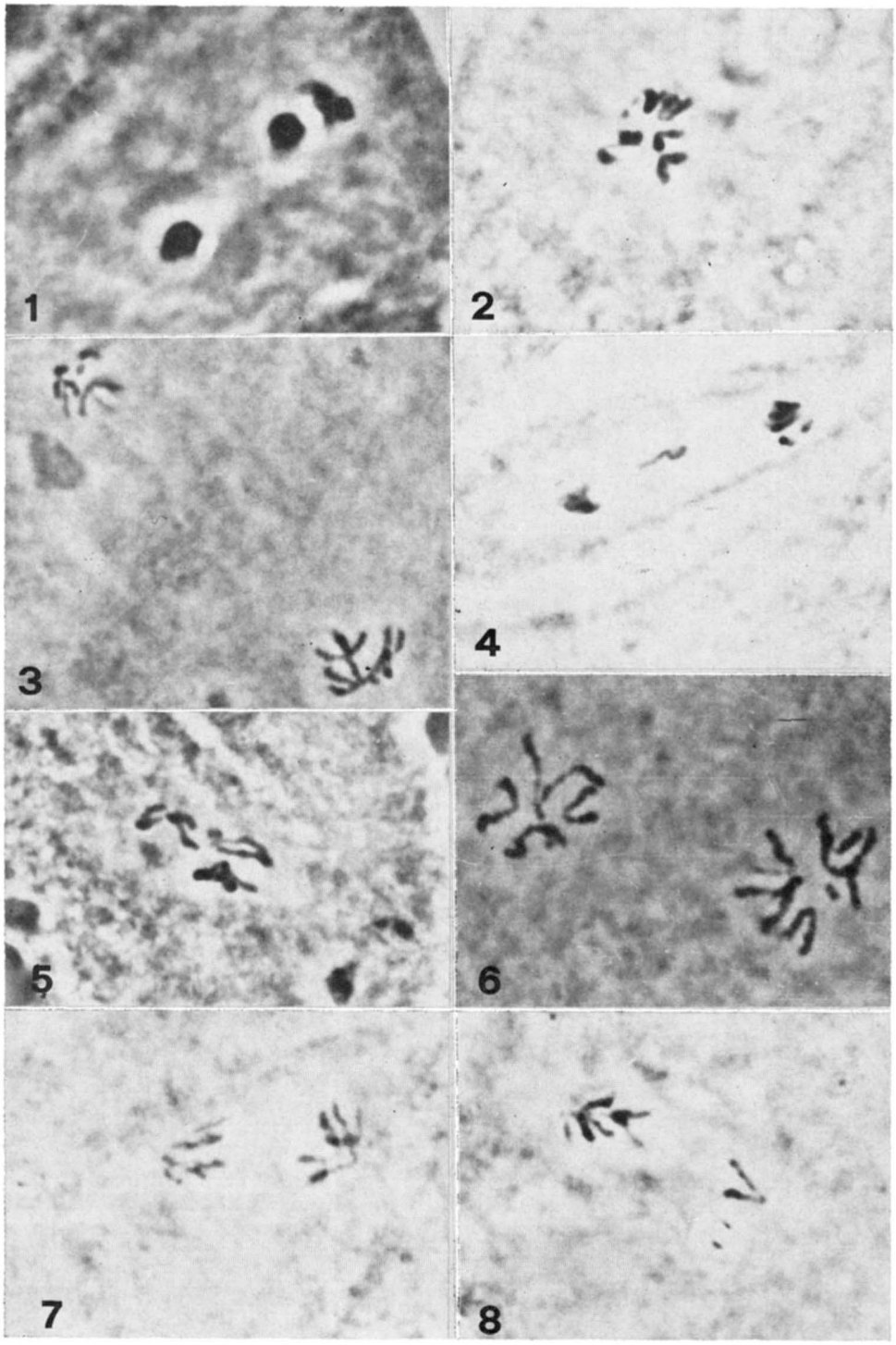
of total fourth chromosome nondisjunction (cross 5). The frequency of equational exceptional diplo-*4* sperm is twice the frequency of spa^{pol} progeny in cross 6. The frequency of reductional exceptional diplo-*4* sperm is obtained by subtracting the frequency of equational diplo-*4* exceptions in cross 6 from total diplo-*4* exceptions in cross 5.

Among 1000 sperm regular for the sex chromosomes, there were 90 equational diplo-*4* exceptions and 47 reductional diplo-*4* exceptions. Thus there are 179 equational exceptions and 94 reductional exceptions for the fourth chromosome per 1000 sperm, provided that the nullo-*4* sperm result from reductional and equational nondisjunction in the same relative frequency as do diploid-*4* sperm. Chromosome-*4* misbehaves less often than the sex chromosomes, but the ratio of reductional to equational exceptions is the same. Sixty-six percent of fourth chromosome diplo exceptions are due to equational nondisjunction, while the fraction of sex-chromosome exceptions resulting from equational nondisjunction varies from 43 to 64%. Equational diplo-*4* exceptions are also recovered independently of total sex-chromosome nondisjunction (24 expected double exceptions, 26 observed), reductional sex chromosome nondisjunction (15 expected double exceptions, 13 observed), and equational *X* nondisjunction (9 expected double exceptions, 13 observed).

Cytology: Testes of newly emerged males were dissected in Ringer's solution, stained with aceto-orcein, and examined with phase optics. Primary spermatocytes from control males contain three darkly staining bivalents (Figure 1). The autosomal bivalents are held together along the entire length of the chromosomes, while the sex chromosomes are more loosely conjoined (COOPER 1950). During anaphase I, all of the chromosomes move to the poles at approximately the same time (Figure 3). Lagging chromosomes were not observed. During meiosis II, sister chromatids are held together at the centromere (Figure 5) until they separate at anaphase (Figure 7). Premature centromere division was not observed in control spermatocytes.

Two distinct meiotic divisions are seen in *ord* spermatocytes. The first division looks roughly normal. The large majority of prophasce I cells contain three normal bivalents. In one cell in this stage (of about 30 examined) the sex-chromosome bivalent was present along with four univalent autosomes (Figure 2). The *X* and *Y* chromosomes in this cell are connected by a thread as is often the case during diakinesis in wild-type males (COOPER 1949, 1950). Most cells in anaphase I also resemble the controls. However, in a number of such cells a single chromosome (chromatid?) lags on the metaphase plate (Figure 4). Such lagging may lead to loss of the lagging chromosome, but, since chromosome loss is not observed genetically, it may be that the laggard eventually proceeds to one of the poles. If this is the case, random segregation of the laggards may produce secondary spermatocytes with more (or less) than the requisite number of chromatids for a particular chromosome pair. These secondary spermatocytes may, in turn, produce reductional diplo exceptional (or nullo exceptional) sperm.

In contrast to the first division, chromosomal misbehavior is frequent during the second meiotic division in *ord* spermatocytes. Sister centromeres are often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separated at metaphase II (Figure 6), and sister chromatids often nondisjoin at anaphase II (Figure 8). As can be seen from Figure 6, there may sometimes be an odd number of chromatids at metaphase II. This suggests that sister centromeres have separated from each other before anaphase I, and the four chromatids of a chromosome pair have segregated three from one.

