A MEIOTIC MUTANT DEFECTIVE IN DISTRIBUTIVE DISJUNCTION IN *DROSOPHILA MELANOGASTER*[1]

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ABSTRACT

The female meiotic mutant *no distributive disjunction* (symbol: *nod*) reduces the probability that a nonexchange chromosome will disjoin from either a nonexchange homolog or a nonhomolog; the mutant does not affect exchange or the disjunction of bivalents that have undergone exchange. Disjunction of nonexchange homologs was examined for all chromosome pairs; nonhomologous disjunction of the *X* chromosomes from the *Y* chromosome in *XXY* females, of compound chromosomes in females bearing attached-third chromosomes with and without a *Y* chromosome, and of the second chromosomes from the third chromosomes were also examined. The results suggest that the defect in *nod* is in the distributive pairing process. The frequencies and patterns of disjunction from a trivalent in *nod* females suggest that the distributive pairing process involves three separate events—pairing, orientation, and disjunction. The mutant *nod* appears to affect disjunction only.

SANDLER *et al.* (1968) and LINDSLEY *et al.* (1968) proposed that the processes involved in meiosis could be dissected by a mutational approach; the analyses of a growing number of meiotic mutants in *Drosophila melanogaster* have substantiated the efficacy of this method. (For a review of meiotic mutants in Drosophila see BAKER and HALL, in preparation.) This report presents the analysis of a new meiotic mutant—*no distributive disjunction* (symbol: *nod*)—in which a function essential for normal distributive disjunction is defective.

GRELL (1962a) proposed that, in the meiosis of *Drosophila melanogaster* females, the regular disjunction of nonexchange homologs (WEINSTEIN 1936) and the nonhomologous disjunction of nonexchange nonhomologs (STURTEVANT 1944; COOPER, ZIMMERING, and KRIVSHENKO 1955; SANDLER and NOVITSKI 1956; GRELL 1959) are achieved by virtue of a single meiotic process which she termed "distributive pairing." Through the analysis of patterns of disjunction in females bearing chromosome complements with structural or numerical rearrangements, many characteristics of the distributive pairing process have been elucidated. The properties thus ascertained that are pertinent to this discussion are as follows: (1) only nonexchange chromosomes and compound chromosomes disjoin by the distributive pairing process (GRELL 1962a; GRELL 1963); (2)

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patterns of disjunction are determined by chromosome size, not sequence homology (GRELL and GRELL 1960; GRELL 1964a; MOORE and GRELL 1972a, 1972b); (3) associations for disjunction may involve more than two elements (STURTEVANT and BEADLE 1936; COOPER 1948; GRELL 1962b); (4) the process may be as efficient as homologous disjunction (GRELL 1963; GRELL 1964a); and (5) the distributive pairing system does not appear to be active in male meiosis (*cf.* GRELL 1970).

MATERIALS AND METHODS

BAKER and CARPENTER (1972) tested a number of *X* chromosomes (recovered among the progeny of males treated with ethyl methanesulfonate) for the presence of meiotic mutants which, when homozygous in females, resulted in increased rates of nondisjunction of the *X* chromosomes. The mutant *nod* was recovered as one such meiotic mutant; its origin is detailed in that work (*nod* = *mei 254*^{a} of BAKER and CARPENTER).

This *X*-linked meiotic mutant maps at 36 on the standard map on the basis of no observed recombinants between *nod* and *m* among 369 tested chromosomes from *cv m f*, *nod*+/+ + +, *nod* females; 117 of these chromosomes were recombinant between *cv* (13.7) and *f* (56.7). There are no structural abnormalities associated with *nod* detectable in salivary chromosome preparations.

All of the crosses reported here were performed on standard Drosophila cornmeal-molasses-agar medium at 25°C. All crosses were performed utilizing one tested parent and two to three tester parents per shell vial with the exception of crosses involving free autosomes by attached autosomes for which mass matings were performed in bottles. Parents were transferred to fresh medium after five days and discarded after an additional five days; all progeny emerging before day 18 were scored (introduction of parents = day 0). Crosses to measure recombination frequencies and most other crosses were initiated with females of uniform age (12–48 hours after eclosion). Progeny of the following types are excluded from the tabulations: haplo-*4*, triploid, intersex, metamale, and metafemale. Haplo-*4*/diplo-*4* mosaics and gynandromorphs are tabulated as the presumptive original diploid. Tetra-*4* progeny are considered to be lethal in calculations of the frequency of fourth chromosome nondisjunction; if the reported viability of terta-*4* progeny (MOORE and GRELL 1972b) were included in such calculations for *nod* females, the frequency of fourth chromosome nondisjunction would be increased by approximately 1%. All frequencies of nondisjunction are expressed as gametic frequencies; the lethality of triplo-*X* and nullo-*X* zygotes is compensated for by doubling the observed numbers of progeny resulting from diplo-*X* and nullo-*X* ova.

For descriptions of chromosomes and mutants mentioned in this paper see LINDSLEY and GRELL (1968).

RESULTS

The meiotic mutant *nod* does not affect exchange. In females homozygous or heterozygous for *nod*, recombination on the left arm of chromosome *2* from the tip to the centromere is approximately normal (Tables 1 and 2, crosses 1–4, 5 and 7). Mutant and control females in these crosses were not co-isogenic; this probably accounts for the slight regional differences in recombination between control and *nod* crosses. Not only is the process of exchange normal in *nod* females, but it also responds in a normal manner to the interchromosomal effect (for review, see LUCCHESI and SUZUKI 1968). The interchromosomal effect—the effect of heterozygosity for a structural aberration on recombination in other chromosomes of the complement—has two main characteristics: an increase in recombination frequency, and therefore an increase in the total map length, and

a shift in the tetrad distribution resulting in an increase in multiple-exchange tetrads (E_2 and E_3) relative to single-exchange and no-exchange tetrads (E_1 and E_0). Both of these effects are clearly present in *nod* females heterozygous for *TM2*, a multiply-inverted third chromosome (Tables 1 and 2, crosses 5–8).

Although *nod* does not affect recombination, the frequency of gametes resulting from nondisjunction is 15- to 800-fold higher in females homozygous for *nod* than in controls (*X* and fourth chromosomes, Table 3; second chromosome, Table 6a; third chromosome, Table 6b). This increase in nondisjunction is not observed in females heterozygous for *nod* (Table 3, cross 2) or in hemizygous *nod* males (Table 4.) The observed increase in nondisjunction of all chromosomes indicates that *nod* is defective in a meiotic process which affects all chromosomes in females. Since recombination is normal in *nod* females, the meiotic process defective in *nod* is presumably not involved in the process of exchange. In order to further delimit the defective process it is necessary to ascertain (1) whether nondisjunction occurs at the first or second meiotic division and (2) what the relationship between exchange and nondisjunction is. Such experiments are discussed below for the *X*, the fourth, and the second chromosome. The results of these experiments indicate that, in *nod* females, nondisjunction occurs at the first (reductional) meiotic division and involves primarily nonexchange tetrads and that the disjunction of most or all nonexchange tetrads is affected by *nod*. These results suggest that *nod* is defective in the process that normally insures the regular disjunction of nonexchange homologs—the distributive system (GRELL 1962b, 1964b).

Relationship between exchange and nondisjunction in nod *females*

The X *chromosome*: An experiment was performed to ascertain at which meiotic division *nod*-induced *X* chromosome nondisjunction occurs and whether exchange chromosomes nondisjoin; this experiment also provided estimates of the frequencies of nonexchange tetrads and of nondisjunction. The *X* chromosomes in this experiment were homozygous for *y* and heterozygous for the markers *pn* at the tip and $Dp(1,1)sc^{v1}$, y^+ at the base. [$Dp(1,1)sc^{v1}$, derived from $In(1LR)sc^{v1}$, is a duplication of the left tip of the *X* onto the minute right arm; it carries the marker y^+ and serves simultaneously as the right-most marker for the *X* and as an absolute centromere marker.] These markers span the entire *X* (66 centimorgans) except the 0.8 units distal to *pn*. Progeny from a cross of $y\ nod^-/y\ pn\ nod{\cdot}y^+$; spa^{pol}/spa^{pol} females (the symbol "—" indicates the absence of the duplication) by $Y^sX{\cdot}Y^L$, *v f B/0*; *C(4)RM*, *ci* $ey^R/0$ males were scored. Of the 21,822 progeny recovered, 138 resulted from nullo-*X* ova and 64 from diplo-*X* ova (gametic *X* nondisjunction = 0.018). By progeny-testing, the *X* chromosome markers of 52 of the 64 diplo-*X* exceptional females were successfully determined (coupling between *pn* and $\cdot y^+$ cannot be determined in these females): 49 were *pn*/+, $-/y^+$ (nonrecombinant, nondisjunction at the first division); one was *pn/pn*, $-/y^+$ (recombinant, first division); one was *pn*/+, −/− (recombinant, second division); and one was *pn*/+, y^+/y^+ (recombinant,

TABLE 1

Recombination data from crosses of X/X; al dp b pr cn/ + + + + +; 3/3; spa^{pol}/spa^{pol} *females* × +/Y; al dp b pr cn/al dp b pr cn; +/+; +/+ *males*
Crosses 1–4 include regular female progeny only; crosses 5–8 include all progeny. The control for cross 2 is cross 1; for cross 4, cross 3; and for crosses 6, 7, and 8, cross 5.

X and third chromosomes of females	Cross: 1* $\frac{y\ +}{-;\ y\ +}$	2 $\frac{y\ pn\ cv\ nod\ +}{y\ pn\ cv\ nod\ +;\ -}$	3 $\frac{y\ +}{-;\ y\ +}$	4 $\frac{y\ pn\ cv\ nod\ +}{y\ +\ +\ +\ +;\ -}$	5 $\frac{y\ +}{-;\ y\ +}$	6 $\frac{y\ TM2}{-;\ y\ +}$	7 $\frac{y\ cv\ nod\ +}{y\ cv\ nod\ +;\ -}$	8 $\frac{y\ cv\ nod\ TM2}{y\ cv\ nod\ +;\ -}$
RECOMBINANT TYPE								
Noncrossover								
al dp b pr cn	1155	1267	1046	937	1394	991	990	807
+ + + + +	2144	1817	1140	1069	3291	2648	3302	1941
Single crossover								
al + + + +	336	327	254	222	654	542	423	371
+ *dp b pr cn*	322	354	256	234	629	658	341	323
al dp b + +	754	680	508	440	896	759	809	674
+ + *b pr cn*	791	727	548	521	1297	1397	1022	795
al dp b + +	97	99	96	83	98	102	107	88
+ + + *pr cn*	123	80	81	76	185	192	201	149
al dp b pr +	34	18	21	9	18	39	49	51
+ + + + *cn*	47	25	18	17	52	73	85	64
Double crossover								
al + + + *cn*	2	3	3	2	5	24	8	5
+ *dp b pr* +	6	6	7	3	11	21	14	15
al + + *pr cn*	15	13	12	11	18	35	15	28
+ *dp b* + +	17	10	6	8	23	43	16	29
al + *b pr cn*	19	18	11	13	37	81	7	31
+ *dp* + + +	21	17	15	12	50	111	39	46
al dp + + *cn*	10	6	6	6	6	20	12	26
+ + *b pr* +	18	6	9	7	17	47	42	28
al dp + *pr cn*	16	9	13	6	14	15	6	23
+ + *b* + +	11	14	10	13	28	56	29	30
al dp b + *cn*	5	3	1	0	2	4	0	2
+ + + *pr* +	1	1	0	0	5	2	8	8
Triple crossover								
al + + *pr* +	0	0	0	0	0	1	1	0
+ *dp b* + *cn*	0	0	0	0	1	1	0	1
al dp + *pr* +	0	0	0	0	0	0	0	1
+ + *b* + *cn*	0	0	0	0	1	0	0	1
al + *b pr* +	0	0	1	0	0	4	0	0
+ *dp* + + *cn*	0	0	0	0	0	2	0	2
al + *b* + +	0	1	1	1	0	3	0	1
+ *dp* + *pr cn*	0	0	0	1	1	1	0	1
X-regular progeny:	5944	5501	4063	3691	8733	7869	7464	5498
X-exceptional progeny								
diplo-*X*	0	19	1	0	0	2	19	10
nullo-*X*	0	55	0	1	0	1	43	33
Total progeny:	11495	7968	7581	6218	8733	7872	7526	5541
No. of parental females:	60	240	30	28	40	37	233	240

* Data from BAKER and CARPENTER (1972).

