CHROMOSOME SEGREGATION INFLUENCED BY TWO ALLELES OF THE MEIOTIC MUTANT *c(3)G* IN *DROSOPHILA MELANOGASTER*[1, 2]

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ABSTRACT

c(3)G is a gene in *Drosophila melanogaster* defined by two independently isolated mutants on the third chromosome. When homozygous in females, the mutants—*c(3)G*^{17} or *c(3)G*^{68}—result in the elimination of meiotic crossing over and a great increase in nondisjunction at the first meiotic division. The gametic frequency of *X*-, second-, or third-chromosome nondisjunction is approximately .3 in *c(3)G*^{17}, and .4 in *c(3)G*^{68}; for the fourth chromosome, the frequency is .2 in *c(3)G*^{17} and .3 in *c(3)G*^{68}. These values are at least two hundred fold greater than for spontaneous nondisjunction, though not high enough to indicate that chromosomes are distributed at random to the first meiotic division poles. Chromosomes loss is inferred from an excess of nullo-exceptional over diplo-exceptional ova. Loss is more frequent in *c(3)G*^{68}. If *c(3)G* females mate at low temperature, crossing over is still absent, but nondisjunction is decreased. *c(3)G*^{17} is more temperature sensitive than *c(3)G*^{68}.——Nonhomologous chromosomes tend to undergo nondisjunction in the same meiotic cells in *c(3)G*. Moreover, there is substantial nonhomologous pairing involving the larger chromosomes of the genome, inferred from the tendency for nonhomologs to disjoin from each other. Nonhomologous segregation is not observed between chromosome *4* and any other chromosome. *c(3)G*^{68} exhibits more nonhomologous segregation than does *c(3)G*^{17}, and, for either allele, the degree of nonhomologous segregation is directly proportional to the similarity in length of the two nonhomologs being considered. The degree of nonhomologous segregation is increased at low temperature.——Heterozygosity for inversions tends to increase *c(3)G*-mediated nondisjunction, and to alter the patterns of nonhomologous segregations. The effects are observed even if the inversion does not disrupt centromeric heterochromatin, and even though the inversions do not change the lengths of the chromosomes involved. In *XXY* females, *c(3)G*^{17} shows more separation of the two *X*'s from the *Y* chromosome than does *c(3)G*^{68}. Fourth-chromosome nondisjunction is increased by the presence of a *Y* chromosome in both kinds of mutant females. But in *XXY; c(3)G* females which are also heterozygous for an *X* inversion, frequencies of fourth-chromosome nondisjunction are little different from those in *XX; c(3)G* females, while the degrees of *XX*-from-*Y* disjunction are increased.——The chromosome behavior of the two alleles of *c(3)G* is readily rationalized by a model which assumes that *c(3)G*+ controls a stage of meiosis prior to synapsis and crossing over. If exchange is directly disrupted in *c(3)G* homo-

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zygotes, disjunctional consequences should be the same in $c(3)G^{17}$ and $c(3)G^{68}$. They are not. If, however, $c(3)G+$ controls a precondition to crossing over—such as the association of homologous and nonhomologous chromosomes—then the two alleles could each abolish crossing over, but lead to different amounts and patterns of nondisjunction.

RECENTLY it has been proposed that meiosis in higher organisms might be more fully understood through the systematic search for and analysis of mutants which affect one or more of the meiotic processes. The isolation of such meiotic mutants has been accomplished by SANDLER *et al.* (1968) in Drosophila, and by BRESCH, MÜLLER and EGEL (1968) and ESPOSITO and ESPOSITO (1969) in yeast. However, many meiotic mutants have been sporadically discovered in a variety of organisms previously (see REES 1961, RILEY and LAW 1965, JOHN and LEWIS 1965, LINDSLEY *et al.* 1968, and NICOLETTI 1968, for reviews).

The first meiotic mutant in *Drosophila melanogaster* was discovered by GOWEN and GOWEN (1922), and is called *c(3)G*. This mutant has been investigated in many ways since its discovery in 1917. The basic features are as follows: (1) *c(3)G* is a point mutant located at 57.4 on chromosome 3 (LINDSLEY and GRELL 1968); the locus is in the salivary gland chromosome region 88F;89B4–5, since it is included in $Df(3R)sbd^{105}$, a small deficiency in the right arm of the third chromosome (LEWIS 1948). (2) When homozygous in females, *c(3)G* causes the near abolition of meiotic crossing over and, in addition, leads to a high frequency of nondisjunction for all chromosomes at the first meiotic division, though not so high a frequency as to indicate that all chromosomes are being distributed at random at anaphase I (GOWEN and GOWEN 1922, GOWEN 1928, 1933). (3) Fertility and egg hatch are very low (SMITH and KING 1968). (4) *c(3)G* has no effect on male meiosis (GOWEN 1933), on mitotic crossing over in females (LE-CLERC 1946), on somatic pairing (STERN and SCHULTZ, in LECLERC 1946), or on somatic repair of DNA damaged by radiation (J. VALENCIA, personal communication). (5) In *c(3)G*, no crossovers can be induced by X rays in euchromatic chromosome regions (WHITINGHILL 1938), but it is possible to induce heterochromatic crossovers (ROBERTS 1969). (6) *c(3)G* oocytes are hypersensitive to the X-ray induction of dominant lethals (WATSON 1969), and this hypersensitivity is not due to increased nondisjunction (D. LINDSLEY, personal communication). (7) There is no synaptonemal complex in oocytes of *c(3)G* females (MEYER 1964, SMITH and KING 1968); and less time is spent by *c(3)G* in stages which, in the wild type, correspond to zygotene and pachytene (SMITH and KING 1968). (8) $Df(3R)sbd^{105}/c(3)G+$ females exhibit some nondisjunction (HINTON 1966, LINDSLEY *et al.* 1968), while *c(3)G* is recessive in respect of disjunction (GOWEN 1933, HINTON 1966).

In addition, it is known that ring chromosomes are lost to a greater extent in females expressing the mutant than in $c(3)G+$ (SANDLER 1965). $Df(3R)sbd^{105}/c(3)G+$ females have reduced crossing over—the greatest decreases being in chromosome regions distal to the centromere (HINTON 1966, LINDSLEY *et al.* 1968)—and prematurely terminated synaptonemal complexes (SMITH and KING 1968). But $c(3)G/c(3)G+$ females show elevated crossing over (GOWEN 1933,

HINTON 1962, 1966). Unlike a putative allele of *c(3)G*—a mutator gene which leads to increased production of sex-linked lethals and reduced crossing over (M. GREEN 1970, and personal communication)—*c(3)G* itself does not induce such mutations in increased frequency (HALL 1971). These matters will be considered in a subsequent report on various components of recombination influenced by *c(3)G*.

In 1968, SANDLER (1971) induced a new meiotic mutant in *D. melanogaster*, called *mei-W22*. This proved to be an allele of *c(3)G* and is here named $c(3)G^{68}$, while the original allele is here named $c(3)G^{17}$. The high degree of first meiotic division nondisjunction caused by *c(3)G* has never been analyzed in detail. The purpose of this investigation is to analyze *c(3)G*-mediated nondisjunction and to compare the effects of the two mutant alleles, in an attempt to deduce the nature of the meiotic defect.

GOWEN (1933) and SANDLER *et al.* (1968) suggested that *c(3)G* affects meiosis before the onset of homologous chromosome pairing and crossing over. It has been concluded from the present study that *c(3)G* indeed acts very early in prophase of meiosis I, such that crossing over is not directly disrupted. Chromosome behavior under the influence of the two mutant alleles of *c(3)G* is, furthermore, consistent with the contention that the gene controls the stabilization of an association of all eight chromosomes in Drosophila females, an event prior to the meiotic recognition of homologous chromosomes for each other.

X- AND FOURTH-CHROMOSOME NONDISJUNCTION

Since the properties of *mei-W22* (SANDLER 1971) are similar to those of $c(3)G^{17}$, the newly induced mutant was tested for allelism to $c(3)G^{17}$. The $c(3)G^{17}$ stock used is *ve h th* $c(3)G^{17}$ *Sb Ubx/st* $c(3)G^{17}$ *ca*. Recombination and disjunction were measured in $c(3)G^{17}$*/mei-W22* females, who were also heterozygous for *X*-chromosome markers ($y\ pn\ v\cdot y^{+}/y$) and homozygous for a fourth-chromosome recessive (spa^{pol}). This allows *X*-chromosome crossing over and *X*- and fourth-chromosome disjunction to be assessed in crosses to attached-*XY*; attached-*4* males ($Y^{S}X\cdot Y^{L}$, *In(1)EN, v f B/0;* $C(4)RM, ci\ ey^{R}/0$) (SANDLER *et al.* 1968). Such tester males produce four types of sperm in roughly equal frequencies: (1) attached-*XY*; attached-*4*, (2) attached-*XY*; nullo-*4*, (3) nullo-*XY*; attached-*4*, and (4) nullo-*XY*; nullo-*4*. These sperm types fertilize the array of nine egg types generated by disjunction and nondisjunction of the *X*'s and *4*'s in females: *X;4*, *XX;4*, *0;4*, *X;44*, *X;0*, *XX;0*, *0;44*, *XX;44*, and *0;0*. Only half of the *X*-chromosome exceptions (from eggs bearing two *X*'s or no *X*) survive relative to *X*-chromosome–fourth-chromosome regulars (from *X;4* ova) and fourth-chromosome exceptions (from *X;44* and *X;0* ova). Thus, the gametic frequencies of nondisjunction in the females being tested can be estimated by doubling the number of progeny exceptional for the *X* chromosome. Nondisjunctional types are distinguishable because the *X*'s and *4*'s are differentially marked in the females and males. Crossing over can be assessed in the regular *X0* male progeny.