The cytological observation that there is chromosome misbehavior at both the first meiotic division and the second in *ord* spermatocytes corroborates the genetic conclusions and suggests that *ord* results in precocious relaxation of the forces that hold tetrads together.

In summary, males homozygous for the meiotic mutant *ord* exhibit increased rates of nondisjunction of all chromosomes at both the first and second meiotic divisions. Nondisjunction of the *X* and fourth chromosomes is independent at both divisions. There is some sequential nondisjunction of the sex chromosomes, as evidenced by the recovery of *XXY* sperm, but this is not frequent for either the sex or fourth chromosomes. The data suggest that homologous chromosomes pair in *ord* males, but the forces responsible for maintaining the integrity of the tetrad are defective. Thus, homologs may fall apart prematurely, resulting in reductional nondisjunction, individual chromatids may not move to the poles at anaphase I, and sister chromatids may separate prematurely, resulting in equational nondisjunction.

DISJUNCTION IN FEMALES

X and fourth chromosomes: Disjunction of the *X* and fourth chromosomes in females was monitored by mating $y\cdot Dp(1,1)sc^{v1}$, y^+/y; spa^{pol}/spa^{pol} females to $Y^sX\cdot Y^L$, *In(1)EN*, *v f B/0*; *C(4)RM*, *ci* $ey^R/0$ males; the results are given in Table 3. The males produce four types of sperm in roughly equal frequencies: *XY;0*, *0;44*, *XY;44*, and *0;0*. Since the females being tested were homozygous B^+, the progeny phenotype with respect to *B* is an assay for *X* chromosome non-

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FIGURE 1.—Normal prophase I from a control male.

FIGURE 2.—Prophase I from an *ord* male. There are four univalent autosomes present. The *X* and *Y* are connected by a thread.

FIGURE 3.—Normal anaphase I from a control male.

FIGURE 4.—Anaphase I from an *ord* male. One chromatid is lagging on the metaphase plate.

FIGURE 5.—Normal prophase II from a control male. Sister chromatids are connected at the centromere.

FIGURE 6.—Prophase II from an *ord* male. The two nuclei shown are presumably products of the same anaphase I. The nucleus on the left contains two *X* chromatids joined at the centromere, and three unpaired autosomal chromatids. The nucleus on the right contains two paired *Y* chromatids, and five unpaired autosomal chromatids. There is a pair of fourth-chromosome chromatids in each nucleus.

FIGURE 7.—Normal anaphase II from a control male. Two major autosomes and a *Y* are going to each pole.

FIGURE 8.—Anaphase II from an *ord* male. Only one metacentric is going to one pole. Several chromosomes are going to the opposite pole.

TABLE 3

Disjunction of the X *and fourth chromosomes in* y·Dp(1,1)sc^{v1}, y+/y; spa^{pol}/spa^{pol} *and* spa^{pol}/+ *females crossed to* Y^{s}X·Y^{L}, In(1)EN, v f B/0; C(4)RM, ci ey^{R}/0

Cross:	1	2	3	4	5	6
Second chromosome:	+/+		*ord*/+		*ord/ord*	
Fourth chromosome:	*spa^{pol}/spa^{pol}*	*spa^{pol}*/+	*spa^{pol}/spa^{pol}*	*spa^{pol}*/+	*spa^{pol}/spa^{pol}*	*spa^{pol}*/+
Progeny phenotype*						
B/+ ♀ ♀ +	4929 (4928.5)	2271 (2271.2)	4433 (4434.9)	3002 (3002.1)	654 (695.7)	1267 (1277.9)
spa^{pol}	0 (0.0)	0 (0.0)	4 (2.2)	0 (0.0)	328 (294.3)	35 (33.1)
ci ey^{R}	3 (3.2)	2 (1.8)	1 (0.9)	1 (0.9)	309 (301.1)	423 (413.8)
B+ ♂ ♂ +	5740 (5739.0)	2842 (2841.7)	5538 (5536.1)	3285 (3285.0)	868 (811.6)	1457 (1417.9)
spa^{pol}	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	331 (343.4)	34 (36.7)
ci ey^{R}	3 (3.8)	2 (2.3)	1 (1.1)	1 (1.0)	307 (351.2)	423 (459.2)
B+ ♀ ♀ +	0 (0.0)	1 (1.0)	0 (0.0)	2 (2.0)	437 (423.0)	657 (667.5)
spa^{pol}	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	140 (179.0)	16 (17.3)
ci ey^{R}	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	208 (183.1)	228 (216.1)
y B+ ♀ ♀ +	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	116 (100.8)	155 (149.6)
spa^{pol}	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	40 (42.6)	2 (3.9)
ci ey^{R}	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (43.6)	45 (48.5)
v f B/0 ♂ ♂ +	3 (4.0)	0 (0.0)	1 (1.0)	0 (0.0)	303 (347.1)	589 (611.9)
spa^{pol}	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	167 (146.8)	20 (15.9)
ci ey^{R}	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	174 (150.2)	217 (198.2)
Total progeny:	10,679	5118	9979	6291	4413	5568
X nondisjunction:	0.0007	0.0004	0.0002	0.0006	0.5361	0.5146
4 nondisjunction†:	0.0007	0.0000	*0.0007*	*0.0000*	0.4611	0.0769

* For a description of progeny phenotype see text and Table 1.
† Total and equational fourth chromosome nondisjunction were calculated according to note in Table 2.

disjunction; because only half of the diplo-*X* and nullo-*X* exceptional ova survive relative to regular mono-*X* ova, the number of regular progeny is halved prior to further calculations. Triplo-*X* and tetra-*X* ova, if they occur, will produce inviable zygotes. To the extent these occur, the calculated nondisjunction will be slightly underestimated. With respect to chromosome-*4* nondisjunction frequencies are calculated as in males (see above).

Dp(1,1)sc^{v1} (abbreviated $\cdot y^+$ in this report) is derived from a pericentric inversion with one breakpoint near the tip, and the other in the short arm, of the *X* such that y^+ is appended to the short arm of the *X*. Thus y^+ is a centromere marker indicating at which meiotic division nondisjunction occurs. In the following discussion "equational" and "reductional" nondisjunction refer only to the centromere.

Diplo-exceptional gametes may be of two kinds: reductional exceptions, indicative of misbehavior of homologs at the first meiotic division, and equational exceptions, indicative of misbehavior of sister chromatids at the second division. Reductional nondisjunction of the *X* produces $y \cdot y^+/y$ females, while equational nondisjunction produces homozygous y females and homozygous $y \cdot y^+$ females. It is possible to distinguish between the two kinds of y^+B^+ females by progeny testing. Reductional and equational diplo-*4* exceptions are not distinguishable in this cross.

In these experiments, a small number of triploid females and intersexes were recovered. These are the result of unreduced ova. Their recovery was erratic.

ord females produced 536 *X* chromosome exceptions per 1000 ova and 187 of the diplo-*X* exceptional progeny were y. Of 203 y^+ exceptional females progeny tested, 35 were homozygous $y \cdot y^+$; thus, of the 785 y^+ exceptional females recovered, 135 were equational. In all, the gametic frequency of *X* chromosome equational nondisjunction is 0.18 and *X* chromosome reductional nondisjunction is 0.32.