TABLE 2

Map distances and tetrad distributions from the data in Table 1

Cross	1	2	3	4	5	6	7	8
MAP DISTANCES								
Region								
al–dp	12.4	13.6	13.9	13.7	16.4	19.4	11.5	15.4
dp–b	27.6	26.9	27.6	27.6	26.9	31.7	26.1	29.9
b–pr	4.8	4.2	5.2	5.4	4.3	5.8	5.1	6.5
pr–cn	2.1	1.2	1.8	1.2	1.4	3.0	2.9	3.7
Total map:	46.9	45.9	48.6	47.9	48.9	59.9	45.6	55.5
TETRADS, PERCENT*								
Tetrad rank								
E_0	15.7	16.0	12.2	13.1	12.2	4.1	19.3	9.0
E_1	74.8	76.4	78.8	78.4	78.0	73.2	70.4	72.0
E_2	9.5	7.5	8.6	8.1	9.5	21.5	10.3	18.0
E_3	0	0.1	0.4	0.4	0.3	1.2	0.1	1.0

* Calculated by the method of WEINSTEIN (1936).

second division). The remaining twelve exceptional females were all phenotypically pn^+y^+; three were gynandromorphs, seven died before producing progeny, and two were sterile. Clearly, most of the nondisjunction of *X* chromosomes ($49/52 = 94\%$) in *nod* females occurs at the first meiotic division and involves nonrecombinant chromosomes (see also Table 11). The frequency of exceptional females bearing recombinant *X* chromosomes in control crosses is approximately 1 per 5000 female progeny (BRIDGES 1916; MERRIAM and FROST 1964); in this experiment, one such exceptional female was observed (*pn/pn*, $-/y^+$) among approximately 10,000 female progeny, a frequency indistinguishable from background. MERRIAM and FROST conclude that the spontaneous frequency of nondisjunction at the second meiotic division in females is very low (less than 1 per 75,000 female progeny); the observation of two second-divisional exceptional females here may, therefore, reflect a very minor component of the nondisjunction induced by the mutant.

The progeny of a subset of this cross were scored for disjunction of the *X* and fourth chromosomes (Table 3, cross 4) and also for recombination between *pn* and y^+ in the regular male progeny to determine the frequency of nonexchange (E_0) tetrads in these females. Of the 1506 males resulting from mono-*X* ova, 389 (*y*) plus 387 (*y pn*·y^+) had parental marker combinations and 386 (*y pn*) plus 344 (*y*·y^+) were recombinant. These results give a recombination frequency of $730/1506 = 0.485$. This calculation does not include the progeny that resulted from *X*-nondisjunctional ova; since most of these ova were derived from meioses in which the *X* chromosomes were nonexchange, the true recombination frequency in this cross becomes $730/(1506 + 23) = 0.477$. Since one-half of all strands from tetrads of rank greater than zero have an odd number of crossovers, and since all strands with an odd number of crossovers will be recombinant for *pn* and y^+, 2 x (observed frequency of recombinants between *pn* and y^+) $= 1 -$

TABLE 3

Disjunction of the X *and fourth chromosomes in females*

Crosses are X/X; spa^{pol}/spa^{pol} females × $Y^{S}X{\cdot}Y^{L}$, *v f B/0*; *C(4)RM, ci* $ey^{R}/0$ males

X chromosomes of female:	Cross: 1* y nod+ / y nod+	2 y pn cv nod / y + + +	3 y pn cv nod / y pn cv nod	4 y pn cv nod·y+ / y + cv nod·—
Gamete type: Female / Male				
Regular				
X4 $\overline{XY}$ $\overline{44}$	6657	1545	503	174
X4 0 $\overline{44}$	9167	1694	455	241
X-nondisjunctional				
XX4 0 $\overline{44}$	0	1	5	1
04 $\overline{XY}$ $\overline{44}$	4	0	10	2
4-nondisjunctional				
X44 $\overline{XY}$ 0	3	1	91	23
X44 0 0	2	0	51	20
X 0 $\overline{XY}$ $\overline{44}$	3	0	2880	989
X 0 0 $\overline{44}$	5	0	2712	1245
X, 4-nondisjunctional				
XX44 0 0	0	0	2	0
XX 0 0 $\overline{44}$	2	0	18	5
044 $\overline{XY}$ 0	1	1	1	1
0 0 $\overline{XY}$ $\overline{44}$	0	1	50	14
Total progeny:	15844	3243	6778	2715
Number of female parents:	120	29	60	20
Gametic *X* nondisjunction:	0.0009	0.0018	0.0251	0.0168
Gametic *4* nondisjunction:	0.0012	0.0015	0.8561	0.8462

* Data from BAKER and CARPENTER (1972).

E_0. Consequently, the frequency of nonexchange *X* tetrads in *nod* females in this cross is 0.046. The standard value is about 0.05 (WEINSTEIN 1936), reaffirming that *nod* does not affect the probability of exchange. However, *nod* does affect the probability that nonexchange tetrads will disjoin; of the meioses in which the *X* chromosomes were nonexchange, 37% (0.017/0.046) resulted in gametes nondisjunctional for the *X* chromosomes. If the observed nondisjunctional gametes are the result of independent assortment of the *X* chromosomes at the first meiotic division, then the observed nondisjunctional gametes reflect only half of the affected meioses—in which case, in this experiment the *X* chromosomes assorted independently in 74% of the meioses in which the *X* chromosomes were nonexchange. This suggests that most, if not all, E_0 tetrads fail to segregate regularly in *nod* females.

In summary, *X*-chromosome nondisjunction in *nod* females occurs at the first meiotic division and involves primarily nonexchange chromosomes. If homologs

TABLE 4

Disjunction of the X *and fourth chromosomes in males*
Crosses are X/y^+Y; spa^{pol}/spa^{pol} males × *y pn/y pn*; *C(4)RM, ci* $ey^R/0$ females

Cross:		1*	2
X chromosome of male:		y nod+	y pn cv nod
Gamete type			
Female	Male		
X $\overline{44}$	X4	2973	2095
X $\overline{44}$	Y4	2758	1827
X $\overline{44}$	XY4	4	2
X $\overline{44}$	04	6	4
X 0	X44	8	0
X 0	Y44	0	1
X $\overline{44}$	X0	11	2
X $\overline{44}$	Y0	0	3
X 0	XY44	0	0
X 0	044	2	3
X $\overline{44}$	XY0	1	0
X $\overline{44}$	00	0	0
Total progeny:		5763	3944
Gametic sex nondisjunction:		0.0023	0.0022
Gametic *4* nondisjunction:		0.0038	0.0022

* Data from BAKER and CARPENTER (1972).

that fail to recombine move to the anaphase I poles independently under the influence of *nod*, most, if not all, E_0 tetrads are *nod*-sensitive.

The fourth chromosome: The minute fourth chromosomes (which are always nonexchange in diploid females) virtually always disjoin regularly in *nod*$^+$ females (Table 3, cross 1). Although it is easy to determine the frequency of gametes exceptional for the fourth chromosomes from *nod* females (86%, Table 3, cross 3), determination of the frequency of meioses in which the fourth chromosomes failed to segregate regularly is not straightforward, since fourth-chromosome loss (defined as an excess of nullo-*4* gametes relative to diplo-*4*) is very high. However, the fourth chromosomes fail to segregate regularly in at least the 86% of meioses which give rise to exceptional gametes; if chromosomes which disjoin are not lost, then the maximum frequency of meioses in which the fourth chromosomes disjoin is equal to the frequency of mono-*4* ova, or 14%.

Fourth chromosomes from *nod* females also exhibit somatic loss. Of the 145 diplo-*4* exceptions recovered from cross 3, Table 3, 27 were haplo-*4*/diplo-*4* mosaics. Thus, somatic loss per fourth chromosome in this experiment is 0.093. (This is the only experiment in which diplo-*4* exceptions were examined for mosaicism, although mosaics were detected in all experiments; see Table 15.) Somatic loss of chromosomes is correlated with irregular chromosome behavior in the prior meiosis in at least some situations (e.g. SEARS 1952). If fourth chromosomes derived from mono-*4* ova from *nod* females also exhibit somatic loss, this

TABLE 5

Somatic loss of fourth chromosomes in fourth chromosomal regular and exceptional progeny
The cross is *y cv nod/y cv nod; spa^{pol}/y+·ci ey^{R}* females × *Y^{S}X·Y^{L}, y v f B/0; C(4)RM, ci ey^{R}/0* males

Female gametes: / Male gametes:	spa^{pol} / 44	y+·ci ey^{R} / 44	spa^{pol}/y+·ci ey^{R} / 0 or 44	spa^{pol}/spa^{pol} / 0	0 / 44
Total progeny:	391	470	138	4	3041
Mosaic progeny:	0	40*	9†, 8‡	0	0

* *y+ ci ey*, mosaic for *y ci ey* non-Minute tissue.
† *y+*, mosaic for *y spa^{pol}* Minute (haplo-4) tissue.
‡ *y+*, mosaic for *y* non-Minute tissue.

would suggest that at least some fraction of the mono-*4* ova were also derived from meioses in which the fourth chromosomes failed to segregate regularly.

To examine fourth chromosome somatic loss in progeny derived from mono-*4* ova, females of the constitution *y cv nod/y cv nod; spa^{pol}/y+·ci ey^{R}* (the *y+·ci ey^{R}* fourth chromosome was the generous gift of DR. DEAN PARKER) were crossed to *Y^{S}X·Y^{L}, y v f B/0; C(4)RM, ci ey^{R}/0* males (Table 5) and all *y+·ci ey^{R}/C(4)RM, ci ey^{R}* progeny were examined for somatic loss of the *y+·ci ey^{R}* fourth chromosome. Of 470 such progeny, 40 exhibited somatic loss of the *y+·ci ey^{R}* chromosome: the frequency of somatic loss per fourth chromosome is, therefore, $40/470 = 0.0852$ for progeny derived from mono-*4* gametes. If somatic loss of chromosomes indicates irregular chromosome behavior in the preceding meiosis, the similarity between the frequencies of somatic loss per fourth chromosome in progeny derived from diplo-*4* (0.093) and mono-*4* (0.085) gametes implies that all or virtually all mono-*4* ova are derived from such meioses. Consequently, it seems reasonable to assume that the fourth chromosomes, which are always non-exchange, segregate irregularly in all meioses of *nod* females and that loss, whether meiotic (resulting in an excess of nullo gametes relative to diplo) or somatic (resulting in mosaic progeny), is an indirect effect of this irregular segregation.

The data presented in Table 5 also permit differentiation between nondisjunction during meiosis I and II. Of the progeny recovered, 138 were derived from diplo-*4* ova reductional for the fourth chromosomes (*y+·ci ey^{R}/spa^{pol}*), whereas only 4 were detectably derived from diplo-*4* ova equational for the fourth chromosomes (*spa^{pol}/spa^{pol}*). Clearly, most of the fourth chromosome nondisjunction occurs at the first division in *nod* females. As a minimum estimate (assuming equal viability of diplo-*4*, triplo-*4*, and tetra-*4* progeny; see MOORE and GRELL 1972b), $138/(138 + 16) = 0.90$ of the diplo-*4* ova resulted from nondisjunction at the first meiotic division.

It should be noted that the high frequency of nullo-*4* gametes drastically reduces the fertility of *nod* females unless they are recovered as euploid progeny. Thus, from Table 1 it can be seen that, in crosses to males bearing free fourth chromosomes, *nod+* females produce approximately 200 progeny per female (crosses 1 and 5), whereas *nod* females (crosses 2 and 7) are approximately 16%

as fertile. This decrease in fertility is due to the high frequency of nullo-*4* ova from *nod* females; in crosses to males bearing attached-fourth chromosomes (*C(4)RM*, Table 3, cross 3), diplo-*4*, mono-*4*, and nullo-*4* ova are equally recoverable, and *nod* females are as fertile as *nod*$^+$ females. In crosses to males bearing free fourth chromosomes, nullo-*4* ova result in haplo-*4* progeny. Haplo-*4* flies have low and erratic survival and consequently have been excluded from all tabulations. The progeny tabulated in such crosses (crosses 2 and 7, Table 1) resulted from mono-*4* and diplo-*4* ova: the estimate of the frequency of these ova types as determined by the number of progeny per female (16%) in these crosses compares favorably to their observed frequency in crosses to males bearing attached-fourth chromosomes (cross 3, Table 3) (16%) in which nullo-*4* ova are recoverable.