The result of the allelism test is that $c(3)G^{17}$*/mei-W22* females exhibit almost no crossing over, and very high frequencies of nondisjunction, *i.e.* .36 for the *X*

TABLE 1

Recombination and X- *and fourth chromosome disjunction under the influence of* c(3)G

	Third chromosome chromosome	Constitution of ova producing recovered progeny								Nondisjunctions per 10^3 ova		Total X chromosome map length
		$X;4$	$XX;4$	$0;4$	$X;44$	$X;0$	$XX;0$	$0;44$	$XX;44$	$0;0$	Total	X	4	
1.	$\frac{+}{+}$	25483	3	5	5	8	—	1	1	—	25506	0.8	0.7	65.57
2.	$\frac{c(3)G^{17}}{+}$	12184	—	1	4	4	—	—	—	—	12193	0.2	0.7	72.45
3.	$\frac{c(3)G^{68}}{+}$	13859	—	1	2	5	—	—	—	—	13857	0.1	0.5	65.51
4.	$\frac{c(3)G^{17}}{c(3)G^{17}}$	12808	1359	1211	990	993	194	267	176	332	18330	323.6	179.2	0.07
5.	$\frac{c(3)G^{68}}{c(3)G^{68}}$	9142	1177	1213	909	1504	295	299	178	564	15281	392.0	267.5	0.10
6.	$\frac{c(3)G^{68}}{c(3)G^{17}}$	6229	691	792	501	649	113	134	108	264	9481	362.9	206.1	0.04
7.	$\frac{c(3)G^{17}}{c(3)G^{17}}$ 19°C	1096	78	75	11	7	1	1	3	6	1278	227.5	27.7	0.00
8.	$\frac{c(3)G^{68}}{c(3)G^{68}}$ 19°C	700	72	66	69	33	10	14	9	10	983	311.0	161.5	0.22

In(1LR)sc^{V1}, y pn v.y$^+$ y*; spa^{pol}/spa^{pol} females were crossed to *Y8X·YL, In(1)EN, v f B/0; C(4)RM, ci ey^R/0* males. For two of these experiments (lines 7 and 8), the mothers were raised and tested at 19°C, as opposed to all other tests for which females were raised and tested at 25°C. The number of nondisjunctions per 10^3 ova is the estimated proportion of, for example, dipl*o*-*X* plus null*o*-*X* ova (see text).

* *In(1LR)sc^{V1}* is not an inversion in the usual sense: rather, an *X* chromosome derived from an inversion (with breakpoints at the extreme tips of the *X*), such that a small duplication bearing y^+ is appended to the small right arm of the *X*, serving as a centromere marker (see LINDSLEY and GRELL 1968). Some of the females tested in these experiments were *y/y* with respect to their *X* chromosomes, in which case a second distinctive duplication was obligatorily present on the fourth chromosome. No difference in terms of disjunction was observed, within any experiment, when comparing the progeny from *y/y* to those from *y pn v.y$^+$/y* females.

and .21 for the fourth chromosomes (Table 1, line 6). Nondisjunction is increased three to five hundred fold relative to the control (Table 1, line 1), and crossing over is reduced more than six hundred fold. Thus, *mei-W22* is an allele of *c(3)G*, and is hereafter called *c(3)G^{68}*.

The frequencies of nondisjunction in homozygous $c(3)G^{17}$ were compared to homozygous $c(3)G^{68}$. In Table 1 (line 4), the data show that nondisjunction frequencies under the influence of the original allele of *c(3)G* are .32 for the *X* chromosome and .18 for chromosome *4*. The values for $c(3)G^{17}$ are very close to those reported by LINDSLEY *et al.* (1968)—.33 for the *X* and .17 for the fourth chromosome. And they are lower than for homozygous $c(3)G^{68}$, for which *X*- and fourth-chromosome nondisjunction frequencies are .39 and .27, respectively. In these two experiments, as for the allelism test, crossing over was negligible. Homozygous $c(3)G^{17}$ and homozygous $c(3)G^{68}$ females tested here were nearly coisogenic, for the *X*, second, and fourth chromosomes. The two stocks were not coisogenic for their third chromosomes, but the higher nondisjunction frequencies induced by $c(3)G^{68}$ persisted for $c(3)G^{68}$-bearing third chromosomes allowed to undergo recombination with nonmutagenized thirds ($c(3)G^{68}$ had been induced with EMS, SANDLER 1971). There is no evidence that the difference between $c(3)G^{68}$- and $c(3)G^{17}$-mediated nondisjunction is not due to a difference at the *c(3)G* locus.

The variance was computed for the frequency of *X*-chromosome nondisjunction in these experiments. It was found that the actual female-to-female variance within an experiment (with respect to the progeny of individual females, all of which were tested singly) is only very slightly higher than binomial variance; and, thus, chi-square contingency tests between experiments are valid. The results indicate that *X*-chromosome nondisjunction in $c(3)G^{68}$ females is significantly higher than in $c(3)G^{68}/c(3)G^{17}$ females ($P < .005$), which is in turn significantly greater than in $c(3)G^{17}$ ($P < .005$). So the new allele of *c(3)G* shows more faulty behavior than the original one with respect to disjunction. Because a deficiency for the *c(3)G* locus heterozygous with $c(3)G^{+}$ is more defective than the mutant in heterozygous condition (HINTON 1966), $c(3)G^{17}$ is not an amorph (according to the definition of MULLER 1950). It seems, then, that $c(3)G^{68}$ is less leaky than $c(3)G^{17}$.

In the experiments just discussed, *c(3)G*-mediated nondisjunction for the *X* chromosome was found to take place almost exclusively at the reductional (first) meiotic division. For $c(3)G^{17}$, no diplo-*X* exceptions (out of 550 from $y\ pn\ v\ y^{+}/y$ females) were *y* or *pn v* in phenotype, which would have resulted from no crossing over, followed by equational nondisjunction of the $y\ pn\ v\ y^{+}$ or *y X* chromosome. For $c(3)G^{68}$, two $y^{+}\ pn\ v\ B^{+}$ diplo-*X* exceptions and two $y\ B^{+}$ diplo-*X* exceptions were recovered (out of 866 from $y\ pn\ v\ y^{+}/y$ females). On progeny testing, these females were shown to bear free, nonrecombinant *X*'s, implying that they did not result from centromere misdivision (to generate isochromosomes), but rather from equational nondisjunction. The greater incidence of such equational nondisjunction in $c(3)G^{68}$, compared to the original allele, may be due to the misbehavior of a small fraction of chromosomes at the second meiotic division, subsequent to the stage in meiosis when *c(3)G* exerts its major effects, *i.e.* meiosis I.

When meiosis is disrupted by a mutant, chromosomes are presumed to be sometimes lost if there is observed an excess of nullo exceptions over diplo exceptions (see, for example, SPIELER 1963); for a nondisjunctional event without

TABLE 2

Chromosome loss caused by c(3)G

Third chromosome constitution	Ratio of diplo-*X* to nullo-*X* ova: Among all data	Among single exceptions	Among double exceptions	Ratio of diplo-*4* to nullo-*4* ova: Among all data	Among single exceptions	Among double exceptions
$\frac{+}{+}$	0.67	0.60	1.00	1.13	0.63	—
$\frac{c(3)G^{17}}{c(3)G^{17}}$	0.96	1.12	0.62	0.92	1.00	0.84
$\frac{c(3)G^{68}}{c(3)G^{68}}$	0.79	0.97	0.55	0.58	0.60	0.56
$\frac{c(3)G^{68}}{c(3)G^{17}}$	0.77	0.87	0.56	0.70	0.77	0.64

The data employed to compute these ratios are in Table 1.

loss will produce diplo exceptional and nullo exceptional gametes equally frequently. On the assumption that loss is inversely proportional to the ratio of diplo gametes to nullo gametes, there is more loss for the *X* and fourth chromosomes in $c(3)G^{68}$ than in $c(3)G^{17}$ females (Table 2). This difference in loss accounts for most of the difference in the frequencies of nondisjunction between the two alleles. For example, the proportions of diplo-*X* ova from $c(3)G^{17}$ and $c(3)G^{68}$ are .16 and .17, respectively; while $c(3)G^{17}$ females generate .16 nullo-*X* ova, compared to .22 from $c(3)G^{68}$ females.