In the cross just described, more diplo-*X* than nullo-*X* ova were recovered. SANDLER and BRAVER (1954) and HARDY (1975) have shown, however, that attached-*XY* chromosomes are included in less than fifty percent of sperm. This inequality between *XY* and nullo-*XY* sperm is reflected in the control sex-ratio. Thus, of 10,669 *X;4* ova recovered in the control, 4929 were female and 5740 male. If this inequality is corrected for in the experimental cross, the recovery of *0;4* ova and *XX;4* ova is 353 *versus* 553. Therefore, it appears that in *ord* females, the *X* chromosome does not get lost, nor are there sequential nondisjunctional events. (The procedure used to estimate loss and sequential nondisjunction of chromosomes in females is the same as that described above for males.)

While an excess of nullo-*X* gametes over diplo-*X* is not observed, an excess of diplo-*X* ova is found in this cross. The factor responsible for this discrepancy is located on the second chromosome but is separable from *ord*. Thus, in the absence of this factor $y\ pn\ v \cdot y^+/y$; *ord/ord*; *spa*^{pol}/*spa*^{pol} females crossed to $Y^sX \cdot Y^L$, *In(1)EN*, *v f B/0* males produce the following ova types: 1762 *X;4*, 330 *XX;4*, and 288 *0;4*. After correcting for the unequal recovery of attached-*XY* and nullo-

TABLE 4

X- and fourth chromosome double exceptions produced by homozygous ord *females. Data listed here are from the cross reported in Table 3*

	Constitution of ova producing recovered progeny			
	XX;44	*XX;0*	*0;44*	*0;0*
Total exceptions	227	315	264	221
Equational-*X* exceptions	61	54	—	—
Reductional-*X* exceptions	64	116	—	—

XY sperm the recovery of *0;4* ova and *XX;4* ova is the same (334 *vs.* 330). Therefore, it appears that in *ord* females the *X* chromosome is not lost.

Females homozygous for *ord* produced 456 total fourth chromosome exceptions and 76 equational fourth chromosome exceptions per 1000 regular-*X* ova (Table 3). Therefore, there must have been 380 reductional exceptions per 1000 ova, and the equational fourth chromosome exceptions must make up 17% of the total fourth chromosome exceptions, compared with 33% for the *X*.

The occurrence of a nondisjunctional event for the *X* chromosome does not influence the likelihood of fourth-chromosome nondisjunction; the frequency of *X-4* double exceptions is approximately the product of the individual frequencies of *X* chromosome and fourth-chromosome exceptions. However, among *X-* and *-4* double exceptions, there is an excess of *XX;0* and *0;44*, and a deficiency of *XX;44* and *0;0* gametes relative to the expectations based on independence (Table 3). This distribution of double exceptional ova suggests that chromosomes-*1* and *-4* pair and segregate from each other. The nonrandomness is evident only in reductional exceptional diplo-*X* ova (Table 4).

Major autosomes: Reductional and equational nondisjunction of chromosomes-*2* and *-3* are increased by *ord*. Exceptions for the major autosomes can be recovered from *ord* females crossed to attached-*2* and *-3* males (y^2/Y; *C(2L)RM, dp*; *C(2R)RM, px*; *C(3L)RM,* $h^2\ rs^2$; *C(3R)RM,* +); the results are given in Table 5. The compound chromosomes in males move to the poles at anaphase I

TABLE 5

Second- and third-chromosome double exceptions produced by ord *females.* y/y; pr ord/ord; st/+ *females were mated in mass cultures to* y^2/Y; C(2L)RM, dp; C(2R)RM, px; C(3L)RM, $h^2\ rs^2$; C(3R)RM; + *males. The only ova recoverable are those nondisjunctional for the second and third chromosomes*

Constitution of females	*X* chromosome constitution of ova	Autosomal constitution of ova				Total	Number of females tested
		22;0	*0;33*	*22;33*	*0;0*		
ord/+	total	0	0	0	0	0	349
ord/ord	*X*	52	147	65	12	276	973
	XX	11	45	13	3	72	
	O	5	34	32	0	71	
	total	68	226	110	15	419	

at random with respect to one another (BALDWIN and CHOVNICK 1967; GRELL 1970). Thus four classes of potentially recoverable sperm, *22;0*, *0;33*, *22;33*, and *0;0*, are produced in equal numbers. Viable progeny are produced when a gamete disomic for one chromosome from one parent unites with the complementary nullosomic gamete from the other parent. Because regular ova are not recovered, it is not possible to measure the absolute frequency of nondisjunction for the major autosomes. It may be noted that nullo-*3* ova are recovered much less frequently than diplo-*3* ova. It is likely that the discrepancy is due to decreased viability of *C(3L)RM*; *C(3R)RM* progeny. Whatever the cause of this inequality, however, the conclusions to be drawn are not dependent on this ratio.

Some of the *ord* females that were crossed to attached-*2* and -*3* males to measure autosomal nondisjunction were heterozygous for the centromere markers *pr* on chromosome-*2* and *st* on chromosome-*3* (Table 6). In these cases, it is possible to measure equational nondisjunction for the major autosomes, since half of the equational exceptions for a particular autosome will be homozygous for the centromere marker for that chromosome. The procedure for estimating the number of equational exceptions among total diplo exceptions is the same as that described previously for chromosome-*4* in males. The data from this experiment are shown in Table 10. About 11% of diplo-*2* ova and 14% of diplo-*3* ova are equational exceptions, compared with 33% for diplo-*X* exceptions and 17% for diplo-*4* exceptions (Table 3).

Distributive pairing: GRELL (1962a) proposed a system (distributive pairing) to account for the regular meiotic segregation of nonexchange homologs (WEINSTEIN 1936; COOPER 1945) and nonexchange nonhomologs (STURTEVANT 1944; COOPER, ZIMMERING and KRIVSHENKO 1955; SANDLER and NOVITSKI 1956; GRELL 1959) in *D. melanogaster* females. The distributive pairing process has the following properties. (1) Only nonexchange chromosomes and compound chromosomes use the distributive pairing system for disjunction (GRELL 1962a; GRELL 1963). (2) Chromosome size, not homology, determines the pattern of segregation because chromosomes of similar size are more likely to pair and separate than chromosomes that are dissimilar in size (GRELL and GRELL 1960; GRELL 1964; MOORE and GRELL 1972a, 1972b). (3) More than two chromosomal

TABLE 6

Equational exceptions among second- and third-chromosome double exceptions produced by ord *females*

Phenotype of progeny	diplo-2 (all data)	diplo-3 (all data)	diplo-2-diplo-3
+;+	121	247	80
pr;+	7	0	4
+;*st*	0	19	6
pr;st	0	0	1
Total	128	266	91

Homozygosis for the centromere markers *pr* and *st* indicate equational nondisjunction of the second and third chromosomes respectively.

elements may pair distributively (COOPER 1948; GRELL 1962b). (4) Distributive pairing does not occur in males (BALDWIN and CHOVNICK 1967; CARPENTER 1973).

As will be demonstrated in the next section, to a first approximation all of the tetrads in *ord* females are nonexchange and should disjoin distributively. Specific predictions about chromosome segregation are difficult to make when all eight chromosomes are simultaneously in the distributive pairing pool because the rules governing distributive pairing may allow complex chromosomal associations to occur. However, it might be expected that if the distributive system is operating in *ord* females, the segregation patterns would resemble those in *c(3)G* females, where all tetrads are nonexchange (GOWEN and GOWEN 1922), and where distributive disjunction is operative (HALL 1972). For this reason, rates of nondisjunction in *ord* females are compared with appropriate frequencies in *c(3)G* females.