The second chromosome: In order to ascertain whether *nod* also increases the frequency of nondisjunction of the second chromosomes, females bearing structurally-normal second chromosomes were crossed to males bearing attached-second chromosomes. Nondisjunction of the second chromosomes in females results in diplo-*2* and nullo-*2* ova; to recover these ova as diploid progeny requires that they be fertilized by nullo-*2* and diplo-*2* sperm, respectively. In this experiment, these sperm types were obtained by utilizing males bearing attached-second chromosomes—one chromosome consisting of two left arms attached to a single centromere (*2L·2L*) plus another chromosome consisting of two right arms attached to a single centromere (*2R·2R*). Such attached-second-bearing males produce four types of sperm with respect to second-chromosome content: *2L·2L*, *2R·2R* (diplo-*2*); *2L·2L,0*; *0,2R·2R*; and *0,0* (nullo-*2*). Apparently each type is produced equally frequently (GRELL 1970; BALDWIN and CHOVNICK 1967). Thus, in crosses of free-second-bearing females by attached-second-bearing males, diploid progeny can be recovered only from diplo-*2* and nullo-*2* ova. Consequently, although such a cross permits the detection of second chromosome nondisjunction in females, it precludes a direct estimation of the frequency of nondisjunction. However, fertility—the number of gametes recovered per female parent—can be used as a rough measure of nondisjunction frequency.

The results of two such experiments are presented in Table 6a. Control females (crosses 1 and 5) exhibit a low level of second-chromosome nondisjunction—15 gametes/1000 females and 6.5 gametes/1000 females, respectively. Homozygous *nod* females (crosses 3 and 6) exhibit a higher frequency of second-chromosome nondisjunction—96 and 101 gametes/1000 females. Consequently, *nod* increases the frequency of second chromosome nondisjunction by at least 6.3-fold, and probably more. If second and fourth chromosome nondisjunction are independent in *nod* females, and if the females in Tables 3 and 6 have equal fecundity, the 96 gametes/1000 females observed in cross 3, Table 6a represents only 16% of the diplo-*2* and nullo-*2* ova. Therefore, the rate of second chromosome nondisjunction in *nod* is approximately 600 gametes per 1000 females, a 40-fold increase relative to the control.

In addition to detecting nondisjunction, the crosses to examine second chromosome behavior were designed to determine at which meiotic division nondisjunc-

TABLE 6a

Disjunction of the X *and second chromosomes in females*

Crosses are *X/X; 2/2; +/+; spa^{pol}/spa^{pol}* females × *+/Y; C(2L)RM, dp; C(2R)RM, px; +/+; +/+* males

Cross X, second chromosomes of female	Gametes Female: / Male:	X 22 / X 0	X 22 / Y 0	X 0 / X 22	X 0 / Y 22	XX 22 / Y 0	XX 0 / Y 22	0 22 / X 0	0 0 / X 22	Total progeny	Number of female parents	Recoverable aneuploid gametes per female	Recoverable aneuploid gametes
1.* y/y; +/pn cn		1	0	6	6	0	0	0	1	14	1000	0.015	
2. y/y; SM1/pr cn		4	8	6	7	0	28	24	0	77	750	0.172	
3. y pn cv nod/y pn cv nod; +/pr cn		28	27	20	13	2	0	2	2	94	1041	0.096	
4. y pn cv nod/y pn cv nod; SM1/pr cn		314	213	179	132	6	0	3	6	853	626	1.386	
5. y al dp b pr cn/y; + + b + cn c bw		1	7	7	4	0	2	2	0	23	4170	0.0065	
6. y pn cv nod al dp b pr cn/y pn cv nod; + + b + cn c bw		58	39	51	23	1	0	1	4	177	1200†	0.101‡	

* Data from BAKER and CARPENTER (1972).

† For this cross parents were permitted an additional 5-day laying period on fresh food; consequently, the progeny recovered are assumed to represent the output of 1800 female-equivalents.

‡ Gametes per 1800 female-equivalents.

TABLE 6b

Disjunction of the X *and third chromosomes in females*

Crosses are *X/X; +/+; +/+; spa^{pol}/spa^{pol}* females × *+/Y; +/+; C(3L)RM, se^{2} h^{2} r^{2}; C(3R)RM, sbd gl e; +/+* males

Cross X, second chromosomes of female	Gametes Female: / Male:	X 33 / X 0	X 33 / Y 0	X 0 / X 33	X 0 / Y 33	XX 33 / Y 0	XX 0 / Y 33	0 33 / X 0	0 0 / X 33	Total progeny	Number of female parents	Recoverable aneuploid gametes per female
1.* y/y		1	0	3	5	0	0	0	1	10	388	0.0283
2. y pn cv nod/y pn cv nod		41	14	12	2	2	0	2	3	76	1426	0.0582

* Data from BAKER and CARPENTER (1972).

tion occurred. All parental females were heterozygous for second-chromosomal centromere markers (*pr cn*/+ + for crosses 1 and 3, *pr*/+ for crosses 5 and 6). Diplo-*2* exceptions which result from nondisjunction reductional for the centromeric region will be heterozygous for centromere markers and phenotypically wild type. One-half of the exceptions from nondisjunction equational for the centromeric region will be homozygous for the centromere markers and phenotypically mutant; the other half will be wild-type and phenotypically indistinguishable from reductional exceptions. For the progeny recorded in Table 6a, the numbers of *pr* (or *pr cn*) progeny per diplo-*2* progeny were: (control) cross 1, 0/1; cross 5, 1/8: (*nod*) cross 3, 0/49; cross 5, 1/84. Thus, in *nod*, nondisjunction of the second chromosomes occurs primarily at the first meiotic division.

In order to ascertain whether *nod*-induced second chromosome nondisjunction involves primarily nonexchange chromosomes (as was shown for the *X*), females bearing fully-marked second chromosomes (*al dp b pr cn* + +/+ + *b* + *cn c bw*) were crossed to males bearing attached-second chromosomes. The second-chromosome genotypes of male and (virgin) female progeny resulting from diplo-*2* ova were determined by progeny-testing. (Because *b* and *cn* were homozygous in the parental females, they are disregarded in the tabulations of results).

The disjunctional results from control and *nod* females are presented in crosses 5 and 6, Table 6a. Progeny resulting from diplo-*2* ova are presented by second-chromosome constitution in Table 7. Tetrad distributions for these crosses, calculated by the equations of MERRIAM and FROST (1964) summed over like parameters, are also presented in Table 7. Finally, the tetrad distribution for second chromosomes that have disjoined regularly is presented for comparison (tetrad distribution calculated by the method of WEINSTEIN 1936; data from RHOADES 1931).

It is clear that a sizable fraction of the second chromosomes that have nondisjoined in *nod* females have undergone exchange. However, a comparison of the tetrad distribution derived from diplo-*2* exceptional ova with that derived from regular disjunction (RHOADES' data) indicates that exchange tetrads nondisjoin less frequently than do nonexchange tetrads. In particular, tetrads with no exchange are most likely to give rise to diplo-*2* ova in *nod* females (40% *versus* 4%) and tetrads with two exchanges are least likely (19% *versus* 69%). Most (77%) of the diplo-*2* ova are derived from tetrads with no or one exchange. Moreover, the distribution of crossovers along the chromosome in diplo-*2* ova may not be normal; somewhat more of the recovered crossovers occurred near the tips of the second chromosome than expected (34/58 = 0.59 of the crossovers recovered from *nod* females were between *al* and *dp* or between *c* and *bw*, compared to 41.9/104.4 = 0.40 expected).

The control data are not sufficiently extensive to compare meaningfully the tetrad distributions derived from diplo-*2* ova from *nod* and *nod*+ females. It is striking, however, to observe that in this control all three of the diplo-*2* ova that resulted from nondisjunction of exchange tetrads resulted from nondisjunction at the second meiotic division; spontaneous (primary) nondisjunction of exchange

TABLE 7

Genotypes of diplo-2 exceptional progeny recovered from crosses 5 and 6, Table 6a and tetrad distributions calculated from these genotypes

Genotypes of the diplo-*2* exceptional progeny were determined by first crossing to +; *SM1, al² Cy+ cn² sp²/al dp b pr Bl c px sp; spa+/spa+* flies, then to *y; b cn c bw/b cn c bw; spa^pol/spa^pol* flies. A standard tetrad distribution calculated from mono-*2* ova (RHOADES 1931) is included for comparison.

Genotype	Cross 5	Cross 6
al dp pr + + + + + c bw	5	42
+ dp pr + + + + + c bw		4
+ dp pr + + al + + c bw		2
al dp pr + + al + + c bw		3
+ + pr + + al dp + c bw		3
al dp pr + + al dp + c bw		3
al dp pr + + + + + + +		3
al dp pr c bw + + + c bw		1
al dp pr + + + + + c +		3
al dp pr + bw + + + c +		3
al dp pr + bw + + + c bw		3
+ dp pr + bw + + + c +		1
al dp pr + + + dp + c bw		1
+ + pr + + al dp + c +		1
+ + pr + + + + + c +		1
+ + pr + bw al dp + c +		1
+ + pr c bw al dp + + +		1
al dp pr + + al dp + + +		1
+ + pr c + al dp + + bw		1
al dp pr + (+/bw)*		1
al dp pr + bw al dp pr c bw		1
al dp + c (+/bw)*		1
al dp + c bw + + + c bw		1
al dp pr + + + + pr + +		1
al + + c bw + + + c bw		1
Sterile:	0	14
Total:	8	98

Tetrads:	Cross: 5†	Cross: 6†	RHOADES (1931):‡
E_0	0.500	0.393	0.038
E_1	0.500	0.378	0.170
E_2	0	0.185	0.687
E_3	0	0.044	0.085
E_4	0	0	0.020

* Parentheses indicate ambiguity with respect to coupling relationships.

† Tetrad distributions calculated by the equations of MERRIAM and FROST (1964) as discussed in text.

‡ Calculated by the method of WEINSTEIN (1936) from data presented in RHOADES (1931) for the cross *al dp b pr c px sp/+ + + + + + +* females × *al dp b pr c px sp/al dp b pr c px sp* males.

tetrads for the *X* chromosome occurs exclusively at the first meiotic division (MERRIAM and FROST 1964).

In summary, although in *nod* females a higher proportion of diplo-*2* exceptions than of diplo-*X* exceptions results from nondisjunction of exchange tetrads, second chromosomes that have undergone exchange are much less likely to nondisjoin than those which have not undergone exchange.

To further examine the relationship between exchange and nondisjunction of the second chromosome in *nod* females, the frequency of E_0 tetrads for chromosome *2* was increased by means of heterozygosity for *SM1*, a multiply-inverted

second chromosome, and the rate of second-chromosome nondisjunction was monitored in control and *nod* females (crosses 2 and 4, Table 6a). Heterozygosity for *SM1* increases the rate of second-chromosome nondisjunction (as measured by fertility) in both control and *nod* females as compared to the *SM1*+ crosses (1 and 3, Table 6a) and to nearly the same extent: 11-fold (0.172/0.015) for *nod*+ compared to 14-fold (1.39/0.096) for *nod*. However, most of the gametes from *nod*+ *SM1* females are not nondisjunctional for the second chromosomes alone. Rather $(52 \times 2)/(77 + 52) = 104/129 = 0.806$ are nondisjunctional for the *X* chromosomes as well. Moreover, if *X* and second-chromosome nondisjunction were independent, the four classes of ova nondisjunctional for both chromosomes would be expected to be recovered equally frequently, but instead all ova simultaneously nondisjunctional for both the *X* and chromosome *2* are either diplo-*X*, nullo-*2* or nullo-*X*, diplo-*2*, indicating that, in some of the meioses in the parental females, both of the second chromosomes disjoined nonhomologously from both of the *X* chromosomes. Thus, most of the increase in fertility of the control *SM1* females is due to gametes resulting from nonhomologous disjunction of (presumably E_0) second chromosomes from (presumably E_0) *X* chromosomes. In *nod* females, on the other hand, heterozygosity for *SM1* does not result in an increase in *X-2* nonhomologous disjunction: this can be seen in two ways. First, the rate of *X* nondisjunction is not higher with *SM1*. For *nod SM1*+ females (cross 3), *X* nondisjunction $= (6 \times 2)/(94 + 6) = 0.12$; for *nod SM1* females (cross 4), *X* nondisjunction $= (15 \times 2)/(853 + 15) = 0.035$. Secondly, there is no excess of diplo-*X*, nullo-*2* and nullo-*X*, diplo-*2* gametes relative to diplo-*X*, diplo-*2* and nullo-*X*, nullo-*2* gametes. Thus, in *nod*, the increase in second chromosome nonexchange tetrads due to heterozygosity for *SM1* results in an increase in second chromosome nondisjunction without involving nonhomologous disjunction of the second chromosome from the *X*'s.