Loss of chromosomes occurs more frequently for either *c(3)G* allele when more than one chromosome undergoes nondisjunction: the ratio of diplo to nullo exceptions among the *X* and *4* double exceptions (from gametes nondisjunctional for both chromosomes) is less than it is among the *X*- or fourth-chromosome single exceptions (Table 2).

The actual diplo : nullo ratios from $c(3)G^{17}$ females, for the *X* and fourth chromosomes, are near unity (Table 2). This implies no loss at all in these females, which is somewhat surprising, since an excess of nullo gametes is usually seen in conjunction with nondisjunction (see, for example, BRIDGES 1916, DAVIS 1971, PARRY 1972). But the near equality of nullo-*X* and diplo-*X* ova could be a spurious result if the attached-*XY* tester males used in these experiments produce nullo-*XY* sperm in excess of fifty percent (as is often the case, see SANDLER and BRAVER 1954). This would favor the recovery of diplo-*X* relative to nullo-*X* eggs. In fact, among the *X*-chromosome regular progeny from crosses of *c(3)G* females to attached-*XY* males, there is an excess of male progeny. For instance, for $c(3)G^{17}$ females, the ratio of males to females among the *X* regulars is 1.33 (*i.e.* 8454/6337). This, too, suggests that the attached-*XY* fathers produce an excess of nullo-*XY* sperm. If the ratio of *XX* to nullo-*X* ova from $c(3)G^{17}$ females (.96—Table 2) is normalized against the male : female ratio for the *X* regulars set equal to 1.00, then the *XX* : nullo-*X* ratio becomes .72.

A control was performed by crossing *y/y; c(3)G^{17}/c(3)G^{17}* females to males bearing free *X* and *Y* chromosomes (+/*Y* or *y B/Y*). The diplo-*X* : nullo-*X* ova ratio from this experiment was .74 (*i.e.* 345/468), in very good agreement with the value computed above, and implying fairly substantial loss of chromosomes from *c(3)G^{17}* meioses. (The sex ratio among the *X*-regular segregants was not significantly different from 1:1). So the difference between *c(3)G^{17}* and *c(3)G^{68}* with respect to loss is one of degree—there being more loss associated with the latter—rather than of kind.

c(3)G-mediated chromosome loss was examined in females carrying an attached-*X* chromosome (two *X*'s attached together at a centromere). An attached-*X* is not lost in *c(3)G^{+}* females carrying no other sex chromosome (Table 3; cf. SANDLER and BRAVER 1954), even though the attached-*X* is univalent at the first meiotic division. Other kinds of univalent chromosomes are, however, often cytologically observed to undergo loss (for example in wheat, SEARS 1952). For *c(3)G^{+}* females in which an attached-*X* has a homolog available to pair with it (e.g. a *Y* chromosome), segregation is not altered (Table 3; cf. SANDLER and BRAVER 1954). Under the influence of *c(3)G^{17}* or *c(3)G^{68}*, the attached-*X* does undergo loss, especially if it is univalent. Thus, the normalized diplo-*X* to nullo-*X* ratios are less than unity (Table 3, experiment A). Moreover, there is a greater degree of loss of the attached-*X* in *c(3)G^{68}* females. Fourth chromosome loss in these experiments is, as before, greater for *c(3)G^{68}*. In attached-*X/Y*; *c(3)G* females, loss of the attached-*X* is reduced in comparison to attached-*X/0* (Table 3, experiments B and C); and, again, loss tends to be greater for *c(3)G^{68}*. The conclusion here is that chromosomes can be lost from *c(3)G* meioses (compared to wild type), irrespective of a situation where homologs attempt to pair and segregate from each other. However, pairing can be important in *c(3)G* females, because loss (of the attached-*X*) is less when a homolog is present.

GOWEN (1933) concluded that homologs in *c(3)G^{17}* do not segregate at random in meiosis I. From the present experiments, this conclusion can be drawn by examining the frequencies of nondisjunction for either chromosome *1* or *4* (Table 1). If, for example, the two *X* chromosomes were being distributed at random in every *c(3)G* meiosis, one would expect .25 *XX* ova, .25 nullo-*X* ova, and .5 regular mono-*X* ova, i.e. a gametic nondisjunction frequency of .5. Loss of chromosomes, if it were occurring in conjunction with random distribution of the *X* chromosomes, would reduce the regular *X* class and the *XX* class, while increasing the nullo-*X* class, and, thus, would lead to a gametic nondisjunction frequency greater than .5. For neither allele of *c(3)G*, nor for either the *X* or fourth chromosome, does gametic nondisjunction approach .5. There is, in short, a tendency for homologs to separate in *c(3)G* meiocytes. This tendency is greater for the fourth chromosomes, which consistently present lower frequencies of exceptions than do the *X* chromosomes.

LINDSLEY *et al.* (1968) mention that, in *c(3)G^{17}* meioses, chromosome pairs of the complement do not disjoin independently. That is, the frequency of double exceptional progeny (nondisjunctional for both the *X* and fourth chromosomes)

TABLE 3

c(3)G-*mediated loss in attached-*X *females*

Third chromosome constitution	Ratio of diplo-*X* to nullo-*X* ova	Ratio of diplo-*4* to nullo-*4* ova	Total progeny
A. *C(1)RM/0* females: sex and fourth chromosome disjunction			
$\frac{+}{+}$	1.00**	2.50	10001
$\frac{c(3)G^{17}}{c(3)G^{17}}$	0.87*	1.04	1960
$\frac{c(3)G^{68}}{c(3)G^{68}}$	0.62*	0.61	2053

	Ratio of diplo-*X* to nullo-*X* ova (all data)	Ratio of attached-*X* to *Y* ova	Ratio of diplo-*4* to nullo-*4* ova	Total progeny
B. *C(1)RM/Y* females: sex and fourth chromosome disjunction				
$\frac{+}{+}$	1.00	1.01	1.00	972
$\frac{c(3)G^{17}}{c(3)G^{17}}$	0.69	0.90	1.09	558
$\frac{c(3)G^{68}}{c(3)G^{68}}$	0.65	0.92	0.49	729

	Ratio of diplo-*X* to nullo-*X* ova (all data)	Ratio of attached-*X* to *Y* ova	Ratio of attached-*X*;*Y* to nullo ova	Sex chromosome nondisjunctions per 10^3 ova	Total progeny
C. *C(1)RM/Y* females: sex chromosome disjunction					
$\frac{+}{+}$	1.00**	1.00**	0.15*	3.5	3171
$\frac{c(3)G^{17}}{c(3)G^{17}}$	1.07*	1.26*	0.52*	178.2	954
$\frac{c(3)G^{68}}{c(3)G^{68}}$	0.76*	0.89*	0.57*	334.9	1260

All females carried *C(1)RM, y pn v*. A. Females carried the attached-*X* but no *Y* chromosome had their fourth chromosomes marked with spa^{pol}/spa^{pol}, and had sex and fourth chromosome disjunction assessed by crossing to attached-*XY*; attached-*4* males (see Table 1). B. Females carried a y^+Y chromosome, had their fourth chromosomes marked with spa^{pol}/spa^{pol}, and had sex and fourth chromosome disjunction assessed by crossing to *y B/Y*; *C(4)RM, ci* $ey^R/0$ males. sex chromosome nondisjunction (producing *C(1)RM*; *Y* and nullo gametes) cannot be measured with great accuracy, because the *C(1)RM*; *Y* nondisjunctionals are recovered as *XXYY* females which are poorly viable; thus, the ratios of attached-*X* to *Y* gametes are the most meaningful. C. Females carried a y^+Y chromosome and had sex chromosome disjunction only assessed by crossing to attached-*XY* males ($Y^sX{\cdot}Y^L$, *In(1)EN, y B/0*); here, all sex chromosome regulars and nondisjunctionals are, on the whole, equally recoverable with respect to progeny viabilities.

* These ratios have been normalized with respect to diplo-*X* to nullo-*X* ratios in the control (*c(3)G*+ females) set equal to 1.00 (**). For experiment A, this ratio was actually 1.36; very likely a spuriously high value resulting from the fact that the attached-*XY* tester males produce fewer attached-*XY* bearing sperm than nullo-*XY* bearing sperm (see text and experiment B). For experiment C, these ratios were actually 1.34, both for all the data and for cases of attached-*X*-from-*Y* segregation—spuriously high values (see above).