Compound chromosomes in Drosophila females always segregate distributively (GRELL 1963). Thus disjunction of an attached-*X* from a *Y* chromosome depends on the efficacy of the distributive system. In *C(1)RM*, $y/y^{+}Y$; *ord/ord* females crossed to $Y^{S}X{\cdot}Y^{L}$, *In(1)EN*, *y B/0* males (Table 7), the attached-*X* and *Y* chromosomes nondisjoin in 358 per 1000 progeny. This may not be an accurate reflection of the gametic rate of reductional nondisjunction if the probability of equational nondisjunction is influenced by the prior occurrence of reductional nondisjunction. Equational nondisjunction of the attached-*X* would produce inviable tetra-*X* ova, while equational nondisjunction of the *Y* would result in *YY* ova that gave rise to *XYYY* progeny which are poorly viable (COOPER 1956), and which, if they survive, are indistinguishable from regular males. The *Y* chromosome appears to be lost a significant fraction of the time, while the attached-*X* does not get lost. This is evidenced by the fact that, after correcting for the unequal recovery of attached-*XY* and nullo-*XY* sperm, the *Y* is recovered in 37% of the progeny while the attached-*X* is present in 52%. An explanation that will account for the high rate of reductional nondisjunction and the loss of the *Y* chromosome is that in 20–25% of meioses, the attached-*X* disjoins from the *Y* during anaphase I, and sister chromatids separate normally at the second anaphase. In the remaining 75–80% of meioses, the attached-*X* and *Y* chromosomes move to the anaphase I poles at random with respect to each other, and the sister *Y* chromatids segregate at random with respect to each other during the

TABLE 7

*Disjunction of an attached-*X *from a* Y *in* C(1)RM, y/y+Y *females crossed to* $Y^{S}X{\cdot}Y^{L}$, In(1)EN, y B/0 *males*

Second chromosome constitution	Constitution of ova				Total	Nondisjunctions per 1000 ova
	XX	*Y*	*XX;Y*	*0*		
+/+	2986	2283	4	7	5280	2.1
ord/+	4419	3281	9	12	7721	2.7
ord/ord	579	243	170	289	1281	358.3

second division. Those ova that receive two *Y* chromosomes die, while the sister chromatids of the attached-*X* segregate from each other normally at the second division. The expected gametic frequencies based on this model fit the observed frequencies well after correcting for the unequal recovery of sperm ($P > 0.5$).

Under this model reductional nondisjunction occurs in 35–40% of ova. The following suggest that this high rate of nondisjunction is consistent with the notion that the distributive pairing system is operating. First, since there is very little recombination in *ord* females and chromosomes segregate virtually independently of exchange (see next section), all eight chromosomes probably associate distributively rather than pairing with a homolog. The chromosomal associations formed may be complex with more than two chromosomes involved at one time (COOPER 1948; GRELL 1962b). It is also possible that a nonhomologous chromosome in the distributive pool may interfere with the segregation of two homologs without segregating from either homolog itself (PARRY 1973). Second, recombination-defective mutants in Drosophila increase the frequency of nondisjunction (BAKER and CARPENTER 1972; HALL 1972; PARRY 1973; CARPENTER and SANDLER 1974); the frequency of nondisjunction is directly proportional to the decrease in crossing over in these mutants (CARPENTER and BAKER 1974). Presumably noncrossover chromosomes in these mutants pair and disjoin distributively, and the increase in nondisjunction is, to some extent, the result of distributive pairing. HALL (1972) noted differences in the frequencies of chromosomal segregation in two alleles of *c(3)G* and suggested that these differences were due to differences in stabilization of chromocentral associations that are prerequisite for both exchange pairing and distributive pairing (NOVITSKI 1964, 1975). In both alleles of *c(3)G*, and in *ord*, there is a tendency for chromosomes to segregate from each other, suggesting that the distributive system is operating. In the case of attached-*X* from -*Y* segregations just mentioned the 35–40% reductional nondisjunction is comparable to the 18% and 33% observed in $c(3)G^{17}$ and $c(3)G^{68}$ (HALL 1972).

Segregation of an attached-*X* from an attached-*4* is affected by *ord* in much the same way as attached-*X* from -*Y* segregation. In the control, the nondisjunction of the attached-*X* and attached-*4* chromosomes, in the absence of a *Y*, occurs in 53 ova per 1000 (Table 8). In homozygous *ord* females, the rate of nondisjunction is 375 exceptions per 1000 ova which is very similar to the attached-*X* from -*Y* results. However, it is not possible to say more about the segregation pattern in

TABLE 8

*Segregation of an attached-*X *and an attached-4 in* C(1)RM, y pn v/0; C(4)RM, ci ey^R/0 *females crossed to* $Y^SX{\cdot}Y^L$, In(1)EN, y B/0; spa^{pol}/spa^{pol} *males*

Second chromosome constitution	Constitution of ova					Nondisjunctions per 1000 ova
	XX;0	*0;44*	*XX;44*	*0;0*	Total	
+/+	43	3948	222	11	4224	53.2
ord/+	40	2373	127	3	2543	50.8
ord/ord	0	80	48	6	134	375.0

attached-*X/0*; attached-*4/0* females. The *0;44* regular ova and *XX;44* reductional exceptional ova are the only recoverable gametes; *XX;0* and *0;0* ova result in Minute progeny while ova containing more than one attached-*X* and/or more than one attached-*4* are not viable.

The addition of a *Y* chromosome to Drosophila females increases the frequency of *X* chromosome exceptions from less than one per 1000 ova in *XX* females (primary nondisjunction) to 20–40 exceptions per 1000 ova in *XXY* females (secondary nondisjunction). BRIDGES (1916) noted that secondary nondisjunction involves only noncrossover chromosomes, and two types of *X*-exceptional gametes, *XX* and *Y*, are formed almost exclusively; *XXY* and nullo-*XY* ova are not produced in appreciable numbers. The hypothesis proposed to explain this segregation pattern is that, in some fraction of meioses, the two *X* chromosomes and the *Y* form a trivalent which orients at anaphase I in such a way that the two *X*'s go to one pole and the *Y* goes to the other (COOPER 1948). Distributive pairing involving only nonexchange *X* chromosomes is responsible for the formation of the *XXY* trivalents (GRELL 1962b; CARPENTER 1973).

The effect of *ord* on recombination and secondary nondisjunction was monitored in *y pn cv m f/y/y*$^+$*Y* females; the data are presented in Table 9. There is no difference between recombination in these females and in *XX* females. Two problems arise in calculating the frequency of nondisjunction in *XXY* females. The first, mentioned previously, is that *XY* and nullo-*XY* sperm are not recovered equally frequently from attached-*XY/0* males. The second is that half of the regular female progeny from this cross, those arising from *XY* ova, are poorly viable *XXYY* females. These problems were obviated by using *X* and *XY* ova, recovered as *y* and *y*$^+$ males, to estimate the number of *X*- from -*XY* segregations, *XX* ova to estimate *XX*- from -*Y* segregations, and *XXY* ova to estimate *XXY*- from -*0* segregations. Thus, all ova used to estimate the rate of *X* chromosome nondisjunction have been fertilized by nullo-*XY* sperm, and *XXYY* females are ignored. All exceptional females were progeny-tested to determine at which meiotic division *X*-chromosome nondisjunction occurred using *f* as a centromere marker. Exceptional females heterozygous for *f* are usually the result of reductional nondisjunction; females homozygous for *f* or *f*$^+$ are usually equational exceptions.