These crosses also permit differentiation between nondisjunction at meiosis I and at meiosis II since all parental females were heterozygous for the centromere markers *pr cn*. Nondisjunction at meiosis I will give rise to *SM1/pr cn* diplo-*2* exceptions; nondisjunction at meiosis II will give rise to *pr cn/pr cn* diplo-*2* exceptions (*SM1* is lethal when homozygous). The numbers of *pr cn* progeny per diplo-*2* progeny were: (control) cross 2, 1/40; (*nod*) cross 4, 1/536. Thus, as before, nondisjunction in *nod* occurs virtually exclusively at the first meiotic division.

The third chromosome: The effect of *nod* on nondisjunction of the third chromosome was examined by crossing *nod* females to males bearing attached-third chromosomes (Table 6b). Homozygous *nod* females exhibit at least a two-fold increase in third-chromosome nondisjunction; if, as discussed above for second-chromosome nondisjunction, the fertility of *nod* females is corrected to compensate for the high frequency of nullo-*4* gametes, *nod* increases the frequency of third chromosome nondisjunction by 13-fold.

In summary, females homozygous for the meiotic mutant *nod* exhibit increased rates of nondisjunction of all chromosomes at the first meiotic division although exchange is normal in these females. Nondisjunction preferentially involves non-

exchange chromosomes: homologs which have undergone exchange virtually always disjoin. GRELL (1962b, 1964b) has proposed that the regular disjunction of nonexchange homologs is insured by the distributive system; it is suggested, therefore, that the distributive system is defective in *nod*. This suggestion is strengthened by the failure to observe nonhomologous disjunction (the diagnostic feature of the distributive system) between the *X* and second chromosomes in *nod* females heterozygous for *SM1*. The effect of *nod* on nonhomologous disjunction is examined more extensively below: the results indicate that *nod* is indeed defective in nonhomologous disjunction.

Nonhomologous disjunction in nod *females*

XX-from-Y: Normally, in *XX* females the gametic frequency of *X*-chromosome nondisjunction (primary nondisjunction) is very low, while in *XXY* females *X* nondisjunction (secondary nondisjunction) is 2%–3%. BRIDGES (1916) demonstrated that secondary nondisjunction involves only nonexchange *X* chromosomes and that only two types of *X*-nondisjunctional gametes are recovered: nullo-*Y*, diplo-*X* and *Y*, nullo-*X*. COOPER (1948) demonstrated that at least some fraction (perhaps all) of secondary nondisjunction involves separation of both *X* chromosomes from the *Y*, which suggests the prior formation of an *XYX* trivalent which disjoins *XX*-from-*Y* (Figure 1, orientation *a*). GRELL (1962b) has shown that the frequency of nonexchange *X* tetrads is the same in *XX* and *XXY* females and concluded that the *Y* chromosome affects the disjunction of nonexchange *X* chromosomes without altering the tetrad distribution of the *X*'s. This defines *XX*-from-*Y* disjunction as distributive.

In order to ascertain the effect of *nod* on secondary nondisjunction, sex-chromosome disjunction was examined in *y nod/y nod/y*$^+$*Y* females and in *y nod/y nod*, *y nod*$^+$*/y nod*$^+$*/y*$^+$*Y* and *y nod*$^+$*/y nod*$^+$ controls (Table 8, crosses 1–4). Although exchange was not monitored in these crosses, an attempt was made to minimize variations in exchange: female parents were of uniform age (12–60 hours post eclosion) and the *nod XX* and *XXY* females were sisters, as were the *nod*$^+$ females.

In *nod*$^+$ females, the frequency of *X*-nondisjunctional ova increases from 0.51% in *XX* females (cross 1) to 3.64% in *XXY* females (cross 2). As expected, most (all but one) of the 165 *X*-nondisjunctional ova are *XX,0* or *0,Y*. In *nod XXY* females, however, (*XX,0* + *0,Y*) ova are no more frequent than (*XX,Y* + *0,0*) *ova*. That is, nondisjunction in *nod XXY* females does not result from separation of the two *X*'s from the *Y*. Since there is apparently loss of both *Y* and *X* chromosomes, it is appropriate to calculate the degree of *XX*-from-*Y* segregation by means of the parameter *N* (HALL 1972), which equals 0.10 for this cross (*N* =0 would indicate a complete lack of *XX*-from-*Y* segregation; *N* = 1 would indicate complete *XX*-from-*Y* segregation). Consequently, *nod* is defective in *XX-Y* nonhomologous disjunction. If the *nod* defect were such that the *Y* had no effect on disjunction of the *X* chromosomes (*i.e.*, if *nod* were defective in the "pairing" aspect of the distributive system), the frequency of *X* nondisjunction

TABLE 8

Sex and fourth chromosome disjunction in XX *and* XXY *females*

Crosses are $X/X/(y^+Y)$; spa^{pel}/spa^{pol} females $\times$ $Y^SX{\cdot}Y^L$, $y\ v\ f\ B/0$; $C(4)RM$, $ci\ ey^R/0$ males.
This attached-XY chromosome was a spontaneous y derivative of the $Y^SX{\cdot}Y^L$, $v\ f\ B$ chromosome used in the experiments presented in Table 3.

Cross	Sex chromosomes of females	Male gametes: Female gametes: X, 4 / Female gametes: Y	$\overline{XY}\ \overline{44}$ X 4	$\overline{XY}$ 0 X 44	$\overline{XY}\ \overline{44}$ X 0	0 $\overline{44}$ X 4	0 0 X 44	0 $\overline{44}$ X 0	0 $\overline{44}$ XX 4	0 0 XX 44	0 $\overline{44}$ XX 0	$\overline{XY}\ \overline{44}$ 0 4	$\overline{XY}$ 0 0 44	$\overline{XY}\ \overline{44}$ 0 0
1.	y/y	—	3080	1	4	4267	0	0	5	0	6	6	5	0
2.	y/y/y+Y	0	1675	153	3	2201	128	5	98	2	1	1	0	0
		Y	336	0	41	1909	4	116	0	0	0	59	4	0
3.	y nod/y nod	—	684	60	3457	756	59	3152	7	0	22	5	0	45
4.	y nod/y nod/y+Y	0	374	32	2383	404	23	2226	12	0	31	9	0	61
		Y	12	2	178	354	22	1686	10	0	16	9	0	46
5.	$\frac{y^2\ cv\ v\ nod\ +\ +}{y\ +\ +\ nod\ f\ car}$	—	505	82	2426	548	67	2346	6	1	17	3	1	28
6.	$\frac{y^2\ cv\ v\ nod\ +\ +}{y\ +\ +\ nod\ f\ car}{y^+Y}$	0	696	81	4237	710	68	3899	18	2	69	11	2	96
		Y	38	21	708	659	69	3018	13	2	26	14	1	94

Cross	Total progeny	Number of parental females	Gametic X nondisjunction*	Gametic 4 nondisjunction†	(#XX,0 + 0,Y): (#XX,Y + 0,0)
1.	7374	57	0.0051	0.0026	——
2.	6736	60	0.0364	0.0574	164:1
3.	8247	61	0.0195	0.8102	——
4.	7890	80	0.0395	0.8376	98:96
5.	6030	37	0.0186	0.8154	——
6.	14552	122	0.0397	0.8375	198:150

* Calculated as # of *X*-exceptional progeny/(# regular males + *X*-exceptional progeny) to avoid complications due to inviability of *XXYY* female progeny.

† Calculated among regular male and *X*-exceptional progeny.

should be the same in *nod XX* and *XXY* females; however, the frequency of *X* nondisjunction is twice as high in *XXY* as in *XX* females (3.95% *vs.* 1.95%). In fact, the frequency of *X* nondisjunction is as high in *nod XXY* females as in *nod*$^+$ *XXY* females, even though there is no or very little *XX-Y* nonhomologous disjunction in *nod* females and complete *XX-Y* nonhomologous disjunction in *nod*$^+$ females. There are three ways the presence of a *Y* might increase *X* nondisjunction in *nod* females without involving *XX-Y* nonhomologous disjunction: (1) by increasing the frequency of nonexchange tetrads; (2) by increasing the frequency of nondisjunction of *X* chromosomes which have undergone exchange; or (3) by altering the pattern of disjunction of nonexchange *X*'s.

These propositions can be examined by simultaneously monitoring recombina-

TABLE 9

Recombination data from nod XX *and* XXY *females*

Genotypes of male progeny resulting from mono-*X*, nullo-*Y* ova from crosses 5 and 6, Table 8

	Cross in Table 8:	5 (X/X)			6 (X/X/Y)*		
	Ova:	X,4	X,44	X,0	X,4	X,44	X,0
RECOMBINANT TYPE							
noncrossover							
y^2 cv v + +		122	21	554	93	10	564
y + + f car		142	18	555	70	8	376
single crossover							
y^2 + + f car		27	4	129	15	2	117
y cv v + +		20	2	118	22	3	131
y^2 cv + f car		41	3	187	27	4	189
y + v + +		45	4	187	57	7	238
y^2 cv v f car		44	4	189	28	1	116
y + + + +		48	6	188	31	4	180
y^2 cv v + car		10	0	42	3	1	18
y + + f +		12	0	38	3	0	13
double crossover							
y^2 + + f +		1	0	9	0	0	7
y cv v + car		1	0	5	3	0	6
y^2 + + + +		7	2	30	8	0	24
y cv v f car		8	1	23	3	0	22
y^2 + v + +		2	0	5	0	0	11
y cv + f car		1	0	4	1	0	9
y^2 cv + f +		3	0	13	0	0	4
y + v + car		1	0	9	0	0	7
y^2 cv + + +		4	1	30	4	0	26
y + v f car		6	1	23	3	0	15
y^2 cv v f +		2	0	2	0	0	2
y + + + car		1	0	4	0	0	0
triple crossover							
y cv v f +		0	0	1	0	0	0
y + v f +		0	0	1	0	0	0
X exceptions:		9	2	45	27	3	136
Total:			3017			2652	

* Recombination scored for the progeny of only half the females tested in Table 8.

tion and disjunction of the *X* chromosomes in *nod XX* and *XXY* females. If the *Y*-mediated increase in *X* nondisjunction in *nod XXY* females results from an increase in nonexchange tetrads, then the frequency of E_0 tetrads in *nod XXY* females should be twice that observed in *nod XX* females and the total map length of the *X* should be somewhat lower. If the increase results from nondisjunction of exchange tetrads, then half of the *X*-exceptional progeny should be derived from meioses in which the *X* chromosomes had undergone exchange. If neither an increase in E_0 tetrads nor an increase in nondisjunction of exchange tetrads is sufficient to explain the two-fold increase in *X* nondisjunction in *nod XXY* females relative to *XX* females, then the effect of the *Y* chromosome must be to alter the disjunction of nonexchange *X* chromosomes.

Recombination of the *X* chromosomes in *nod XX* and *XXY* females was followed by using the markers *y* or y^2 (0.0); *cv* (13.6); *v* (33.0); *f* (56.7); and *car* (62.5). These markers span the *X* chromosome except for the 4 map units between *car* and the centromere. The progeny from *nod XX* and *XXY* females are presented in Table 8, crosses 5 and 6; genotypes of male progeny are presented in Table 9; and map distances and tetrads distributions (calculated under the assumption that all *X*-exceptional progeny resulted from nonexchange tetrads) are presented in Table 10. Because, as before, the y^+Y was used to monitor disjunction of the *Y* chromosome in the *XXY* crosses, recombination between y^2 and *cv* could be detected only in males that did not receive the maternal *Y*. Recombination data are presented in Table 9 only for males derived from nullo-*Y* ova (phenotypically *y* or y^2); recombination in the interval *cv–car* did not differ significantly in comparisons between males receiving the maternal *Y* and males not receiving it.