TABLE 4

Non-independence of X *and fourth chromosome nondisjunction*

Third chromosome constitution		Constitution of ova producing recovered progeny								
		X;4	*XX;4*	*0;4*	*X;44*	*X;0*	*XX;0*	*0;44*	*XX;44*	*0;0*
+ / +	observed	25483	3	5	5	8	—	1	1	—
	expected	25481.0	4.0	6.0	7.0	8.0	0.0	0.0	0.0	0.0
$c(3)G^{17}$ / $c(3)G^{17}$	observed	12808	1359	1211	990	993	194	267	176	332
	expected	12408.9	1450.6	1518.6	1156.3	1225.7	143.3	141.5	135.2	150.0
$c(3)G^{68}$ / $c(3)G^{68}$	observed	9142	1177	1213	909	1504	295	299	178	564
	expected	8720.1	1245.2	1566.6	1048.0	1786.9	255.2	188.3	149.6	321.0
$c(3)G^{68}$ / $c(3)G^{17}$	observed	6229	691	792	501	649	113	134	108	264
	expected	6002.1	741.9	967.8	578.5	798.4	71.5	98.7	93.3	128.7

Data from all experiments listed here were reported in Table 1. Expected numbers are based on the hypothesis of independent disjunction of chromosomes *1* and *4* (see text).

is greater than what one would expect according to the product of the individual frequencies of *X*-chromosome and fourth-chromosome exceptions. Table 4 presents an analysis of independence. A consistent excess of observed over expected double exceptions for the control (cf. HALL 1970) and for both alleles of *c(3)G* can be seen. The departures from independent chromosome behavior observed here are apparently not due to nonhomologous pairing and segregation of the *X* and fourth chromosomes. Such dependent behavior of nonhomologs will tend to produce *XX;0* and *0;44* double exceptions, i.e. both *X*'s would have disjoined from both *4*'s. However, no preponderance of these two ova types is observed (Table 4).

Certain miscellaneous properties of $c(3)G^{17}$ and $c(3)G^{68}$ are described as follows. To confirm that the new meiotic mutant is at the *c(3)G* locus, it was mapped in three separate ways: (1) $Df(3R)sbd^{105}/c(3)G^{68}$ females were found to exhibit a mutant phenotype, as do $Df(3R)sbd^{105}/c(3)G^{17}$ flies (LEWIS 1948, HINTON 1966). (2) $c(3)G^{68}$ was mapped with respect to the third chromosome marker *Sb* (map position 58.2, 0.8 units from *c(3)G*). Of 118 third chromosomes from $Sb/c(3)G^{68}$ females, one was found, on further testing, to have undergone crossing over between *Sb* and $c(3)G^{68}$, which again maps the new meiotic mutant to the same place as $c(3)G^{17}$. (3) An attempt was made directly to separate $c(3)G^{68}$ and $c(3)G^{17}$. Females bearing both alleles in repulsion ($ry\ c(3)G^{68}/c(3)G^{17}\ Sb\ Ubx$), and carrying an *X* chromosome into which had been inserted a segment of the third chromosome which contains the normal allele of *c(3)G* (from *T(1;3)05*—see LINDSLEY and GRELL 1968), were constructed. Of 725 third chromosomes recovered from such females—39 of which had undergone recombination between *ry* and *Ubx*—none was found on further testing to carry $c(3)G^{+}$.

In the *X*- and fourth-chromosome nondisjunction experiments, a small number of triploid females and intersexes were recovered (approximately one per

thousand progeny). These are the result of unreduced or virtually unreduced eggs. GOWEN (1933) recovered such segregants in his investigation of *c(3)G*^{17}.

Chromosomes inherited from *c(3)G* females exhibit some mitotic instability. About 2.5×10^{-4} and 7.0×10^{-4} of recovered progeny from *c(3)G*^{17} and *c(3)G*^{68}, respectively, show mitotic loss of an *X* or fourth chromosome. These somatic loss values are roughly ten fold higher than for the control (cf. Table 1, line 1), but much less than what is observed for certain other meiotic mutants in Drosophila (such as claret-nondisjunctional, LEWIS and GENCARELLA 1952).

c(3)G^{68} heterozygous with *c(3)G*$^{+}$ does not increase nondisjunction above the control rate (Table 1—compare line 1 to line 3). This is also true of *c(3)G*^{17} (GOWEN 1933, HINTON 1966; and Table 1, line 2, in the present study). Males homozygous for *c(3)G*^{68}, as initially isolated by SANDLER (1971), were sterile. However, this sterility has been separated from *c(3)G*^{68} by recombination. *y B/y*$^{+}$*Y*; *c(3)G*^{68}*/c(3)G*^{68}; *spa*^{pol}*/spa*^{pol} males (crossed to *y pn/y pn*; *C(4)RM, ci ey*^{R}*/0* females) have normal meioses, in that only eight sex- and fourth-chromosome exceptions were recovered in 5120 progeny, which is not significantly different from what is observed—in a similar test cross—for males free of meiotic mutants (SANDLER *et al.* 1968). Third chromosomes bearing *c(3)G*^{17} or *c(3)G*^{68} were observed in salivary gland preparations to be free of cytological abnormalities.

The *c(3)G* phenotype is temperature sensitive. *c(3)G*^{17} or *c(3)G*^{68} females raised and then crossed to tester males at 19°C have lower *X*- and fourth-chromosome nondisjunction (Table 1, lines 7 and 8) than for females raised and tested at 25°C (the temperature used for all other crosses). *c(3)G*^{17} is more temperature sensitive than *c(3)G*^{68}; and fourth-chromosome nondisjunction is more temperature sensitive than *X*- chromosome nondisjunction for either allele. Crossing over is still absent at the lower temperature. Further experiments showed that raising *c(3)G* females at low temperature but testing them at 25°C, or treating virgin *c(3)G* females with low temperature, has no effect on nondisjunction. The crucial factor was found to be mating *c(3)G* females to tester males at 19°C. Here, the lower nondisjunction frequencies prevail, whether the females are raised at low or high temperature, and even for two-day 19°C treatments of the mated *c(3)G* females (which leads to decreased nondisjunction for the progeny coming from eggs laid within two days after the short treatment). These results imply that the temperature-sensitive stage for *c(3)G*-mediated nondisjunction is metaphase I or anaphase I. Oocytes in *D. melanogaster* are arrested at metaphase I prior to insemination (HUETTNER 1924, SONNENBLICK 1965, KING 1970; the triggering of egg laying also stimulates oocytes to pass through the arrest—DOANE 1960). Only if *c(3)G* oocytes are passing through metaphase I arrest is nondisjunction temperature sensitive. The results of these experiments do not imply that the meiotic stage which *c(3)G* affects is metaphase I or anaphase I. Rather, it seems that the final result of a *c(3)G* meiosis is labile with regard to temperature, but that the stage of action of this gene is earlier. Otherwise, one must assume that crossing over—abolished by *c(3)G*—occurs at or subsequent to metaphase I.

c(3)G-MEDIATED NONDISJUNCTION OF ALL CHROMOSOMES

The frequencies and the patterns of nondisjunction for chromosomes *2* and/or *3* in *D. melanogaster* cannot be determined in a straightforward fashion, because aneuploidy for either invariably leads to zygotic lethality. Major autosomal exceptions can be recovered if females producing them are crossed to males bearing attached autosomes (e.g., DAVIS 1969), but no regular progeny can be recovered from such a cross, so the frequency of second- or third-chromosome nondisjunction cannot be assessed.

It is possible, however, simultaneously to determine the frequencies and patterns of nondisjunction for not only the major autosomes, but for the *X*'s and *4*'s as well, if females are crossed to males bearing the meiotic mutant, *mei-S332*. This is a mutant discovered by SANDLER *et al.* (1968), and characterized by DAVIS (1971). It is a second-chromosome semidominant which results in a high frequency of equational nondisjunction in both sexes, which is about the same for all four chromosome pairs. Furthermore, nonhomologous chromosomes nondisjoin in a roughly independent fashion.

Using *mei-S332* males, nondisjunction of all four chromosome pairs in *c(3)G* females and in controls was examined. *y/y*$^{+}$*Y*; *cn mei-S332/cn mei-S332*; *e/e*; *gvl/gvl* males were crossed to *y B/y B*; *bw/bw*; *th c(3)G/th c(3)G*; *spa*^{pol}*/spa*^{pol} females. With all chromosomes differentially marked in males and females, all of the eighty-one theoretically possible ova types can be reflected in the progeny produced by this cross. For example, if a nullo-*2*; diplo-*3* egg is fertilized by a diplo-*2*; nullo-*3* sperm, it will lead to a *cn*; *th* progeny recognizable as having arisen from the union of nondisjunctional gametes.

Using the observed proportion of, say, *cn* progeny (from nullo-*2* eggs) and the frequency of diplo-*2* sperm estimated by DAVIS (1971), one can estimate the frequency of nullo-*2* eggs using equations which involve the product of sperm type frequencies and egg type frequencies. For chromosome *2* or chromosome *3*, there are four equations, containing two independent unknown parameters (frequencies of diplo and nullo ova), and two independent observations (total progeny from diplo eggs fertilized by nullo sperm, and total progeny from nullo eggs fertilized by diplo sperm). Thus, these equations have a unique solution. One of the four equations is for the (unobserved) "lethal class" containing, for example, the product of the frequency of mono-*2* eggs and diplo-*2* sperm, and so forth with respect to all zygotic constitutions which are aneuploid for the major autosome in question. For the fourth chromosome, similar equations are employed, but the lethal class equation has two less terms in it, because mono-*4* eggs fertilized by diplo-*4* sperm, and diplo-*4* eggs fertilized by mono-*4* sperm lead to viable progeny. For the sex chromosomes, there are eight independent progeny types (see Table 5), and thus, ten equations (including one for the lethal class) and two independent unknowns (frequencies of diplo-*X* and nullo-*X* eggs). There is not a unique solution for these equations, but the best one can be obtained by minimum chi-square.