In the *ord*$^+$ control, the frequency of *X* chromosome nondisjunction increased from 0.7 exceptions per 1000 ova in *XX* females (Table 3) to 53 exceptions per 1000 ova in *XXY* females (Table 9). All of the 119 *X* chromosome exceptions are either *XX* or *Y*. In *ord/ord*$^+$ females, secondary nondisjunction occurs in 143 ova per 1000 (Table 9), compared with 0.2 primary exceptions per 1000 ova in *XX* females (Table 3). Of the 434 secondary exceptions produced by heterozygous *ord* females, all but one are the result of *XX*- from -*Y* segregations. The increase in secondary nondisjunction in *ord/+* females, compared with control females, is consistent with the increase in the frequency of zero exchange tetrads observed in these females (see below). All exceptional diplo-*X* ova produced by *ord*$^+$*/ord*$^+$ and *ord/ord*$^+$ females were the result of reductional nondisjunction of the *X* chromosome.

TABLE 9

Disjunction and recombination in XXY *females. Crosses are* y pn cv m f/y/y+Y *females* × $Y^{S}X{\cdot}Y^{L}$, In(1)EN, y B/0 *males*

Gametes		Chromosome constitution of females		
Female	Male	+/+	*ord*/+	*ord/ord*
X	*XY*	1460	1879	252
X	*0*	1410	1588	284
XY	*XY*	544	885	107
XY	*0*	1141	1537	280
XX	*0*	72	261	248
Y	*XY*	47	172	123
XXY	*0*	0	0	163
0	*XY*	0	1	96
Total		4674	6323	1553
Crossover region*				
0		1272	1753	555
1		272	207	1
2		669	722	6
3		258	399	2
1,2		9	1	0
1,3		29	16	0
2,3		42	27	0
Total		2551	3125	564
Map		53.3	45.3	1.6
Sex chromosome Segregations† per 10^2 ova				
$X \leftrightarrow XY$		94.7	86.7	40.7
$XX \leftrightarrow Y$		5.3	14.3	35.8
$XXY \leftrightarrow 0$		0.0	0.0	23.5
Ratio of equational diplo-*X* ova to total diplo-*Y* ova × 10^2‡				
XX (nullo-*Y*) ova		0.0	0.0	20.7
XXY ova		—	—	26.0

* The crossover regions are as follows: 1 is *pn-cv*, 2 is *cv-m*, 3 is *m-f*.

† Such segregations were calculated using the two classes of regular males to estimate *X*-from-*XY* segregations, and the diplo-*X* exceptional females (*XX* and *XXY*) to estimate *XX*-from-*Y* and *XXY*-from-*0* segregations. The exceptional classes were doubled because these ova are only recovered half as frequently as regular ova. Such estimates avoid the problems associated with the unequal recovery of *XY* and nullo-*XY* sperm, because all such progeny are the product of nullo-*XY* sperm. Such estimates also obviate the problem of the underestimation of *XY* ova due to the poor viability of *XXYY* females.

‡ Estimates of the numbers of diplo-*X* reductional and equational exceptional ova were made by progeny testing exceptional females and using *f* as a centromere marker.

In *XXY*; *ord/ord* females, the *X* chromosome nondisjoins in 593 ova per 1000 compared with 536 in *XX*; *ord/ord* females (Table 3). Thus the *Y* chromosome may slightly increase the frequency of *X* nondisjunction. This is also true of *c(3)G* where *X* nondisjunction is increased by a *Y* from 32% to 54% in $c(3)G^{17}$ and from 39% to 51% in $c(3)G^{68}$ (HALL 1972).

The *X* chromosomes do not segregate independently of the *Y*. A comparison of the distribution of *X* chromosome ova types, with and without a *Y* chromosome, reveals that there is an excess of *XX* reductional exceptional and *Y* exceptional ova, and a deficiency of *XXY* reductional exceptional and nullo-*XY* exceptional ova, compared with the expected numbers based on the hypothesis of independence of the *X*'s and the *Y*. This suggests that, in some fraction of meioses, the two *X* chromosomes pair and segregate from the *Y* chromosome at the first division. Segregation of the *X*'s at the second division is not influenced by the *Y* chromosome (Table 9).

XXY; *ord/ord* females show 36% *XX*- from -*Y* and 24% *XXY*- from -*0* segregations. If, when the two *X* chromosomes nondisjoin, they move at random with respect to the *Y*, equal numbers of *XX*- from -*Y* and *XXY*- from -*0* segregations will result. Therefore, it is suggested that the frequency of meioses in which the two *X*'s are oriented to disjoin from the *Y* is the difference between the frequency of *XX*- from -*Y* segregations and the frequency of *XXY*- from -*0* segregations. In other words, the excess of *XX*- from -*Y* segregations over those expected on the hypothesis of random segregation is assumed to be due to directed segregation. In *ord* females the frequency of oriented *XX*- from -*Y* segregations is 12%. This frequency is 10% and 22% for the two alleles of *c(3)G*. Thus, the level of *XX*- from -*Y* segregations attributable to distributive disjunction in *ord* females is comparable to that observed in *c(3)G* females.

The major autosomes tend to segregate from each other in *ord* females. Of 419 exceptional-*2*, exceptional-*3* ova recovered from *ord* females crossed to attached-*2*- and -*3* males, 70% (294/419) were either *22;0* or *0;33* ova (Table 5). If the frequency of *22;33* plus *0;0* ova is subtracted from the frequency of *22;0* plus *0;33* ova, it can be seen that the second and third chromosomes are oriented to opposite poles in 40% of ova. In $c(3)G^{17}$ the major autosomes are oriented to opposite poles in 72% of ova.

There is little, if any, difference in *X* chromosome segregation between regular-*2*, regular-*3* and exceptional-*2*, exceptional-*3* ova. In the former the *X* chromosome nondisjoins in 43–50% of ova; in the latter the *X* chromosome nondisjoins in 51% of ova. Nor does the *X* segregate from either of the major autosomes in ova that are exceptional for the *X*, *2* and *3*. The frequencies of *X*- from -*2* and *X*- from -*3* segregations are 0.59 and 0.56, respectively.

Another way to ask about the degree of nonhomologous segregation for a pair of nonhomologs is to calculate the parameter, *N*, which HALL (1972) has defined as $1-d_1d_2/(d_1 \times d_2)$. The terms in the formula are defined as frequencies of gamete types among all double exceptions for a particular pair of nonhomologs. d_1d_2 is the frequency of diplo-diplo double exceptions, d_1 is the frequency of diplo exceptions for one chromosome, and d_2 is the frequency of diplo exceptions for

the other chromosome, among the double exceptions for these two chromosomes. Thus, N is an estimate of the frequency of nonhomologous segregation that varies from 0 when there are no nonhomologous segregations for a given pair of nonhomologs to 1 when two given heterologs always segregate from each other.