The frequency of E_0 tetrads is not increased in *nod XXY* females (Table 10). Furthermore, the total map distances in the two types of females are identical;

TABLE 10

Map distances and tetrad distributions for the data presented in Table 9

For cross 5, map distance is calculated as recombinants/(total males + *X* exceptions); for cross 6, map distance is calculated as recombinants/(total males + 1/2 *X* exceptions). Tetrads are calculated by the method of WEINSTEIN (1936) with the assumption that all *X* exceptions are derived from E_0 tetrads.

Map interval	Cross 5 (X/X)	6 (X/X/Y)
y^2–cv	13.26	14.95
cv–v	18.93	23.43
v–f	20.75	18.18
f–car	5.14	2.61
Total map:	58.07	59.17
Tetrads:		
E_0	0.105	0.058
E_1	0.634	0.701
E_2	0.256	0.241
E_3	0.005	0

the regional differences—a proximal decrease and a distal increase in crossing over in *XXY* females relative to *XX* females—are similar to those observed previously (GRELL 1962b). Thus, the two-fold increase in *X* nondisjunction in *nod XXY* females relative to *nod XX* females is not due to a decrease in exchange. (It should be noted that, since crossing over between *car* and the centromere was not monitored in these crosses, the calculated frequencies of E_0 tetrads are probably somewhat higher than the true frequencies.) Moreover, the two-fold increase in *X* nondisjunction in *nod XXY* females is not attributable to nondisjunction of exchange tetrads. To ascertain the fraction of *X* nondisjunction due to nondisjunction of exchange tetrads, diplo-*X* exceptions were progeny-tested to

TABLE 11

Genotypes of diplo-X exceptional progeny recovered from crosses 5 and 6, Table 8 and tetrad distributions calculated from these genotypes

Genotype	5*	Cross 6 — XX,0 ova	XX,Y ova
$\frac{y^2\ cv\ v\ +\ +}{y\ +\ +\ f\ car}$	41	69	31
$\frac{y^2\ cv\ v\ +\ +}{y^2\ +\ +\ f\ car}$	1	2	0
$\frac{y\ cv\ v\ +\ +}{y^2\ +\ +\ f\ car}$	0	2	0
$\frac{y\ cv\ v\ +\ +}{y\ +\ +\ f\ car}$	0	4	0
$\frac{y\ +\ v\ +\ +}{y^2\ cv\ +\ f\ car}$	0	2	1
$\frac{y\ +\ v\ +\ +}{y\ +\ +\ f\ car}$	0	0	1
$\left(\frac{y}{y^2}\right)\frac{cv\ v\ +\ +}{cv\ v\ f\ car}$ †	0	0	1
$\frac{y^2\ cv\ +\ f\ car}{y\ +\ +\ +\ +}$	0	0	1
$\frac{y^2\ cv\ v\ +\ +}{y^2\ cv\ v\ +\ +}$	0	3	0
$\frac{y\ +\ +\ f\ car}{y\ +\ v\ +\ car}$	0	1	0
Sterile:	2	6	6
Total:	44	89	41
Tetrads‡			
E_0	0.968	0.840	
E_1	0.032	0.123	
E_2	0	0.037	

* Includes 20 additional diplo-*X* exceptional progeny (not included in Table 8) which were obtained from a subset of cross 5, Table 8 for which *X* and fourth chromosome disjunction were not scored.

† Parentheses indicate ambiguity with respect to coupling relationships.

‡ Calculated by the equations of MERRIAM and FROST (1964) as discussed in text.

determine their X chromosome genotype (Table 11). Tetrad distributions were calculated from the observed array of genotypes by the equations of MERRIAM and FROST (1964) summed over like parameters. If the two-fold increase in X nondisjunction in *nod XXY* females were due to nondisjunction of exchange tetrads, 50% of the diplo-X exceptions should have been derived from meioses in which the X chromosomes had undergone exchange; only 15% were so derived. It is of interest to note, moreover, that the few observed exchange exceptions resulted primarily from a single distal exchange. (The exchange exceptions observed in this experiment may not be the result of the mutant *nod*: a similar frequency of exchange exceptions was observed in a control cross performed simultaneously. These observations are discussed in the APPENDIX.)

Since neither an increase in the frequency of nonexchange tetrads nor nondisjunction of exchange tetrads explains the two-fold increase in X nondisjunction in *nod XXY* females relative to *nod XX* females, this increase must reflect an effect of the Y chromosome on the segregation of nonexchange X chromosomes.

The model I would like to propose accounts for both the abnormal segregation of nonexchange bivalents and for the effect of the Y chromosome in XXY females. This model is based on the hypothesis of GRELL (1962a) but proposes that, in the distributive system, the process by which two chromosomes in a trivalent are oriented toward the same anaphase I pole is separate from the process that insures that these two chromosomes disjoin from the third member of the trivalent, and that, in *nod* females, orientation is normal, but the process that insures disjunction to opposite poles is faulty. As a result of the defect in disjunction, the two unipolar-oriented chromosomes (as a unit) and the third member of the trivalent move independently to the anaphase poles. With reference to Figure 1,

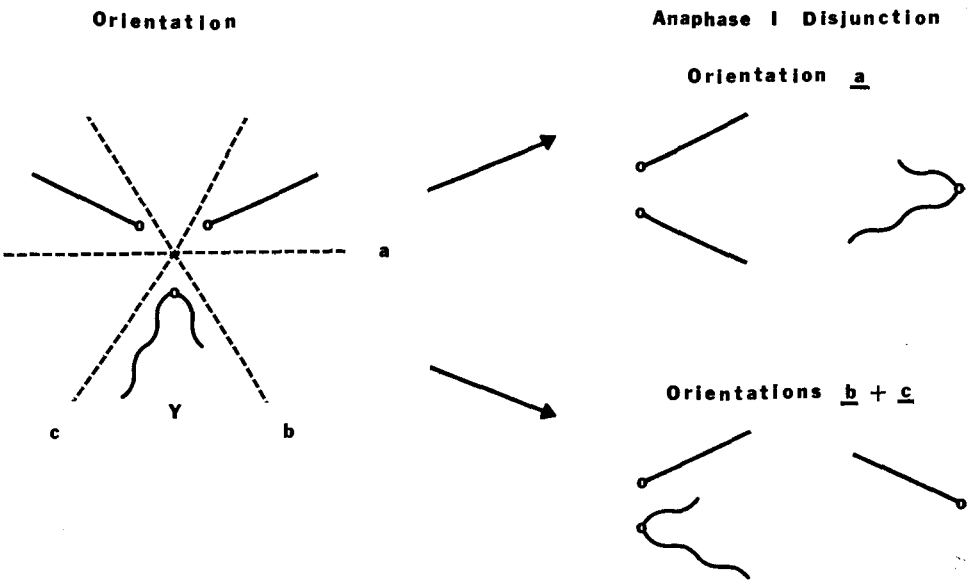

FIGURE 1.—Orientation and disjunction of three elements from a trivalent.

this model proposes that in *nod* females chromosomes on opposite sides of a plane of orientation move independently to the anaphase I poles, but that, as in *nod*$^+$ females, chromosomes on the same side of the plane of orientation (the two *X*'s for orientation *a*) are constrained to move to the same pole. If there are only two chromosomes under consideration—for example, the nonexchange *X* chromosomes in an *XX* female—the single plane of orientation lies between them and, in *nod* females, they will move independently to the anaphase I poles. Thus, if the nonexchange *X* bivalents which fail to disjoin in *nod XX* females are, in *nod XXY* females, converted to *XYX* trivalents of orientation *a* which fail to disjoin, the 1:2:1 ratio of *XX:X:0* gametes in *XX* females will be converted to a 2:0:2 ratio of *XX:X:0* gametes in *XXY* females, which will result in a two-fold increase in diplo-*X* and nullo-*X* gametes with equal numbers of (*XX,Y* + *0*) and (*XX,0* + *0,Y*) gametes. This is what is observed.

Attached autosomes: As discussed previously, in males bearing attached autosomes the two compound chromosomes (*C(3L)* and *C(3R)* in this experiment) assort independently or nearly so. However, in *nod*$^+$ females the two attached autosomes *C(3L)* and *C(3R)* disjoin nonhomologously most of the time producing almost exclusively *C(3L),0* or *0,C(3R)* ova (BALDWIN and CHOVNICK 1967; GRELL 1970).

Two sets of crosses were performed to examine the disjunction of attached autosomes in *nod* females. The two sets differed in that the *C(3L)* chromosomes were not derived from a common synthesis. Since the two sets give somewhat different results, they are presented separately. In each cross, each of the maternal and paternal chromosomes is differentially marked and can consequently be distinguished in the progeny.

In *nod*$^+$ females, *C(3L)* segregates regularly from *C(3R)* (crosses 1 and 2, Table 12); if gametes containing only *C(3L)* or *C(3R)* are considered "disjunctional" and gametes containing both chromosomes or neither "nondisjunctional", then in *nod*$^+$ females nondisjunction is only 3.5% (cross 2) to 7.5% (cross 1). Nondisjunction of the compound chromosomes is correlated with nondisjunction of the *X* chromosomes. In cross 1, $84/(60 + 84) = 0.582$ and in cross 2, $46/(30 + 46) = 0.607$ of the gametes nondisjunctional for the *X* chromosomes were also nondisjunctional for the compound chromosomes; in contrast, 0.023 (cross 1) and 0.013 (cross 2) of the gametes disjunctional for the *X* chromosomes were nondisjunctional for the compound chromosomes. Furthermore, the four types of gametes nondisjunctional for both the compound chromosomes and the *X* chromosomes are not produced equally frequently; [*0,C(3L)C(3R)* + *XX,0*]: [*XX,C(3L)C(3R)* + *0,0*] = 64:1 for crosses 1 and 2 summed. Thus, in virtually all meioses in *nod*$^+$ females, compound autosomes disjoin nonhomologously either from each other or from the (presumably nonexchange) *X* chromosomes. In addition, the high frequencies of *X* nondisjunction in crosses 1 and 2 suggest that most of the meioses in which the *X* chromosomes are nonexchange result in gametes nondisjunctional for the *X* chromosomes.

In *nod* females (crosses 3 and 4, Table 12), the compound chromosomes do not disjoin regularly; the gametic frequency of nondisjunction of the compound chro-

TABLE 12

Disjunction of the sex and compound chromosomes in XX *and* XXY *attached-third females*

Crosses are *X/X/(B^{S}Y)*; *C(3L)RM, ri*; *C(3R)RM, sbd gl e* females × +/*Y*; *C(3L)RM, se^2 h^2 rs^2*; *C(3R)RM, sr* males (crosses 1, 3, 5, and 7) and *X/X/(B^{S}Y)*; *C(3L)RM, ri*; *C(3R)RM, sr* females × +/*Y*; *C(3L)RM, se^{2}h^2 rs^2*; *C(3R)RM, sbd gl e* males (crosses 2, 4, 6, and 8).