The results of crosses of fully marked *c(3)G*^{17} females, *c(3)G*^{68} females, and

TABLE 5

c(3)G-*mediated* X *chromosome nondisjunction*

Third chromosome constitution	Progeny phenotypes (sex chromosome ova types producing these progeny)										Nondisjunctions per 10^3 ova
	y B / y + ♀ (X)	B ♂ (X)	y B ♂ (X)	B / + ♀ (X)	B / B ♀ (XX)	y B / y B ♀ (XX)	y ♂ (0)	y ♀ (0)	+ ♂ (0)	Total	
+ / +	12498	9155	5077	201	3	5	6	8	4	26957	3.6
$c(3)G^{17}$ / $c(3)G^{17}$	2343	1775	942	36	373	172	718	67	20	6446	343.9
$c(3)G^{68}$ / $c(3)G^{68}$	2886	2444	1201	62	492	317	1257	71	27	8757	399.3

y B/y B females were crossed to *y/y+Y*; *mei-S332/mei-S332* males. With each progeny phenotype is, in parenthesis, the sex chromosome ovum type which leads to that phenotype. See text for explanation of procedure used to estimate nondisjunction frequencies.

females bearing no meiotic mutant to fully marked *mei-S332* males are presented in Tables 5 and 6, for which data have been pooled for each chromosome. Also presented in these tables are the frequencies of exceptional ova. Both alleles of *c(3)G* clearly induce substantial degrees of nondisjunction for all four chromosome pairs.

The procedures used to determine the autosomal nondisjunction frequencies had to be modified. Using DAVIS's estimates for the frequencies of diplo-*4* and nullo-*4* sperm from *mei-S332* males (.12 and .20, respectively) led to estimates of *c(3)G*-mediated fourth chromosome nondisjunction frequencies that were much lower than those obtained in a more direct manner (cf. Table 1). This could result from *mei-S332*-mediated nondisjunction, for the stock employed here, being lower than determined previously. This turned out to be the case, for a direct determination of *mei-S332* fourth chromosome nondisjunction (in crosses to *C(4)RM, ci ey^R/0* females) revealed a fourth-chromosome nondisjunction frequency for these males of only .14 (i.e. 1615/11360). Presumably, modifiers leading to less nondisjunction in the presence of *mei-S332* had accumulated. Selection for such modifiers is possible because *mei-S332* even in heterozygous condition (in which the stocks are maintained) causes some disruption of meiosis (DAVIS 1971). Indeed, after outcrossing the low-nondisjunction *mei-S332* stock (by replacing the sex, third, fourth, and part of the second chromosomes by recombination), *mei-S332* males gave a fourth chromosome nondisjunction frequency of .30 (i.e. 1162/3812).

As a result of these conclusions, the frequencies of major autosomal nondisjunction, quoted in Table 6, were arrived at by normalizing them with respect to fourth chromosome frequencies set equal to the frequencies which appear in Table 1. There was no way of determining what the frequency of nondisjunction was for the *mei-S332* males used in the actual tests of *c(3)G^{17}* and *c(3)G^{68}*

TABLE 6

c(3)G-*mediated autosomal nondisjunction*

	Autosomal constitution of ova producing recovered progeny				
	Regular	Diplo	Nullo	Total	Nondisjunctions per 10^3 ova
Chromosome 2					
$\frac{+}{+}$	26954	2	1	26957	0.2
$\frac{c(3)G^{17}}{c(3)G^{17}}$	6057	243	146	6446	270.6
$\frac{c(3)G^{68}}{c(3)G^{68}}$	8271	281	205	8757	407.4
Chromosome 3					
$\frac{+}{+}$	26955	2	—	26957	0.1
$\frac{c(3)G^{17}}{c(3)G^{17}}$	6086	194	166	6446	262.7
$\frac{c(3)G^{68}}{c(3)G^{68}}$	8365	172	220	8757	359.2
Chromosome 4					
$\frac{+}{+}$	26948	6	3	26957	0.7
$\frac{c(3)G^{17}}{c(3)G^{17}}$	6259	88	99	6446	179.2
$\frac{c(3)G^{68}}{c(3)G^{68}}$	8520	99	138	8757	267.5

bw/bw; *th/th*; $spa^{pol}/^{pol}$ females × *cn mei-S332/cn mei-S332*; *e/e*; *gvl/gvl* males (see Table 5). See text for procedure used to estimate nondisjunction frequencies.

(which were not performed at the same time, and which were carried out before the retest of *mei-S332*-mediated fourth chromosome nondisjunction). The frequencies of autosomal nondisjunction in $c(3)G^{+}$ females crossed to *mei-S332* males (Table 6) were normalized with respect to the frequency of spontaneous fourth chromosome nondisjunction reported in Table 1.

The difficulties just discussed do not apply to *c(3)G*-mediated *X*-chromosome nondisjunction, measured in crosses to *mei-S332* males. Such estimates are relatively independent of the behavior of the sex chromosomes in the males (since one can recover progeny from exceptional ova, if they are fertilized by regular or exceptional sex chromosome sperm, unlike the case for the autosomes). Indeed, the *X*-chromosome nondisjunction frequencies in Table 5—about .3 for $c(3)G^{17}$ and .4 for $c(3)G^{68}$—are the same as determined previously (Table 1). And, for

TABLE 7

Distribution of double exceptions produced by c(3)G *females*

Double exceptional types	*c(3)G*^{17}	*N*	*c(3)G*^{68}	*N*
XX;0	32		47	
0;22	67	0.63	82	0.84
XX;22	10		5	
0;0	11		15	
Total	120		149	
XX;0	19		46	
0;33	54	0.55	69	0.64
XX;33	8		13	
0;0	13		6	
Total	94		134	
XX;0	194		295	
0;44	267	—0.04	299	—0.05
XX;44	176		178	
0;0	332		564	
Total	969		1336	
22;0	18		20	
0;33	10	0.85	19	1.00
22;33	1		—	
0;0	2		3	
Total	31		42	
22;0	—		3	
0;44	—	—0.40	2	1.00
22;44	5		—	
0;0	2		2	
Total	7		7	
33;0	1		1	
0;44	4	0.11	2	—0.73
33;44	2		4	
0;0	1		6	
Total	8		13	

Such double nondisjunctionals involving the *X* and the second chromosome, *X* and *3*, *2* and *3*, *2* and *4*, and *3* and *4* were detected by crossing *y B/y B*; *bw/bw*; *th c(3)G/th c(3)G*; *spa*^{pol}*/spa*^{pol} females to *y/y+Y*; *cn mei-S332/cn mei-S332*; *e/e*; *gvl/gvl* males (cf. Tables 5 and 6). The *X* and *4* double exceptions are from the experiments whose results appear in Table 1 (*c(3)G* females × attached-*XY*; attached-*4* males). The expression used to calculate *N*, the degree of nonhomologous segregation, is described in the text.

each *c(3)G* allele, the *X*-chromosome nondisjunction nondisjunction frequency is roughly the same as for chromosome *2* or chromosome *3*, but about 30% greater than for chromosome *4* (Table 6). In summary, all four chromosome pairs tend to segregate homologously, under the influence of either mutant allele.

Chromosome loss is also observed in these experiments, for both alleles of

c(3)G and for almost all chromosomes. The ratios of diplo to nullo ova for the *X*, second, third, and fourth chromosomes are, respectively, .68, 1.00, .69, and .69 for $c(3)G^{17}$; and .53, .82, .47, and .56 for $c(3)G^{68}$. Thus, loss is greater in $c(3)G^{68}$ females, as was concluded earlier.

The most striking aspect of *c(3)G*-induced nondisjunction of all chromosomes involves the ova nondisjunctional for two nonhomologous chromosomes. The pattern among the four kinds of such double exceptions—considering any two nonhomologs separately—reveals that, for the three large chromosome pairs of the genome, there is a considerable degree of nonhomologous segregation. That is, for "*X–2*," "*X–3*," or "*2–3*" double exceptions, there is a preponderance of diplo-nullo and nullo-diplo types (Table 7); which results from meioses during which nonhomologs have disjoined from each other. However, when considering double exceptions involving chromosome *4* and any other chromosome (though the data for some of these are not extensive), there is in general no preponderance of the types which are diagnostic of nonhomologous segregation (Table 7).