Based on the values calculated for N, it is concluded that each of the chromosomes in *ord* females, even the tiny fourth chromosome, pairs and segregates nonhomologously from each of the other chromosomes, in some fraction of meioses. Among double exceptions the value for N in each case is 0.2–0.3, except in those instances in which nonhomologous segregation of chromosome-*3* is monitored. In these cases N is small owing to the unusually low recovery of the attached-*3* chromosomes. It is of interest to note that N calculated for *X*- and *-4* double exceptions is 0.29, indicating that the *X* and fourth chromosomes regularly segregate from each other. This is in contrast to what has been found for other meiotic mutants, in which fourth-chromosome nondisjunction is correlated with nondisjunction for the *X*, but nonhomologous segregation is not observed (HALL 1972; BAKER and CARPENTER 1972; PARRY 1973; CARPENTER and SANDLER 1974). The frequent occurrence of nonhomologous segregation of the *X* and fourth chromosomes in *ord* females suggests the possibility that, in these females, the chromosomes do not pair distributively according to size similarities, as they do in the absence of a meiotic mutant (GRELL 1964). The mutant *mei-S51* also seems to interfere with the recognition of size similarity (ROBBINS 1971).

To recapitulate, the frequency of nondisjunction for all chromosomes, in homozygous *ord* females, is increased at both the first and second meiotic divisions. All autosomes display about the same distribution of reductional and equational nondisjunction; between 10 and 20% of exceptions for any one chromosome result from equational nondisjunction. This number is slightly higher for the *X* (33%), but seems to be constant for this chromosome under a variety of conditions. The distributive system of chromosome segregation (GRELL 1962a) is operative in *ord* females; when two nonhomologs are simultaneously nondisjunctional, they tend to pair and segregate from each other. However, distributive disjunction of chromosomes-*2* and *-3* is less frequent than might be expected, and distributive disjunction of the *X* and *4* is much more frequent than expected, suggesting that size recognition is impaired in *ord* females. Two *X*'s also tend to pair and segregate from a *Y* in *XXY* females. In all cases, nonhomologous segregation occurs at the first meiotic division.

RECOMBINATION IN FEMALES

X *chromosome recombination*: The effect of *ord* on recombination was examined in females having different sets of chromosome markers. Recombination in *X/X* females was monitored by crossing *y pn cv m f·y*$^{+}$*/y*; *spa*^{pol}*/spa*^{pol} females to *Y*^{s}*X·Y*^{L}, *In(1)EN*, *v f B/0*; *C(4)RM*, *ci ey*^{R}*/0* males (Tables 10). Recombination was examined on the *X* and third chromosomes simultaneously by crossing *y f/+ +*; *ve st ca/ + + +* females to *y f*; *ve st ca* males. The results of this cross are presented in Table 11. Since *ord* causes a reduction in crossing over

TABLE 10

Recombination in y pn cv m f·y^+/y *females crossed to* $Y^sX{\cdot}Y^L$, In(1)EN, v f B/0 *males*

			ord/ord		
	+/+	*ord*/+	reg ♂♂†	red ♀♀	eq ♀♀
Crossover region*					
0	2742	2803	1200	1831	625
1	539	360	8	11	5
2	1519	1255	18	17	10
3	592	663	10	11	2
4	315	254	27	17	19
1, 2	49	7	0	0	0
1, 3	94	49	0	0	0
1, 4	88	33	0	0	0
2, 3	128	73	1	1	0
2, 4	154	74	0	0	1
3, 4	16	10	0	0	0
1, 2, 3	0	1	0	0	0
1, 2, 4	2	1	0	0	0
1, 3, 4	1	1	0	0	0
2, 3, 4	1	0	0	0	0
Total	6240	5584	1264	1888	662
Map length					
1	12.4	8.1	0.6	0.6	0.8
2	29.7	25.3	1.5	1.0	1.5
3	13.3	14.3	0.9	0.6	0.3
4	9.2	6.7	2.1	0.9	3.0
Total map	64.7	54.3	5.1	3.1	5.6
Map/control map					
1	1	0.65	0.05	0.05	0.06
2	1	0.85	0.05	0.03	0.05
3	1	1.07	0.07	0.05	0.02
4	1	0.72	0.23	0.10	0.33
Total map/control	1	0.84	0.08	0.05	0.09
Coefficient of coincidence‡					
C(1, 2)	0.223 ± 0.030	0.078 ± 0.026	—	—	—
C(2, 3)	0.523 ± 0.039	0.369 ± 0.039	—	—	—
C(3, 4)	0.236 ± 0.053	0.210 ± 0.061	—	—	—
Exchange rank§					
E_0	0.05	0.09	0.90	0.94	0.89
E_1	0.61	0.73	0.10	0.06	0.11
E_2	0.33	0.17	0.00	0.00	0.00
E_3	0.01	0.00	0.00	0.00	0.00

* The crossover regions are as follows. Region 1 is *pn-cv*, region 2 is *cv-m*, region 3 is *m-f* and region 4 is *f-y*+.

† The term "reg ♂ ♂" designates regular males, "red ♀ ♀" designates reductional exceptional females, and "eq ♀ ♀" designates equational exceptional females.

‡ The standard errors on the coefficients of coincidence were calculated according to MULLER and JACOBS-MULLER (1925).

§ Exchange ranks were calculated according to WEINSTEIN (1936) for regular male data and MERRIAM and FROST (1964) for the reductional exceptional female data.

TABLE 11

Recombination on chromosome-1 and -3 in y f/+ +; ve st ca/+ + + *females crossed to* y f; ve st ca *males*

Crossover region*	Second chromosomes of females +/+	*ord*/+	*ord/ord*
0	331	549	1837
1	242	296	31
2	216	324	52
3	260	462	127
1,2	184	180	2
1,3	222	201	5
2,3	180	264	7
1,2,3	120	135	0
Total	1755	2411	2061
Coefficient of coincidence†			
C(1,2)	0.992 ± 0.033	1.036 ± 0.037	1.778 ± 1.204
C(1,2)	0.999 ± 0.030	0.939 ± 0.032	1.951 ± 0.799
C(2,3)	0.962 ± 0.033	1.003 ± 0.030	1.701 ± 0.590

* Crossover regions are as follows: Region 1 is between *y* and *f* on the *X*. Region 2 is *ve-st*, and region 3 is *st-ca* on chromosome-3.

† Standard errors were calculated following MULLER and JACOBS-MULLER (1925).

and an increase in nondisjunction of crossover chromosomes, it is of interest to inquire how *ord* affects the rate of crossing over between two homologs that are physically attached. Thus attached-*X*; *ord/ord* females, heterozygous for the *X*-linked markers *cv v f*, were mated to $Y^{s}X{\cdot}Y^{L}$, *In(1)EN, y B/0* males and the frequencies of homozygosis for these markers were monitored.

In *ord*/+ females, total *X* chromosome recombination is reduced to 84% of the control (Table 10). This reduction, however, is neither polar along the length of the *X*, as has been found for the majority of recombination-defective mutants in Drosophila (SANDLER *et al.* 1968; LINDSLEY *et al.* 1968; BAKER and CARPENTER 1972; PARRY 1973; CARPENTER and SANDLER 1974), nor uniform, as in other recombination-defective mutants (ROBBINS 1971; BAKER and CARPENTER 1972; CARPENTER and SANDLER 1974). Rather, the frequency of recombination is reduced at either end of the *X* and increased in the middle (Figure 9).