Female gametes: Y	Cross: 1	2	3	4	5		6		7		8	
	Sex chromosomes of females: y/y	y/y	y cv nod/y cv nod	y cv nod/y cv nod	y/y B^{S}Y		y/y B^{S}Y		y cv nod/y cv nod B^{S}Y		y cv nod/y cv nod B^{S}Y	
Male gametes	Female gametes: X,3	—	—	—	no Y	Y	no Y	Y	no Y	Y	no Y	Y
X,3R	X,3L	400	478	58	40	65 34	61	46	4	5	8	3
Y,3R	X,3L	347	463	42	7	45 25	60	30	2	4	1	1
X,3L	X,3R	317	492	45	47	37 34	43	47	7	5	4	3
Y,3L	X,3R	325	464	23	25	26 32	37	45	1	2	8	2
X,0	X,3L+3R	9	9	30	28	62 0	167	0	6	12	16	2
Y,0	X,3L+3R	6	5	9	18	59 0	119	0	2	0	7	2
X,3L+3R	X,0	11	7	25	27	1 49	0	67	8	10	4	2
Y,3L+3R	X,0	7	3	20	4	0 60	0	68	7	3	0	1
Y,3R	XX,3L	7	2	5	0	2 0	6	0	0	0	0	0
Y,3L	XX,3R	7	4	2	1	6 0	3	0	0	0	0	0
Y,0	XX,3L+3R	0	1	2	1	0 0	0	0	0	0	0	0
Y,3L+3R	XX,0	20	5	2	0	1 0	0	0	0	0	0	0
X,3R	0,3L	11	4	4	2	0 6	1	6	1	1	0	0
X,3L	0,3R	5	5	3	3	0 3	0	4	0	0	0	0
X,0	0,3L+3R	22	17	4	3	5 3	0	3	1	0	0	0
X,3L+3R	0,0	0	0	2	3	0 0	0	0	1	0	0	0
Total progeny:		1494	1959	276	209	555		813		82		64
Number of female parents:		63	60	99	212	34		31		56		57
Gametic *X*-nondisjunction:		0.0920	0.0381	0.1600	0.1171	0.0395		0.0550		0.0930		0
Gametic third nondisjunction:		0.0747	0.0351	0.3457	0.4099	0.4286		0.5108		0.6047		0.5312

mosomes is 35% (cross 3) to 41% (cross 4). Nondisjunction of the compound chromosomes shows much less correlation with nondisjunction of the *X* chromosomes; 46% (cross 3) and 54% (cross 4) of the gametes nondisjunctional for the *X* chromosomes were also nondisjunctional for the compound chromosomes, whereas 33% (cross 3) and 40% (cross 4) of the gametes disjunctional for the *X* chromosomes were nondisjunctional for the compound chromosomes. Furthermore, there is no evidence of *X*-compound autosome nonhomologus disjunction, although the gametic frequencies of *X* nondisjunction are actually slightly higher than the control values; *[0,C(3L)C(3R) + XX,0]* : *[XX,C(3L)C(3R) +0,0]* = 8:10 (crosses 3 and 4 summed). If *C(3L)* and *C(3R)* move at random in all meioses in *nod* females, the expected frequency of gametes nondisjunctional for the compound chromosomes is 0.50. The frequencies of nondisjunction of the compound chromosomes in *nod* females approach this value (0.35, cross 3; 0.41, cross 2). Clearly, *nod* greatly reduces the frequency with which the nonhomologs, *C(3L)* and *C(3R)*, disjoin.

Attached autosomes-Y: In *nod*$^+$ females bearing a *Y* chromosome in addition to attached autosomes, the presence of the *Y* affects the disjunction of the attached autosomes in a manner analogous to the effect of the *Y* chromosome on the disjunction of nonexchange *X* chromosomes in *XXY* free-autosome females. Thus, GRELL (1970) demonstrated that 0.24–0.30 of the gametes from *XXY* attached-second-chromosome females were nondisjunctional for the compound chromosomes, as compared to 0.01–0.08 nondisjunctional gametes from *XX* females (his Tables 1, 2, and 3). Furthermore, virtually all of the nondisjunctional gametes from the *Y*-bearing females contained either both compound chromosomes and no *Y* or the *Y* and neither compound chromosome, suggesting that they resulted from disjunction of both compound chromosomes from the *Y*. These results suggest the possibility that the Y chromosome may have formed a trivalent with both compounds in all meioses, but that there was no preferred orientation of disjunction of these trivalents (that is, orientations *a*, *b*, and *c*, Figure 1 were equally likely), since gametes resulting from orientation *a* represented approximately one-third of the total gametes recovered. If disjunction in *XXY* attached-autosome females does involve disjunction from a trivalent composed of the *Y* and the compound chromosomes, then the model proposed for *X* nondisjunction in *nod XXY* free-autosome females predicts that the frequency of nondisjunction of the compound chromosomes in *nod XXY* females should be increased relative to that seen in *nod XX* females; and, furthermore, nondisjunction of compound chromosomes should be higher in *nod XXY* females than in *nod*$^+$ *XXY* females, since orientations *b* and *c*, Figure 1, will yield some nondisjunctional gametes in *nod* females but none in *nod*$^+$ females.

The results of experiments involving *XXY* attached-autosome females are presented in crosses 5–8, Table 12. The compound third chromosomes used were the same as those present in crosses 1–4; the *Y* chromosome carries a small *X* duplication marked with the dominant B^s (BROSSEAU *et al.* 1961) which permits its detection in the parental females as well as in the progeny. *XX* sisters of the *XXY*

females used for crosses 5–8 were also tested; these results are included in the data presented in crosses 1–4, Table 12.

In *nod*$^+$ *XXY* attached-third females, nondisjunction of the compound chromosomes increases dramatically relative to *XX* females—to 0.43 (cross 5, Table 12) and 0.51 (cross 6) of the total gametes recovered. These values are greater than 0.33, indicating that, for these particular compound chromosomes, the preferred plane of orientation of the *Y*-compound chromosome trivalent is orientation *a*. Figure 1. Virtually all gametes nondisjunctional for the compound chromosomes contain either both compound chromosomes and no *Y* or the *Y* and neither compound; for cross 5, among mono-*X* gametes, $[C(3L)C(3R),0 + 0,Y] : [C(3L)C(3R),Y + 0,0] = 230{:}1$, indicating that these gametes result from nonhomologous disjunction of both compound chromosomes from the *Y*. Among progeny which resulted from nondisjunction of the *X* chromosomes, this ratio is 5:4; however, the observation that these gametes contain either both *X* chromosomes and neither compound chromosome or neither *X* chromosome and both compound chromosomes suggests that they result from nonhomologous disjunction of both *X* chromosomes from both compound chromosomes. This type of disjunction is relatively rare in comparison to *Y*-compound disjunction, presumably because the *X* chromosomes disjoin nonhomologously only when they are nonexchange, whereas the *Y* chromosome is always nonexchange.

Nondisjunction in *nod XXY* attached-third females also increases relative to the *nod XX* controls; for cross 7, gametes nondisjunctional for the compound chromosomes comprise 0.60 of the total gametes, a frequency that is nearly twice that seen in *nod XX* females (0.35, cross 3) and is higher than that in *nod*$^+$ *XXY* females (0.43, cross 5). Moreover, although the presence of the *Y* increases the frequency of nondisjunction of the compound chromosomes, in this cross the gametes that result do not indicate disjunction of the *Y* from the compound chromosomes; thus, $[C(3L)C(3R),0 + 0,Y] : [C(3L)C(3R),Y + 0,0] = 23{:}29$. If a Y-compound chromosomes trivalent is formed in each meiosis of *XXY* attached-autosome females, then the model proposed for *XXY* trivalent behavior in *nod* can be applied to the results obtained in crosses 3 and 5, Table 12. First, in *nod XX* females, 35% of the gametes are nondisjunctional for the compound chromosomes; under the model, this indicates that in 30% of the meioses the compound chromosomes have disjoined (i.e., *nod* is not an absolute defective); in the remaining 70% of meioses, the two compound chromosomes orient, but then segregate at random across the plane of orientation, resulting in gametes disjunctional for the compounds half of the time (35%), nondisjunctional the other half (35%). This implies that 35% of the gametes resulting from any given plane of orientation will be nondisjunctional *for that plane of orientation*. Second, in *nod*$^+$ females (cross 5), the *Y* disjoined from the compound chromosomes in 43% of the meioses, indicating that the trivalent attains orientation *a* (Figure 1) 43% of the time; in the remaining 57% of meioses, orientation is either *b* or *c*. If these same frequencies obtain in *nod XXY* females, then all meioses with orientation *a* should result in gametes nondisjunctional for the compound chromosomes (0.43

of total gametes) because in orientation *a* the two compounds are oriented to the same pole. In orientations *b* and *c*, the *Y* and one of the compound chromosomes are oriented to the same pole; half of the gametes resulting from random segregation across the plane of orientation will be nondisjunctional for the compound chromosomes ($0.35 \times 0.57 = 0.20$ of total gametes). Thus, $(0.43 + 0.20) = 0.63$ of the total gametes obtained from the *nod XXY* females in cross 7 should be nondisjunctional for the compound chromosomes; the observed frequency was 0.60. Moreover, the relative frequencies of the types of gametes nondisjunctional for the compound chromosomes should be unequal, because, although all gametes resulting from orientation *a* will be nondisjunctional for the compound chromosomes, 35% of these will be nondisjunctional across the plane of orientation, or *C(3L)C(3R),Y* and *0,0*; the remaining 65% will be disjunctional across the plane of orientation, or *C(3L)C(3R),0* and *0,Y*. The gametes nondisjunctional for the compound chromosomes which result from nondisjunction across the planes of orientation *b* and *c*, on the other hand, will all be *C(3L)C(3R),Y* and *0,0*. Summing the expected numbers of gametes of these four types are: $[C(3L)C(3R),Y + 0,0] = [(0.35 \times 0.43) + 0.20] \times 52/0.63 = 29$; $[C(3L)C(3R,)0 + 0,Y] = [(0.65 \times 0.43) + 0.00] \times 52/0.63 = 23$. These are exactly the numbers observed.

Consideration of the impressive agreement between the model and the results of cross 7 should be tempered by noting the rather low number of progeny obtained in that experiment. Furthermore, calculations for cross 8 based on the results of crosses 4 and 6 do not compare well with the observed results. For example, gametic nondisjunction of the compound chromosomes should be 0.71, but only 0.53 was observed. However, the results from cross 8 are considered not to reflect accurately the effects of *nod* on disjunction for the following reasons: (1) *nod XX* females bearing attached autosomes are expected to be 16% as fertile as controls, since 84% of the gametes from *nod* females are nullo-4 (see previous discussion of fertility), but the females in cross 4 were only 3% as fertile as controls (1.05 progeny/female parent, cross 4 compared to 33.3, cross 2); *nod XX* females in cross 3, on the other hand, were 12% as fertile as controls (3.03 progeny/female, compared to 24.95, cross 1) which is close to the expected fertility. (2) Reciprocal products of *Y*-compound chromosome disjunction are not recovered equally frequently in the *nod*$^+$ *XXY* control (cross 6); *C(3L)C(3R),0* gametes = 286, whereas *0,Y* gametes = 135. Although other inequalities are present in the data presented in Table 12, this is the most striking. On the one hand, it may indicate lowered viability for progeny receiving the maternal *Y*; but if so, no predictions can be made about the viability of progeny resulting from *C(3R)C(3L),Y* and *0,0* gametes in cross 8, since no gametes of these types were recovered in cross 6. On the other hand, it may indicate meiotic irregularities resulting from the particular chromosomes present in the females. Consequently, the results obtained in cross 7 are considered more likely to be typical of chromosomal behavior in *nod XXY* attached-autosome females.

It should be pointed out that thus far it has been assumed that disjunction of the compound chromosomes is completely nonhomologous and, therefore, the

observation that the frequency of nondisjunction of the compound chromosomes in *nod XX* females is less than 0.50 indicates that *nod* is not an absolute defective. However, the converse assumption—that *nod* is an absolute defective, but that in some meioses the compound chromosomes disjoin in spite of the defect in *nod*—cannot be eliminated out of hand. First, it has not been demonstrated that all disjunction of a pair of compound autosomes is nonhomologous; this demonstration would require the observation of 100% nondisjunction under some condition affecting nonhomologous disjunction; the observation of 51% reported here is a high value. Second, if the same proportion of compound chromosmes which do not segregate at random in the presence of *nod* disjoin from a bivalent in the presence of a *Y* chromosome (whether or not *nod* is present), then from the frequencies of nondisjunction observed in crosses 4 and 6, Table 12, the expected frequency of nondisjunction for cross 8 is 0.55; 0.53 was observed. The expected frequency for cross 7 becomes 0.56; 0.60 was observed. Consequently, whether or not *nod* is an absolute defective, the results of this experiment substantiate the hypothesis that the defect in *nod* affects the disjunction of nonexchange and compound chromosomes with respect to their plane of orientation but does not affect the disjunction of chromosomes in a trivalent which are oriented to the same anaphase I pole.

TABLE 13

Disjunction of the X, *second, and third chromosomes in females*

Crosses are *X/X*; *SM1/+*; *TM2/+*; spa^{pol}/spa^{pol} females × y^2/Y; *C(2L)RM, dp*; *C(2R)RM, px*; *C(3L)RM,* h^2 rs^2; *C(3R)RM, +*; *+/+* males

Gametes		Cross:	1	2	3
Female	Male	*X* chromosomes of female:	y / y	y cv nod / y cv nod	y + + / y cv nod
X 22 33	X 0 0		0	12	1
X 22 33	Y 0 0		0	1	0
X 0 33	X 22 0		34	22	75
X 0 33	Y 22 0		38	7	49
X 22 0	X 0 33		30	12	68
X 22 0	Y 0 33		30	7	55
X 0 0	X 22 33		0	2	0
X 0 0	Y 22 33		0	5	0
XX 22 33	Y 0 0		0	4	2
XX 0 33	Y 22 0		0	8	0
XX 22 0	Y 0 33		0	1	0
XX 0 0	Y 22 33		0	1	0
0 22 33	X 0 0		0	2	0
0 0 33	X 22 0		0	9	1
0 22 0	X 0 33		0	3	0
0 0 0	X 22 33		0	3	0
Total progeny:			132	99	251
Number of female parents:			350	3400	1000
Recoverable aneuploid gametes/female:			0.377	0.0383	0.254
(#22,33 + 0,0): (#22,0 + 0,33) [as gametes]			0:132	41:90	5:249

Seconds from thirds: The effect of *nod* on nonhomologous disjunction of second chromosomes from third chromosomes was examined in females heterozygous for multiply-inverted second (*SM1*) and third (*TM2*) chromosomes. The heterozygous inversions were utilized to increase the frequency of nonexchange tetrads for these chromosomes. Progeny resulting from nondisjunction of both the second and third chromosomes were recovered by crossing to males carrying both attached-second and attached-third chromosomes. Only ova resulting from nondisjunction of both major autosomes are recoverable in this cross.