A formula has been derived to express the degree of nonhomologous segregation, *N*, which is equal to $[1 - d_1d_2/(d_1 \times d_2)]$. Here, d_1d_2 is the frequency of diplo-diplo double exceptions, among all double exceptions for a given pair of nonhomologs (e.g. *XX;22* types among *X*-second chromosome double exceptions); d_1 is the frequency of diplo exceptions, of one kind, among double exceptions for a given pair of nonhomologs (*e.g.* the total frequency of diplo-*X* exceptions, or the frequency of *XX;22* plus *XX;0* types); and d_2 is the frequency of diplo exceptions of the other kind, among the double exceptions being considered (e.g. the frequency of *XX;22* plus *0;22* types). Thus, *N* measures the departure from independent behavior of nonhomologs (within the framework of simultaneous nondisjunction of two nonhomologous chromosome pairs), based on the observed proportion of diplo-diplo double exceptions compared to the independence expectation for this class. The diplo-diplo class does not come from nonhomologous segregation of two pairs of heterologs, and it cannot be contributed to by chromosome loss (unlike what is so for the other three kinds of double exceptions). Therefore, *N* has the desirable property that it is independent of any overall discrepencies between diplo and nullo types, which could be caused by loss superimposed on nonhomologous pairing. *N* is zero (thus no nonhomologous segregation) when the observed proportion of diplo-diplo double exceptions matches the expectation for this class based on independent behavior of heterologs. *N* is 1.0 (thus maximal nonhomologous segregation) when there are no diplo-diplo types, even if there are nullo-nullo types (which presumably result from loss).

Based on the above criteria, it is concluded that, for the large chromosomes of the genome, there are greater degrees of nonhomologous segregation in $c(3)G^{68}$ than in $c(3)G^{17}$ females (Table 7). Furthermore, for either allele of *c(3)G*, there is more nonhomologous segregation between chromosomes *2* and *3* than between the *X* and either major autosome. Chromosomes *2* and *3* are very similar in total length, and are both longer than the *X*. Also, chromosome *2* is more similar in size to the *X* than is chromosome *3* (reviewed by COOPER 1965); and

TABLE 8

Second chromosome–third chromosome double exceptions from c(3)G^{17} *females*

	Second- and third-chromosome constitutions	Constitution of ova producing recovered progeny 22;0	0;33	22;33	0;0	Total 2–3 double exceptions (number of females tested)	N
1.	$\frac{+}{+}; \frac{+}{+}$	—	—	—	—	0 (127)	—
2.	$\frac{+}{+}; \frac{c(3)G^{17}}{c(3)G^{17}}$	182	184	36	23	425 (782)	0.68
3.	$\frac{+}{+}; \frac{c(3)G^{17}}{c(3)G^{17}}$ 19°C	314	303	6	7	630 (814)	0.96
4.	$\frac{SM1}{+}; \frac{c(3)G^{17}}{c(3)G^{17}}$	174	175	53	27	429 (755)	0.56

y/y; *c(3)G^{17}/c(3)G^{17}* females were crossed in mass cultures to *y^2/Y*; *C(2L)RM, dp*; *C(2R)RM, px*; *C(3L)RM, h^2 rs^2*; *C(3R)RM* males. The only ova recoverable are those nondisjunctional for the second chromosomes and the third chromosomes. For one experiment (line 3), the mothers, though raised at 25°C, were crossed to the attached-2-and-3 males at 19°C. The inversion used in one experiment (*SM1*—line 4) is described in Table 9. See text for an explanation of the degree of nonhomologous segregation, *N*.

the values of *N* are slightly greater for *X-2* than for *X-3* double exceptions (Table 7). Since the fourth chromosome—much smaller than any other chromosome—exhibits in general no nonhomologous segregation from other elements of the genome, it is apparent that in *c(3)G* meioses, the degree of nonhomologous segregation is directly proportional to the extent to which nonhomologous elements are similar in size. This conclusion, moreover, is not dependent solely on the mathematics of the parameter *N*, but may be appreciated qualitatively by a simple examination of the distribution of segregants among the several kinds of double exceptions.

c(3)G-mediated nonhomologous segregation is temperature sensitive. In crosses of *c(3)G^{17}* females to attached-2-and-3 males (*y^2/Y*; *C(2L)RM, dp*; *C(2R)RM, px*; *C(3L)RM, h^2 rs^2*; *C(3R)RM*), which allow the recovery of second-chromosome–third-chromosome double exceptional ova, the degree of nonhomologous segregation, *N*, for females crossed at 19°C was found to be substantially greater than for such females tested at 25°C (Table 8). Lower temperature, therefore, improves chromosome segregation generally, allowing more regular disjunction (Table 1), and, among nondisjunctionals, more nonhomologous segregation.

In summary, the defective meiosis in *c(3)G* females still achieves fairly substantial degrees of directed chromosome segregations, with respect to an overall tendency for homologs to separate from each other and an ability for nonhomologs

to disjoin from each other if they are similar in size. Also, meiosis in $c(3)G^{68}$ differs from that in $c(3)G^{17}$ on three grounds, i.e. greater nondisjunction, loss, and nonhomologous segregation in the former kind of females.

c(3)G-MEDIATED NONDISJUNCTION AFFECTED BY INVERSION HETEROZYGOSITY

To further explore chromosome interactions in *c(3)G* meioses, the effects of chromosome aberrations were examined. Inversion heterozygosity accentuates disjunctional abnormalities caused by meiotic mutants in Drosophila (ROBBINS 1971, PARRY 1972). The effects on disjunction of three different inversions in heterozygous condition have been measured in females homozygous for either mutant allele of *c(3)G* and, as controls, in $c(3)G^{+}$ females: *In(1)dl-49*, a medium size *X* inversion with two euchromatic breakpoints; *In(1)FM6*, a multiply inverted *X* chromosome, one of whose breakpoints disrupts the centromeric heterochromatin; and *In(2LR)SM1*, a multiply inverted second chromosome with only euchromatic breakpoints. *X*- and fourth-chromosome nondisjunction was assessed in crosses of inversion-bearing females to attached-*XY*; attached-*4* males (Table 9—cf. Table 1). *X*- and second-chromosome nondisjunction was assessed in crosses to attached-*2* males (+/*Y*; *C(2L)RM, dp*; *C(2R)RM, px*—Table 10).

The controls confirm the results of previous investigators (STURTEVANT and BEADLE 1936, STURTEVANT 1944, COOPER 1948, COOPER, ZIMMERING and KRIVSHENKO 1955), in that an inverted chromosome in heterozygous condition with a chromosome in normal sequence leads to slight increases in nondisjunction, while heterozygosity for inversions on two nonhomologs causes substantial increases in nondisjunction (Table 9, lines 1, 3, 4, and 5—compare to Table 1, line 1). An inversion in homozygous condition has no effect (Table 9, line 2).

The control data on *X*- and second-chromosome disjunction indicate that *FM6*/+ has no effect on the second chromosomes (Table 10, line 2—compare to line 1). But, *SM1*/+ affects the behavior of chromosome *2* in two ways: Many more second chromosome exceptions (per mother) are recovered from *SM1*/+ females than from +/+ females (Table 10, line 3—compare to line 1). Among the second chromosome nondisjunctionals, the *X* and second chromosomes have not behaved independently. Thus, 45% of second-chromosome nondisjunctionals are also nondisjunctional for the *X* chromosomes, compared to less than 1% *X* nondisjunction among second-chromosome regulars (cf. Table 9, line 3, for which all progeny are second chromosome regulars). Furthermore, all 22 *X-2* double exceptions from *SM1*/+ females are cases of *X*-from-second-chromosome segregation, i.e. from *XX;0* or *0;22* ova. Nonindependent chromosome segregation is revealed most dramatically in *FM6*/+; *SM1*/+ females. Among second chromosome nondisjunctional ova from such females (Table 10, line 4), about 89% are nondisjunctional for the *X* chromosomes, compared to only 6% *X* nondisjunctions among second chromosome regulars (cf. Table 9, line 5). And, of 1474 *X-2* double exceptions from *FM6*/+; *SM1*/+ females, all are cases of *X*-from-*2* segregation (Table 10, line 4). This confirms in striking fashion the conclusions of COOPER *et al.* (1955), derived from zygotic lethality studies.