Single exchanges in +/+ females occur primarily in the middle portion of the *X*, and double exchanges occur primarily with one exchange on either end (CHARLES 1938). The distribution of exchanges in *ord*/+ females is compared with the distribution of single crossovers in the control in Figure 9. In distal regions the two distributions are similar. Furthermore, the coefficient of coincidence is reduced in distal and medial regions (Table 10), suggesting that the major effect of *ord* in heterozygous females is a reduction in double exchange tetrads in which both exchanges are distally located. The increase in recombination in the *m-f* region in heterozygous females relative to the control may be due to the decrease in double-exchange tetrads and a simultaneous increase in single-exchange tetrads. The frequency of double-exchange tetrads in *ord*/+

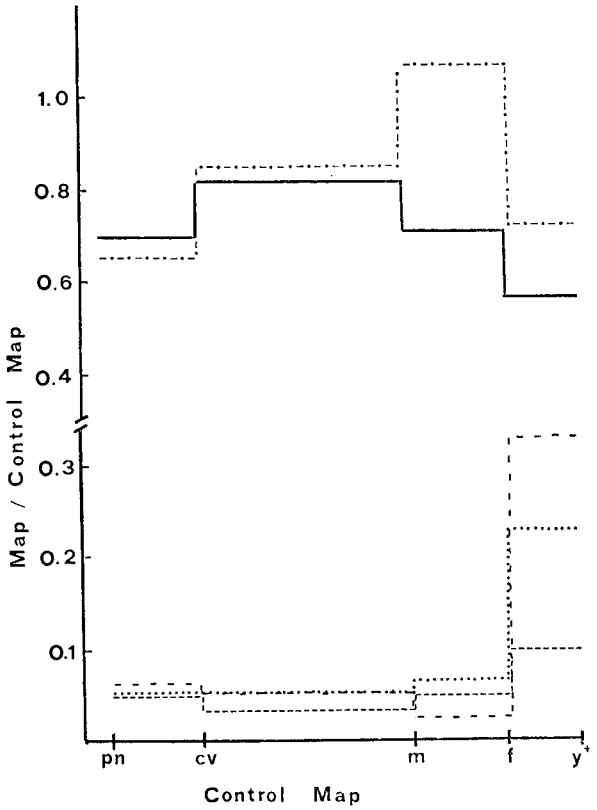

FIGURE 9.—Recombination along the *X* chromosome. Map intervals are drawn to scale on the abscissa; ordinate values are (experimental maps for an interval) ÷ (control map for that interval). Curves depict the contribution of single crossover chromosomes to the control map (———) and the values for *ord/ord*+ (–.–.–.–.), *ord/ord* recovered as regular males (. . . . .), *ord/ord* recovered as reductional exceptional females (– – – – –), and *ord/ord* recovered as equational exceptional females (– – – –).

females is 0.17 compared with 0.33 in the control, while the frequency of single-exchange tetrads in *ord*/+ females is 0.73 compared with 0.61 in the control.

Recombination in homozygous *ord* is reduced to 5.1 units (8% of controls). The frequency of crossing-over is reduced more in distal regions than it is near the centromere (Table 10). Two exceptional female progeny were recovered from the control, and two others were recovered from *ord/ord*$^+$ females. All four of these exceptions were the result of reductional nondisjunction, and none carried a recombinant *X* chromosome. Among diplo-*X* exceptional progeny tested from homozygous *ord* females, 944 resulted from reductional nondisjunction and 331 from equational nondisjunction. Chromosomes recovered in these two classes of progeny gave map lengths for the *X* of 3.1 units and 5.6 units, respectively.

Tetrad analyses (WEINSTEIN 1936) have been performed on the recombination data collected in regular males from control females, heterozygous and homozygous *ord* females, and on the recombination data collected in reductional

exceptional females (following the method of MERRIAM and FROST 1964), and equational exceptional females (Table 10). The mutant increases the frequency of nonexchange tetrads and decreases the frequencies of single and multiple exchange tetrads relative to the control. The distribution of exchange rank is virtually the same for all three disjunctional classes. Thus, unlike all other recombination-defective mutants in Drosophila where only nonexchange tetrads nondisjoin (BAKER and CARPENTER 1972; PARRY 1973; CARPENTER and SANDLER 1974), in *ord* females an exchange has very little effect on disjunction at either meiotic division.

The distribution of crossovers along the *X* chromosome recovered in the two types of exceptional females closely parallels the distribution along chromosomes recovered in regular male progeny. While overall the reduction in crossing over is polar in *ord* females, with the greatest reduction in distal regions, chromosomes recovered in reductional exceptional females show a uniform reduction in crossing over. Statistically, there is no difference between the distribution of crossovers along chromosomes recovered in regular males and equational exceptions, but there is a difference between each of these and the distribution of crossovers recovered in reductional exceptions. This suggests that, even though disjunction at either division is independent of distal exchanges, very proximal exchanges will, with some probability, prevent first-division nondisjunction.

Recombination in an attached-X: In the presence of *ord*, homologous chromosomes evidently pair since some recombination does occur. If proper pairing relationships involve alignment of centromere regions in Drosophila females, and if this aspect of pairing is defective in *ord* females, it might be possible to increase the frequency of exchange in *ord* females by physically keeping two homologs in proximity as with a compound-*X* reversed metacentric (attached-*X*) chromosome. Homozygosis for the *X*-linked markers *cv*, *v* and *f* was measured in attached-*X*-bearing females. In *ord/ord*$^+$ these frequencies were 0.16, 0.09 and 0.02; in *ord/ord* they were 0.05, 0.04 and 0.02, respectively.

In the absence of the meiotic mutant there is no difference in the rate and distribution of recombination between free-*X* and attached-*X* tetrads. Among 2783 attached-*X* chromosomes from *ord/ord*$^+$ females, the distance from *cv* to the centromere is 42.3 units. This is very close to the 46.3 observed for the same region in *X/X*; *ord/ord*$^+$ females (Table 10). In the case of *ord/ord*, as well, the recombination frequency is the same in free-*X* and attached-*X* females. In the latter, 10 attached-*X* chromosomes homozygous for one or more of the markers were observed among 585 chromosomes. Thus the *cv* to centromere distance is about 7 units compared with 4.5 for the same region in *X/X*; *ord/ord* females (Table 10). Thus it is clear that there is no dramatic change in the rate of recombination in attached-*X* tetrads compared with free-*X*.

Simultaneous X *and third-chromosome recombination*: The question of simultaneous recombination on the *X* and third chromosomes was examined in *y f*/+ +; *ve st ca*/+ + + females. The data are presented in Table 11. Each of the regions in which recombination was scored consisted of roughly one chromosome arm, so as to allow reasonable frequencies of crossing over in *ord/ord*

females. However, the observed frequencies of crossing over in *ord*/*ord*$^+$ and controls do not accurately reflect the actual rates of recombination because of undetected double crossovers.