From control females (cross 1, Table 13), all 132 progeny recovered resulted from *0,33* and *22,0* ova and therefore presumably from nonhomologous disjunction of both second chromosomes from both third chromosomes. From homozygous *nod* females, the progeny recovered resulted not only from *22,0* and *0,33* ova, but also from *22,33* and *0,0* ova; the ratio $(22,33 + 0,0):(22,0 + 0,33) = 41:90$. It is clear that *nod* drastically reduces the frequency of nonhomologous disjunction in this situation as it does in all other situations examined.

This experiment, however, also showed an unexpected feature. The frequency of *X* nondisjunction among the gametes recovered from *nod* females was 0.488, suggesting that the two *X* chromosomes were segregating independently of one another. There does not, however, appear to be any correlation between *X* and autosomal constitution of the ova. Thus, the number of *X*-exceptional ova/$(22,33 + 0,0)$ ova $= 22/41$ and the number of *X*-exceptional ova/$(22,0 + 0,33)$ ova $= 42/90$. This high frequency of *X* nondisjunction is observed only in *nod* females. Moreover, it appears to be restricted to gametes in which both pairs of major autosomes are nondisjunctional; among sisters of the females tested in Table 13, crossed to males bearing free second and third chromosomes, the frequency of *X* nondisjunction among mono-*2*, mono-*3* ova is in agreement with that observed in other *nod* crosses (0.0189, Table 14, cross 2).

There are two possible explanations for this observation: (1) the probability that the *X* chromosomes will nondisjoin is the same for all meioses, but gametes nondisjunctional for both major autosomes can be recovered from *nod* females only from meioses in which the *X* chromosomes segregate independently of one another (although this is not observed in nod^+ females) or (2) the probability that the *X* chromosomes will fail to segregate regularly is much greater in meioses in which both the second and third chromosomes fail to segregate regularly than in other meioses. Under the first alternative, only approximately 4% of the meioses in which both the second and third chromosomes nondisjoin (i.e., those in which the *X* chromosomes are E_0) produce ova recoverable in the cross presented in Table 13. This prediction cannot be tested directly because the fraction of such meioses is not known. However, the observation (Table 13) that *nod* females are nearly as fertile as expected considering the high frequency of nullo-*4* gametes—0.0385 gametes per *nod* female (cross *2*)/0.378 gametes per nod^+ female (cross 1) $= 0.102$, compared to 0.16 expected—argues against this hypothesis. The second alternative predicts that, in these meioses, the *X* chromosomes segregate independently of one another whether or not they have undergone exchange. It is unlikely that the frequency of exchange *X* tetrads is de-

TABLE 14

Disjunction of the X *and fourth chromosomes in mono-2, mono-3 ova from sisters of the females used in the experiments presented in Table 13*

Crosses are *X/X*; *SM1/+*; *TM2/+*; spa^{pol}/spa^{pol} females × $Y^{S}X{\cdot}Y^{L}$, *v f B/0*; +/+; +/+; *C(4)RM, ci* $ey^{R}/0$ males

Cross:	1	2	3
X chromosomes of female:	y y	y cv nod y cv nod	y + + y cv nod
Female gametes			
X 4	2159	36	1938
X 44	3	3	34
X 0	2	271	19
XX 44	0	0	0
XX 4	0	0	2
XX 0	0	2	0
0 44	0	0	0
0 4	0	0	1
0 0	0	1	0
Total progeny:	2164	313	1994
Number of female parents:	20	10	20
Gametes/female:	108.2	31.6	99.7
Gametic *X*-nondisjunction:	0	0.0190	0.0030
Gametic 4 nondisjunction:	0.0023	0.8861	0.0265

creased in these meioses, since it has been shown that the interchromosomal effect on recombination is expressed in *nod* females (Tables 1 and 2) and ZIMMERING (1958) has demonstrated that, among *X*-exceptional progeny of females bearing a heterozygous *X* inversion, crossing over is normal or increased on uninverted autosomes. Because *X* exchange was not monitored in these crosses, it is not known whether exchange *X* chromosomes nondisjoin. Experiments in which the frequency of *X* exchange as well as the frequencies of second and third chromosome nondisjunction are monitored are necessary to distinguish between the two possibilities. However, if this more probable alternative is true, it means that in this situation the defect in *nod* results in the failure of exchange chromosomes to disjoin. This would imply that the nod^{+} function is, at least in some cases, necessary for the disjunction of exchange chromosomes as well as nonexchange chromosomes.

The dominance of *nod* was also examined in these experiments; surprisingly, heterozygous *nod* females heterozygous for multiply-inverted second and third chromosomes do exhibit an increased rate of fourth chromosome nondisjunction (Table 14, cross 3) relative to homozygous nod^{+} females (cross 1). This slight dominant effect was not found in heterozygous *nod* females with structurally-normal autosomes (Table 3, cross 2).

In summary, the meiotic mutant *nod* drastically reduces nonhomologous disjunction in all situations examined. Consequently, these results suggest that *nod* is defective in the process governing the distributive disjunction of nonhomologous chromosomes.

Meiotic and somatic loss in nod *females*

Meiotic loss (defined as an excess of nullo gametes relative to diplo) and somatic loss (loss of a chromosome during development) were discussed above with respect to fourth chromosome behavior in *nod* females. Neither meiotic loss nor somatic loss is restricted to the fourth chromosomes in *nod* females; however, both types of loss are more frequent for the fourth chromosomes than for the *X* or *Y* chromosomes. Thus, for the fourth chromosomes, there is a 40-fold excess of nullo gametes relative to diplo, whereas for the *X* chromosomes there is only a two-fold excess. The *Y* chromosome shows little complete loss—44% of the male + *X*-exceptional progeny from *nod XXY* females resulted from *Y*-bearing ova (cross 4, Table 8). Similarly, somatic loss is most frequent for the fourth chromosomes and least frequent for the *Y* (Table 15). It might be supposed that the high frequency of loss of the fourth chromosomes is related to the observation that the fourth chromosomes never undergo exchange: however, the *Y* chromosome in an *XXY* female also never undergoes exchange, yet loss of the *Y* chromosome is much less frequent than loss of the fourth chromosome. Perhaps the high frequency of loss of fourth chromosomes is, instead, a function of their small size.

It should be noted that meiotic and somatic loss are observed in a number of other meiotic mutants (BAKER and CARPENTER 1972 and unpublished observations; HALL 1972; DAVIS 1971; DAVIS 1969). Since these mutants present a wide range of primary defects [from complete absence of exchange in *c(3)G* (HALL 1972) to precocious separation of sister centromeres prior to or during meiosis II in *mei-S332* (DAVIS 1971)], it is very likely that meiotic and somatic loss are

TABLE 15

Somatic loss of maternally-derived chromosomes in the progeny of homozygous nod *females*
Although not examined in detail, patches of nullo-chromosome-derived tissue were large, suggesting that loss occurred during the early cleavage divisions of the zygotes. No mosaics attributable to somatic loss of paternally-derived *X* or fourth chromosomes have been detected among the progeny of *nod* females

	Number of progeny	Loss per maternal chromosome
Regular females:	44,330	0.0005
Gynandromorphs:	21	
Exceptional females:	395	0.0152
Gynandromorphs:	12	
Diplo-*4* exceptions:	784	0.0561*
Diplo-*4*/haplo-*4* mosaics:	88	
Progeny from *Y*-bearing ova:	6,926	0.0027
Somatic *Y* loss:	19	

* Data from Table 5 not included.

secondary effects (due to irregular segregation?) in all meiotic mutants, including *nod*.

DISCUSSION

GRELL (1962a) has proposed that, in *Drosophila melanogaster* females, the disjunction of nonexchange nonhomologs and the regular disjunction of nonexchange homologs are insured by the same process—distributive pairing. The phenotype of the meiotic mutant *no distributive disjunction* (symbol: *nod*) supports this hypothesis in that in females homozygous for *nod* nonexchange chromosomes often fail to disjoin from either nonexchange homologs or nonexchange nonhomologs. It is therefore proposed that *nod* is defective in some part of the distributive pairing process, with the result that *nod* females exhibit little or no distributive disjunction. The evidence that suggests this hypothesis includes the following: (1) *nod* has no effect in males; (2) nondisjunction occurs at the first (reductional) meiotic division and involves primarily nonexchange chromosomes; (3) other parameters of meiosis—exchange, interchromosomal effects on recombination, disjunction at the second meiotic division—appear to be normal; (4) the frequencies of nondisjunction for the different chromosomes are proportional to their frequencies of nonexchange tetrads; and (5) the inequality of gamete types indicative of distributive disjunction of nonhomologs is not observed. The inference, therefore, is that nod^+ is necessary for distributive disjunction; furthermore, it is suggested that the product of the nod^+ allele may be normally produced in a limiting amount, since *nod* is slightly dominant under conditions of high distributive disjunction.

The question of whether *nod* is an absolute defective—that is, whether there is no distributive disjunction in *nod* females or a low frequency—has not been entirely resolved. While there is no distributive disjunction of the fourth chromosomes in *nod* females, all other chromosomes examined exhibited distributive disjunction in approximately 30% of the meiocytes. For none of these latter situations, however, has it been established that all of the disjunction is insured by the distributive system; consequently, it may be either that *nod* is hypomorphic and more severely affects the distributive disjunction of the fourth chromosomes than the others or that *nod* eliminates all distributive disjunction with the residual *nod*-insensitive disjunction occurring independently of the distributive system. Nevertheless, in either case *nod* drastically reduces distributive disjunction.

The observation that virtually all chromosomes that have undergone exchange do disjoin in *nod* females indicates that the function of the nod^+ allele, and therefore presumably the process of distributive disjunction, is not essential for the disjunction of exchange bivalents at metaphase I. However, exchange bivalents occasionally nondisjoin in *nod* females. If this nondisjunction of exchange chromosomes is a result of the *nod*-induced defect in distributive disjunction, this would imply that the disjunction of some exchange bivalents is insured by the distributive system. It is known that the occurrence of an exchange does not necessarily preclude distributive disjunction because compound chromosomes (two homologous chromosome arms attached to a single centromere) recombine

normally yet disjoin distributively (GRELL 1963; BALDWIN and CHOVNICK 1967; ANDERSON 1925). This suggests that a precise definition of the domain of the distributive system is *any chromosome for which any existing exchange is insufficient to insure disjunction of its centromere from another centromere.* The observation that the exchange tends to be distal in the few exchange bivalents which nondisjoin in *nod* females suggests that some distal exchanges are not sufficient to insure disjunction of homologous centromeres. Moreover, it is possible that, in one circumstance (simultaneous nondisjunction of the second and third chromosomes), nondisjunction of the *X* chromosomes occurs regardless of exchange. For these reasons, the phenotype of *nod* does not necessarily imply an absolute distinction between disjunction following exchange and distributive disjunction. In most circumstances, however, disjunction following exchange is clearly much more regular in *nod* females than is distributive disjunction.

The defect in *nod* permits the resolution of two processes in the distributive system inseparable in nod^+ females: orientation and disjunction. Analysis of the distributive disjunction of trivalents in *nod* females suggests that the process by which the plane of orientation of a trivalent is determined (in the sense that chromosomes on the same side of the plane of orientation are oriented to and proceed to the same anaphase I pole) is separable from the process that insures that chromosomes on opposite sides of the plane of orientation disjoin. In *nod* females, orientation appears to be normal, but the process that insures that chromosomes on opposite sides of the plane of orientation proceed to opposite poles appears to be defective. In the case of a bivalent, the plane of orientation is always between the chromosomes so that orientation and disjunction cannot be distinguished.