TABLE 9

The effects of inversion heterozygosity on c(3)G*-mediated nondisjunction*

Constitution of chromosomes 1, 2 and 3	Constitution of ova producing recovered progeny								Total	Nondisjunctions per 10^5 ova	
	$X;4$	$XX;4$	$0;4$	$X;44$	$X;0$	$XX;0$	$0;44$	$XX;44$	$0;0$	X	4
1. $\frac{dl\text{-}49}{+};\frac{+}{+}\cdot\frac{+}{+}$	22957	14	11	10	1	1	4	2	5	23005	3.2	1.5
2. $\frac{dl\text{-}49}{dl\text{-}49};\frac{+}{+};\frac{+}{+}$	9835	1	2	—	1	1	—	—	—	9840	0.8	0.3
3. $\frac{+}{+};\frac{SM1}{+};\frac{+}{+}$	9945	—	5	15	17	—	—	4	3	9989	2.4	4.6
4. $\frac{FM6}{+};\frac{+}{+};\frac{+}{+}$	18237	7	6	3	4	—	2	—	2	18261	1.9	0.8
5. $\frac{FM6}{+};\frac{SM1}{+};\frac{+}{+}$	7670	129	88	35	34	4	11	—	—	7971	56.5	12.0
6. $\frac{dl\text{-}49}{+};\frac{+}{+};\frac{c(3)G^{17}}{c(3)G^{17}}$	4569	500	497	254	321	56	83	85	177	6542	352.1	173.4
7. $\frac{dl\text{-}49}{dl\text{-}49};\frac{+}{+};\frac{c(3)G^{17}}{c(3)G^{17}}$	2860	331	238	209	264	55	56	59	92	4174	335.3	202.8
8. $\frac{+}{+};\frac{SM1}{+};\frac{c(3)G^{17}}{c(3)G^{17}}$	1567	247	154	213	278	31	46	72	132	2740	398.6	307.7

	Constitution of chromosomes *1*, *2* and *3*	Constitution of ova producing recovered progeny *X;4*	*XX;4*	*0;4*	*X;44*	*X;0*	*XX;0*	*0;44*	*XX;44*	*0;0*	Total	Nondisjunctions per 10^3 ova *X*	*4*
9.	$\frac{FM6}{+};\frac{+}{+};\frac{c(3)G^{17}}{c(3)G^{17}}$	1398	128	150	129	107	17	32	13	43	2017	319.2	185.9
10.	$\frac{FM6}{+};\frac{SM1}{+};\frac{c(3)G^{17}}{c(3)G^{17}}$	1189	161	129	109	155	31	37	29	90	1930	396.3	265.0
11.	$\frac{dl\text{-}49}{+};\frac{+}{+};\frac{c(3)G^{68}}{c(3)G^{68}}$	3381	471	549	414	559	122	144	95	274	6009	431.9	292.7
12.	$\frac{dl\text{-}49}{dl\text{-}49};\frac{+}{+};\frac{c(3)G^{68}}{c(3)G^{68}}$	1321	180	200	136	187	41	36	19	64	2184	396.5	236.0
13.	$\frac{+}{+};\frac{SM1}{+};\frac{c(3)G^{68}}{c(3)G^{68}}$	704	138	228	172	356	55	48	25	213	1939	534.3	457.3
14.	$\frac{FM6}{+};\frac{+}{+};\frac{c(3)G^{68}}{c(3)G^{68}}$	1525	162	248	169	223	46	61	27	99	2560	401.5	267.8
15.	$\frac{FM6}{+};\frac{SM1}{+};\frac{c(3)G^{68}}{c(3)G^{68}}$	559	93	100	90	162	27	22	18	102	1173	471.7	384.3

The inversions used (see left-most column of table) were as follows: *dl-49/+* = *In(1)dl-49, y w B/y* or *In(1)dl-49, y fa^n/y* dl-49/dl-49* = *In(1)dl-49, y fa^n/In(1)dl-49, y fa^n*, *SM1/+* = *In(2LR)SM1, al^2 Cy cn^2 sp^2/+*, *FM6/+* = *In(1)FM6, y^{s1d} sc^8 dm B/y* (see LINDSLEY and GRELL 1968, for further descriptions of these inversions). All females tested had their fourth chromosomes marked with *spa^{pol}/spa^{pol}*, and all were crossed to attached-*XY*; attached-*4* males (see Table 1). See text for an explanation of procedure used to estimate nondisjunction frequencies.

* Disjunctional data in the presence of *dl-49/+* from these two sources were nearly homogeneous (i.e., within the control or within tests of either allele of *c(3)G*), so the results of these separate tests have beeen pooled.

TABLE 10

X *and second chromosome nondisjunction*

Constitution of chromosomes 1, 2 and 3	Constitution of ova producing recovered progeny X;22	X;0	XX;0	0;22	XX;22	0;0	Total progeny (number of females tested)	*N*	*X*-chromosome nondisjunctions per 10^2 second-chromosome nondisjunctions
1. $\frac{y}{y}; \frac{+}{+}; \frac{+}{+}$	13	10	1	1	—	—	25 (1036)	1.00	14.8
2. $\frac{FM6}{y}; \frac{+}{+}; \frac{+}{+}$	2	4	1	3	—	1	11 (861)	1.00	62.5
3. $\frac{y}{y}; \frac{SM1}{+}; \frac{+}{+}$	12	41	8	14	—	—	75 (778)	1.00	43.4
4. $\frac{FM6}{y}; \frac{SM1}{+}; \frac{+}{+}$	228	155	532	942	—	—	1857 (657)	1.00	88.5
5. $\frac{FM6}{y}; \frac{SM1}{+}; \frac{TM2}{+}$	8	383	2	10	1	6	410 (505)	0.42	8.9
6. $\frac{y}{y}; \frac{+}{+}; \frac{c(3)G^{17}}{c(3)G^{17}}$	778	936	254	298	103	115	2484 (504)	0.45	47.3
7. $\frac{FM6}{y}; \frac{+}{+}; \frac{c(3)G^{17}}{c(3)G^{17}}$	798	698	248	350	55	69	2218 (422)	0.68	49.1
8. $\frac{y}{y}; \frac{SM1}{+}; \frac{c(3)G^{17}}{c(3)G^{17}}$	491	536	131	194	71	88	1511 (317)	0.36	48.5
9. $\frac{FM6}{y}; \frac{SM1}{+}; \frac{c(3)G^{17}}{c(3)G^{17}}$	673	687	229	353	44	74	2060 (281)	0.72	50.7
10. $\frac{y}{y}; \frac{+}{+}; \frac{c(3)G^{68}}{c(3)G^{68}}$	381	484	164	166	25	68	1288 (503)	0.71	49.4
11. $\frac{FM6}{y}; \frac{+}{+}; \frac{c(3)G^{68}}{c(3)G^{68}}$	495	647	232	266	37	84	1761 (415)	0.72	52.0
12. $\frac{y}{y}; \frac{SM1}{+}; \frac{c(3)G^{68}}{c(3)G^{68}}$	300	392	108	129	36	93	1058 (314)	0.45	51.4
13. $\frac{FM6}{y}; \frac{SM1}{+}; \frac{c(3)G^{68}}{c(3)G^{68}}$	525	534	175	276	58	71	1639 (308)	0.57	52.3

All females in these experiments were crossed in mass cultures to $+/Y$; *C(2L)RM, dp; C(2R)RM, px* males. The only ova recoverable are nondisjunctional for the second chromosomes. The *X* and second chromosome inversions used (*FM6* and *SM1*) are described in Table 9. *TM2* designates the third-chromosome multiple inversion (used in the experiment whose results appear in line 5) *In(3LR)Ubx*^{130}, *Ubx*^{130} *e*^{8}. See text for an explanation of the degree of nonhomologous segregation *N*. The frequencies of *X* chromosome nondisjunctions among second chromosome nondisjunctional ova were estimated by doubling the number of *X–2* double exceptions (since they are recovered relatively half as frequently as second chromosome single exceptions), and calculating proportions based on these corrected numbers.

The effects of inversion heterozygosity in *c(3)G* females indicate that these chromosome aberrations tend to interact with the effects of the meiotic mutants, increasing the extents of nondisjunction and altering the patterns of nonhomologous segregation. In Table 9, the *X*- and fourth-chromosome disjunctional data show that *dl-49/+* or *SM1/+* cause increases in nondisjunction in the presence of $c(3)G^{17}$ or $c(3)G^{68}$. *dl-49/+* increases *X* nondisjunction in $c(3)G^{17}$ by about 9% (Table 9, line 6 *vs.* line 4 in Table 1), and in $c(3)G^{68}$ by about 10% (line 11 *vs.* line 5 in Table 1). Nondisjunction of chromosome *4* is increased by *dl-49/+* in $c(3)G^{68}$ by 9%, while there is no effect of this inversion on chromosome *4* in $c(3)G^{17}$. Though these increases are slight, they are significant by chi-square contingency tests. The effects of the multiply inverted *SM1* chromosome in heterozygous condition are much greater than those of *dl-49*. *X* and *4* nondisjunction in *SM1/+*; $c(3)G^{17}$ females are increased by 23% and 72%, respectively (Table 9, line 8); and in *SM1/+*; $c(3)G^{68}$ by 36% and 71%, respectively (line 13). Again, these increases are statistically significant.