In *ord*$^+$/*ord*$^+$ and *ord*/*ord*$^+$, the coefficients of coincidence for the *X* and either arm of the third chromosome are very close to 1.0, indicating that recombination on each arm is independent of the other arms. In *ord*/*ord*, however, the results are ambiguous. Recombination is reduced on both the *X* and third chromosomes. Chromosome-3 has one-tenth the wild-type levels of recombination and the *X*, one-twentieth. The coefficients of coincidence range from 1.7–2.0 indicating that if a crossover is present on one arm, the probability of a crossover on another arm is increased. However, the standard errors on these values are so large that the incidence values are not significantly different from 1.0. In a contingency test of independence, the data agree with the hypothesis of independence ($0.1 > P > 0.05$) of recombination on the *X* and third chromosomes.

In *ord* females the map lengths of the two marked regions on chromosome-3 are proportional to the euchromatic lengths of these regions in salivary gland chromosomes. The fact that the *st-ca* distance is not greater suggests that there is little, if any, crossing over in the centromeric heterochromatin. Crossing over on the *X* in this experiment is very low compared with chromosome-3, but the difference can be largely eliminated by estimating and disregarding the undetectable *X* chromosome exceptions that are phenotypically noncrossover. In any case, the genetic map to salivary chromosome map relationship for the *X* in *y pn cv m f*·*y*$^+$/*y*; *ord*/*ord* females is the same as for the two third-chromosome regions in this experiment.

Simultaneous recombination on two chromosomes has been monitored in only one other meiotic mutant (*mei-S282*; PARRY 1973). In that test, recombination on the *X* and second chromosomes was independent. The coefficient of coincidence for the *X* and *2L* was 1.05; in a contingency test for independence *P* was about 0.25.

To summarize, in *ord* females, recombination is drastically reduced on the *X* and third (and, by inference, all) chromosomes. Most *X* chromosome recombination is independent of *X* chromosome segregation at either the first or second meiotic division; however, very proximal exchanges decrease the probability of nondisjunction at the first division. The frequency of recombination on the *X* chromosome in *ord* females is not affected by the addition of a *Y* chromosome, which has been shown to disjoin from the *X* distributively, nor is the frequency of recombination on the *X* in *ord* females changed when the two homologs are attached to one centromere. The data are consistent with recombination on the *X* and third chromosomes being independent in *ord* females, although there are too few data for a definitive conclusion in this regard.

DISCUSSION

ord is unique among meiotic mutants in Drosophila in that it induces a wide range of defects in both sexes; it decreases meiotic exchange in a polar fashion in

females and increases nondisjunction at both meiotic divisions in males and females. In addition, *ord* may interfere with size recognition at distributive pairing, but does not disrupt distributive disjunction.

Because several steps in meiosis are defective, it might be that *ord*$^+$ is a control gene regulating several loci, each controlling a specific step in meiosis. This, while a possibility, is unlikely for two reasons. First, recombination and segregation in the first division of meiosis are under separate control in males and females (SANDLER *et al.* 1968; LINDSLEY *et al.* 1968; DAVIS 1971; BAKER and CARPENTER 1972), but *ord* causes reductional nondisjunction in both sexes. Second, all the *ord* meiotic defects relate to abnormalities in chromatid associations; chromosome movement at both divisions is normal in both sexes (as evidenced by no chromosome loss) and distributive pairing is operative in *ord* females.

If it is assumed that *ord* results in a defect in only one step in meiosis, it seems most reasonable that both the decrease in crossing over in females and the segregational anomalies are the result of an *ord*-induced abnormality in an early stage of chromosome association. There are three arguments against the hypothesis that the primary defect in *ord* is the reduction in meiotic exchange. First, if the primary defect in *ord* were a decrease in recombination, it should have no effect in males, where there is normally no meiotic recombination; but nondisjunction is increased in *ord* males. Second, unlike the case of other recombination-defective mutants (BAKER and CARPENTER 1972; PARRY 1973; CARPENTER and SANDLER 1974), homologs nondisjoin in *ord* females approximately independently of exchange; thus, the increase in reductional nondisjunction is not a consequence of the presence of no exchange tetrads. Third, equational nondisjunction is increased by *ord* while disjunction at the second division is unaffected by other recombination-defective mutants (BAKER and CARPENTER 1972; PARRY 1973; CARPENTER and SANDLER 1974).

SANDLER *et al.* (1968) proposed that meiotic mutants can be used to construct a flow chart of the events that take place during meiosis. Because recombination-defective mutants increase reductional nondisjunction (SANDLER *et al.* 1968; HALL 1972; BAKER and CARPENTER 1972; PARRY 1973; CARPENTER and SANDLER 1974), and disjunction-defective mutants have no effect on recombination (DAVIS 1969; DAVIS 1971; CARPENTER 1973; WRIGHT 1974), they proposed that recombination-defectives represent blocks in early events in meiosis, while disjunction-defective mutants are blocked in steps after recombination. In addition, it has been proposed that the first division of meiosis is under separate control in males and females because disjunction of homologs in males does not depend on crossing over and because all mutants affecting the first division of meiosis are sex-specific (SANDLER *et al.* 1968; DAVIS 1971; BAKER and CARPENTER 1972). *ord*, however, is a defect in the first division of meiosis, presumably before recombination, yet is not sex-specific. *ord*, therefore, probably represents a block in a very early step in meiosis that occurs before the two sexes come under separate control. Indeed, *ord*$^+$ may even be responsible for a process that occurs during the gonial

mitotic divisions that somehow influences chromosome pairing in both sexes. In this respect *ord*$^+$ may be analogous to one of the premeiotic processes necessary for homologous pairing in wheat (RILEY 1973).

Alternatively, *ord* may be a defect in a step after the initial chromosomal association has occurred in both sexes, but before completion of exchange in females and before establishment of segregation patterns in males. The evidence for this in males is that bivalents are observed cytologically early in meiosis, but pairing is not seen later in meiosis. In females some recombination is observed, but this recombination is not sufficient to determine segregation. Apparently, once bivalents have formed, the forces responsible for holding chromatids together relax prematurely. Thus, homologous pairing in male and female meiosis involves at least two steps, the first responsible for the initial associations and the second for maintaining the orientation of chromatids within the tetrad. STERN and HOTTA (1973) proposed that the synaptinemal complex is, at least in part, responsible for stabilizing these associations. It is suggested that *ord* is defective in the latter process and, therefore, that *ord* is necessary for recombination in females and independently for reductional and equational disjunction in both sexes.

The differences observed in the segregation patterns of *ord* males and females may be a reflection, not of the difference in the action of *ord* in the two sexes, but of the differences in the genetic control of the first division of meiosis, after the *ord*-mediated step. The data are consistent with the hypothesis that the only differences in the segregation pattern in *ord* males and females are during anaphase I and the rates of nondisjunction are the same during anaphase II. This observation is in turn consistent with the proposal that the second division of meiosis in the two sexes is under a common genetic control (SANDLER *et al.* 1968; DAVIS 1971).

I would like to thank DR L. SANDLER for the guidance and encouragement he has given me during the course of this project. I would also like to express my appreciation to B. S. BAKER, A. T. C. CARPENTER, B. GANETZKY and J. S. HAEMER for many helpful discussions and suggestions; S. YOKOYAMA, J. OTT and J. FELSENSTEIN for help with the computer analysis of the data, C. KLEBANOFF for technical assistance with the cytology, and A. T. C. CARPENTER for critically reading the manuscript.

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