Orientation must occur prior to disjunction, but presumably after distributive pairing; the sequence of events in the distributive system, therefore, is pairing–orientation–disjunction. The observation that orientation is normal in *nod* females implies that the process of distributive pairing is also normal. These considerations suggest that, with respect to the distributive system in *nod* females, pairing and orientation proceed normally, but that disjunction does not; the defect in distributive disjunction manifests itself both as nondisjunction (segregation to the wrong anaphase I pole) and as loss (failure to reach a pole).

There is another mutant in Drosophila in which disjunction following exchange and distributive disjunction appear to be differentially affected—the meiotic mutant ca^{nd}. This mutant, first characterized in *Drosophila simulans* by STURTEVANT (1929) and subsequently in *Drosophila melanogaster* (DAVIS 1969), increases the frequency of nondisjunction of all chromosomes but does not affect recombination. DAVIS (1969) demonstrated that the tetrad distributions derived from exceptional females and regular males were very similar, which suggests that nondisjunction is independent of exchange in this mutant. However, from the data presented by DAVIS, it may be observed that the frequency of exceptional gametes for chromosomes whose disjunction should have been distributive is up to two-fold higher (50%–67%) than the frequency of exceptional gametes for chromosomes with normal tetrad distributions (30%); this suggests that in ca^{nd},

as in *nod*, disjunction following exchange is more regular than distributive disjunction.

These considerations do not eliminate the possibility that there is but a single process that acts to insure that all co-oriented pairs of chromosomes separate at metaphase I (GRELL 1963). However, if there is only one such process, then the phenotypes of both *nod* and ca^{nd} suggest that the regular disjunction of tetrads following exchange may also be facilitated by some other factor—perhaps the physical existence of exchange itself.

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APPENDIX

On the nondisjunction of exchange tetrads in XXY females

BRIDGES (1916) found 3 w^e/w^e equational exceptions among 455 exceptional females from $w^e/+/Y$ mothers. Since w^e is very close to the tip of the *X*, this corresponds to a tetrad distribution of $E_0 = 0.9737$ and $E_1 = 0.0263$ for the meioses which gave rise to secondary nondisjunction. ZIMMERING (1958) found 10 y^2/y^2 equational exceptions among 742 exceptional females from $y^2\ w^a/In(1)B^{M1}/Y$ females, which corresponds to a tetrad distribution of $E_0 = 0.946$, $E_1 = 0.054$; seven of the ten equational exceptions were the result of a single crossover between y^2 and w^a. Consequently, the results presented in Appendix Tables 1, 2, 3, and 4 were unexpected. There, 25% of the exceptional daughters of *XXY* females resulted from nondisjunction of exchange tetrads.

APPENDIX TABLE 1

Sex and fourth chromosome disjunction in XX *and* XXY *females*

Crosses are $X/X/(y+Y)$; spa^{pol}/spa^{pol} females $\times$ $Y^{S}X{\cdot}Y^{L}$, *y v f B/0*; *C(4)RM, ci* $ey^{R}/0$ males

Cross	Sex chromosomes of female	Female gametes : Y	$\overline{XY}\ \overline{44}$ X 4	$\overline{XY}$ 0 X 44	$\overline{XY}\ \overline{44}$ X 0	0 $\overline{44}$ X 4	0 0 X 44	0 $\overline{44}$ X 0	0 $\overline{44}$ XX 4	0 0 XX 44	0 $\overline{44}$ XX 0	$\overline{XY}\ \overline{44}$ 0 4	$\overline{XY}$ 0 0 44	$\overline{XY}\ \overline{44}$ 0 0
1.	$\frac{y^2\ cv\ v\ +\ +}{y\ +\ +\ f\ car}$	—	1940	1	0	2286	0	0	7	0	0	3	1	0
2.	$\frac{y^2\ cv\ v\ +\ +}{y\ +\ +\ f\ car}{y+Y}$	0	1655	15	0	1882	10	1	140	0	0	0	0	0
		Y	46	0	0	1607	2	9	0	0	0	105	0	0

Cross	Total progeny	Number of parental females	Gametic X-nondisjunction*	Gametic 4-nondisjunction†	(#XX,0 + 0,Y): (#XX,Y + 0,0)
1.	4238	30	0.0048	0.0004	—
2.	5472	48	0.0652	0.0059	245:0

* Calculated as # of *X*-exceptional progeny/(# regular males + *X*-exceptional progeny) to avoid complications due to inviability of *XXYY* female progeny.

† Calculated among regular males + *X*-exceptional progeny.

APPENDIX TABLE 2

Recombination data from XX *and* XXY *females*

Genotypes of male progeny resulting from mono-*X*, nullo-*Y* ova from crosses 1 and 2, Appendix Table 1

Cross in Appendix Table 1:	1	2	Cross in Appendix Table 1:	1	2
X chromosome genotype			*X* chromosome genotype		
noncrossover			double crossover		
y^2 cv v + +	508	427	y^2 + + + +	20	21
y + + f car	572	490	y cv v f car	24	12
single crossover			y^2 + v + +	7	6
y^2 + + f car	123	119	y cv + f car	5	4
y cv v + +	113	94	y^2 cv + f +	16	4
y^2 cv + f car	170	199	y + v + car	10	7
y + v + +	215	202	y^2 cv + + +	17	13
y^2 cv v f car	145	106	y + v f car	25	17
y + + + +	196	142	y^2 cv v f +	2	1
y^2 cv v + car	47	11	y + + + car	0	1
y + + f +	40	16	triple crossover		
double crossover			y^2 + + + car	1	0
y^2 + + f +	11	0	y^2 + v f car	0	1
y cv v + car	19	0	*X* exceptions:	11	245
			Total:	2297	2138

The probability that an exceptional daughter will be recombinant appears to be uniform for the parental females in cross 2, if one parental female (which produced 7 recombinant exceptions out of 10 exceptional female progeny, 11 exceptional males, one intersex (*2X3A*) and a *normal* number of regular males and females) is excluded. Thus the high frequency of exchange exceptions observed does not appear to be due to an unsuspected factor segregating in the parental

APPENDIX TABLE 3

Map distances and tetrad distributions for the data presented in Appendix Table 2

For cross 1, map distance is calculated as recombinants/(total males + *X* exceptions); for cross 2, map distance is calculated as recombinants/(males + 1/2 *X* exceptions). Tetrads are calculated by the method of WEINSTEIN (1936) with the assumption that all *X* exceptions are derived from E_0 tetrads.

	Cross 1	Cross 2
Map interval		
y^2–cv	14.06	12.75
cv–v	20.24	22.48
v–f	18.72	15.58
f–car	6.36	1.98
Total map:	59.38	52.79
Tetrads		
E_0	0.086	0.117
E_1	0.644	0.714
E_2	0.266	0.165
E_3	0.003	0.004

APPENDIX TABLE 4

Genotypes of diplo-X exceptional progeny recovered from crosses 1 and 2, Appendix Table 1
Tetrad distributions calculated by the equations of MERRIAM and FROST (1964) as discussed in text. Ambiguity with respect to coupling relationships is indicated by parentheses

Genotype	Cross 1	Cross 2
$\frac{y^2\ cv\ v\ +\ +}{y\ +\ +\ f\ car}$	2	111
$\frac{y^2\ cv\ v\ +\ +}{y^2\ +\ +\ f\ car}$	0	4
$\frac{y\ cv\ v\ +\ +}{y^2\ +\ +\ f\ car}$	1	4
$\frac{y\ cv\ v\ +\ +}{y\ +\ +\ f\ car}$	0	4
$\frac{y^2\ cv\ v\ +\ +}{y^2\ cv\ +\ f\ car}$	0	5
$\frac{y\ +\ v\ +\ +}{y^2\ cv\ +\ f\ car}$	1	2
$\frac{y\ +\ v\ +\ +}{y\ +\ +\ f\ car}$	1	5
$\left(\frac{y}{y^2}\right)\frac{cv\ v\ +\ +}{cv\ v\ f\ car}$	0	3
$\frac{y\ +\ +\ f\ +}{y\ +\ +\ f\ car}$	1	0
$\frac{y^2\ cv\ v\ +\ car}{y\ +\ +\ f\ +}$	1	0
$\frac{y^2\ +\ +\ +\ +}{y\ cv\ v\ f\ car}$	0	1
Not tested:	0	1
Total:	7	140

Tetrads			Cross 2*
E_0	0.048	0.742	0.791
E_1	0.952	0.216	0.175
E_2	0	0.042	0.034

* Tetrad distribution excluding progeny from the one female discussed in text.

females. All chromosomes except the *X*'s should be segregating in the tested females; consequently, if the cause of this high frequency is genic, the causal gene or genes are probably located on the *X*.

These crosses were performed as controls for *nod XX* and *nod XXY* crosses (crosses 5 and 6, text Tables 8, 9, 10, and 11). The results from *nod XXY* females (cross 6, text Table 11) are similar to those from *nod*+ *XXY* females; and again, there is no evidence that the high frequency of exchange exceptions is the result of an unsuspected factor segregating in the parental females. The similarity in frequency of exchange exceptions and distributions of exchanges between *nod*+ and *nod XXY* females suggests that the high frequencies of exchange exceptions in both types of females are due to the same cause; however, the observations that recombination frequency (Appendix Table 3) is apparently lower in *nod*+ *XXY* females than in *nod*+ *XX* females (even when calculated as recombinant males/total males the total map = 0.562 in XXY females as compared to 0.597 in *XX* females) and that the frequency of nonexchange exceptions in *nod*+ *XXY* females (Appendix Table 1) is higher than expected ($0.0652 \times 0.75 = 0.049$, compared to 0.036, cross 2, text Table 8) may indicate that the causes of the high frequencies of exchange exceptions are different in the two experiments.

A deliberate attempt was made to insure that any differences between the *nod* and *nod*+ females tested in this experiment would be due solely to the effects of *nod*. Consequently, the *nod* and *nod*+ *y f car* chromosomes carried *X*-chromosome material of identical origin in at least the regions *y-cv* and *f*-centromere; similarly the *nod* and *nod*+ y^2 *cv v* chromosomes carried *X*-chromosome material of identical origin in at least the regions *y-v* and *wy*-centromere. Consequently, if the high frequency of exchange exceptions in *nod* and *nod*+ *XXY* females is the result of a (presumably dominant) *X*-linked gene, the derivation of the chromosomes indicates that this gene may map anywhere on the *X except* at *nod*. The effects of this presumptive dominant are extremely interesting. It apparently has no effect in *XX* females (the high frequency of exchange exceptions observed in *nod*+ *XX* females, cross 1, Appendix Table 4, is normal for primary exceptions; see MERRIAM and FROST 1964); however, in *XXY* females it results in the

nonhomologous disjunction of exchange *X*'s from the *Y* (note that all exceptional progeny in cross 2, Appendix Table 4 resulted from *XX*-from-*Y* disjunction). Furthermore, virtually all of the exchange tetrads recovered as exceptions had the exchange located in the distal half of the *X* (i.e., between y^2 and *v*) and a disproportionate fraction had the exchange located between y^2 and *cv*, the most distal region followed in this cross; from cross 6, text Table 11 and cross 2, Appendix Table 4 summed, the number of exceptions with an exchange between y^2 and *cv* equals 25, compared to 17 with an exchange between *cv* and *v*. From Appendix Table 2 it can be seen that if nondisjunction and exchange were independent, exchange between y^2 and *cv* should be approximately ⅔ as frequent as between *cv* and *v*. Moreover, a comparison of the results in Appendix Tables 2 and 4 indicates that approximately three times as many of the exceptions recombinant between y^2 and *cv* were derived from single-exchange tetrads as expected. Therefore the major effect of this presumptive gene is to greatly increase the fraction of tetrads with a single distal exchange that disjoin from the *Y*. Experiments are in progress to isolate this presumptive gene; so far the *nod*+ chromosomes *y f car* and y^2 *cv v* have been tested as homozygous *XX* females. Neither chromosome increases the frequency of *X* or fourth chromosome nondisjunction above control values.

Since exchange tetrads nondisjoin in both *nod* and *nod*+ *XXY* females, it cannot be determined in this experiment whether exchange tetrads can be *nod*-sensitive; however, these results do not exclude the possibility that some exchange tetrads in *nod XXY* females nondisjoin as a result of the *nod* defect.