The stronger effects of *SM1/+* on *X* and fourth chromosome nondisjunction may not be simply because *SM1*—unlike *dl-49*—is a multiply inverted chromosome. For *X* and *4* nondisjunction are unaltered in the presence of heterozygosity for the *X*-chromosome multiple inversion, *FM6*. This conclusion obtains for *FM6/+*; $c(3)G^{17}$ females (Table 9, line 9), and *FM6/+*; $c(3)G^{68}$ females (line 14). *FM6/+* does, however, affect *c(3)G* meioses, for when *SM1/+* is also present, nondisjunction frequencies tend to be significantly lower than in the presence of *SM1/+* alone. In *FM6/+*; *SM1/+*; $c(3)G^{68}$ females, both *X* and *4* nondisjunction are lower than in *SM1/+*; $c(3)G^{68}$ (Table 9, line 15 *vs.* line 13); while in *FM6/+*; *SM1/+*; $c(3)G^{17}$ only fourth-chromosome nondisjunction is lower than in *SM1/+*; $c(3)G^{17}$ (Table 9, line 10 *vs.* line 8). These results are very much different from those obtained from $c(3)G^{+}$ females.

Controls performed with *c(3)G* bearing an inversion in homozygous condition suggest (though not very forcefully) that the effects of inversion heterozygosity are due to structural heterozygosity per se (as is true for $c(3)G^{+}$ females): *dl-49/dl-49*; $c(3)G^{68}$ females do not exhibit a further increase in *X*- or fourth-chromosome nondisjunction (Table 9, line 12 *vs.* line 5 in Table 1); though *dl-49/dl-49*; $c(3)G^{17}$ do show increases in *X* and *4* nondisjunction of 5% and 13% respectively (Table 9, line 7 *vs.* line 4 in Table 1).

X- and second-chromosome nondisjunction in *c(3)G* females bearing inversions was examined, both to clear up questions raised by the *X*- and fourth-chromosome experiments, and to gain information on possible interactions between inversions and nonhomologous segregation among the large chromosomes. It was predicted that the apparent failure of *FM6/+* (*vs. dl-49/+*) to affect the *X* chromosomes is the result of increased nonhomologous segregations involving the *X*'s and the major autosomes. This should result in an increase in the frequency of *X* nondisjunction. But in crosses of *FM6/+*; *c(3)G* females to attached-*XY*; attached-*4* males (Table 9) this hypothesized effect would go undetected; since an increase in the proportion of *X-2* double exceptional ova (for example) resulting from increased nonhomologous segregation would have invariably led

to zygotic lethality. Similarly, introduction of *FM6/+* into *SM1/+*; *c(3)G* females may actually lower *X*-chromosome nondisjunction, because of a greater degree of *X*-major autosome nonhomologous segregation than in *SM1/+*; *c(3)G*. Again, this would cause an appreciable proportion of *X* nondisjunctional ova to be lost because of correlated major autosome aneuploidy.

For the *X* and second chromosome disjunctional results from *c(3)G* females (Table 10), the degree of *X-2* nonhomologous segregation is computed with the expression employed for previous experiments (cf. Table 7). In the absence of inversion heterozygosity, $c(3)G^{17}$ and $c(3)G^{68}$ exhibit tendencies for *X-2* nonhomologous segregation, as was concluded from the crosses of *c(3)G* females to *mei-S332* males. Furthermore, the degree of nonhomologous segregation in $c(3)G^{17}$ is only 63% as great as in $c(3)G^{68}$: concluded from dividing the value of *N* for $c(3)G^{17}$ females (.45—Table 10, line 6) by the *N* value for $c(3)G^{68}$ females (.71—Table 10, line 10). This is in agreement with the results of the *c(3)G* × *mei-S332* crosses, for which a similar calculation implies that *X-2* nonhomologous segregation in $c(3)G^{17}$ is 75% as great as that in $c(3)G^{68}$ (cf. Table 7).

In *c(3)G* females, *FM6/+* tends to increase the degree of *X-2* nonhomologous segregations, as predicted. However, the magnitudes of the effect are different for the two mutant alleles: for *FM6/+*; $c(3)G^{17}$ females, the degree of *X-2* nonhomologous segregation is increased by 52% (Table 10, line 7 *vs.* line 6) but in *FM6/+*; $c(3)G^{68}$ females by only 2% (Table 10, line 11 *vs.* line 10). Yet *FM6/+* has the same absence of effect on *X* and *4* nondisjunction for both $c(3)G^{17}$ and $c(3)G^{68}$ (Table 9). The simultaneous effects of *FM6/+* and *SM1/+* are also equivocal. In $c(3)G^{17}$ these inverted chromosomes lead to a 60% increase in *N* (Table 10, line 9 *vs.* line 6). But in *FM6/+*; *SM1/+*; $c(3)G^{68}$ females, *N* is 30% less than in $c(3)G^{68}$ females lacking inversions (Table 10, line 13 *vs.* line 10).

The above anomalies are not inexplicable, because the effects of *SM1/+* on *X-2* nonhomologous segregation in the two mutant alleles of *c(3)G* are different. That is, *SM1/+*; $c(3)G^{68}$ exhibits a marked decrease in the degree of nonhomologous segregation, to a value which is almost 40% less than for $c(3)G^{68}$ females without inversions (Table 10, line 12 *vs.* line 10). The effect in $c(3)G^{17}$ is smaller, though in the same direction, i.e. about a 20% decrease in *X-2* nonhomologous segregation (Table 10, line 8 *vs.* line 6). This might explain why *FM6/+*; $c(3)G^{17}$ females exhibit the same *X*- and second-chromosome behavior as *FM6/+*; *SM1/+*; $c(3)G^{17}$ females, i.e. SM1/+ here has relatively little effect on the *X* and second chromosomes. *FM6/+*; *SM1/+*; $c(3)G^{68}$ females would then show, primarily, the effects of *SM1/+*, i.e. this second chromosome inversion would decrease nonhomologous segregation, and *FM6/+* would have relatively little effect.

To determine how general are the disruptive effects of heterozygosity for *SM1*, *c(3)G*-mediated second- and third-chromosome nondisjunction was examined. $c(3)G^{17}$ females heterozygous for *SM1* were crossed to attached-*2*-and-*3* males. From $c(3)G^{17}$ females without *SM1*, the value computed for the degree of second chromosome–third chromosome nonhomologous segregation is .68 (Table 8).

From the *c(3)G*^{17} × attached-*2* male crosses, the *N* value for *X*-second chromosome nonhomologous segregation is .45 (Table 10). Thus, *2–3* nonhomologous segregation is about 50% greater than *X-2* nonhomologous segregation in these females. This conclusion is in reasonably good agreement with that derived from *c(3)G*^{17} × *mei-S332* male crosses: from that experiment, *2–3* nonhomologous segregation is approximately 35% greater than *X-2* nonhomologous segregation (cf. Table 7). For *SM1*/+; *c(3)G*^{17} females, the value of *N* is some 18% less than for +/+; *c(3)G*^{17}, i.e. .56 for the inversion-bearing females (Table 8). Therefore, it appears that heterozygosity for *SM1* weakens both homologous and nonhomologous chromosome associations in the presence of *c(3)G*.

In summary, one is forced to conclude that, whereas inversion heterozygosity interacts with the effects of *c(3)G*, the quantitative nature of these interactions is unclear. In spite of the quantitative anomalies, however, it is certain that a disruption of the sequence integrity of euchromatin can have pronounced effects on *c(3)G*-mediated nondisjunction. A disruption of the basal *X* heterochromatin tends to accentuate nonhomologous segregation of the *X* from a large heterologous chromosome. But it is too early to conclude that any inversion with a heterochromatic breakpoint, or that any disruption of heterochromatin, will exert the same influence.

A final conclusion from these experiments concerns the general stability of nonhomologous pairing in *c(3)G*. The tendency for nonhomologs to separate in meiosis I of these mutant females is definite among ova which are double exceptional for the large chromosomes. However, the interchromosomal interactions which allow for eventual nonhomologous separation are not as strong, or as stable, as is possible. The frequency of *X*-from-second-chromosome segregation in *FM6*/+; *SM1*/+; *c(3)G*$^{+}$ females makes this evident. In these non-mutant individuals, the third chromosomes may be viewed as not free to interfere with *X–2* associations. That is, unlike the case of *c(3)G* meioses, the third chromosomes will presumably always undergo exchange and segregation from each other. When the thirds are free, in *c(3)G*, they are able to interfere with *X–2* nonhomologous pairing. At least is true that chromosome *3* participates in nonhomologous associations with chromosome *1* or *2* (cf. Table 7). Viewing only *X*- and second-chromosome segregation, then, one finds that many *X–2* double exceptions are not cases of nonhomologous segregation (Table 7; Table 10). Whether this is really due to the interference of the third chromosomes regarding the initial establishment of *X–2* associations, or rather because of an eventual instability of the *X-2* associations, is unclear.

The initial strength or later stability of *X–2* pairings in *c(3)G* is, however, greater than in another situation whereby all large chromosomes are, formally, free from their homologs (at least in terms of an absence of recombination). That is, females bearing *FM6*, *SM1*, and *TM2* (a third chromosome multiple inversion), all in heterozygous condition, exhibit little *X–2* nonhomologous segregation—compared to that in either *FM6*/+; *SM1*/+ or in *c(3)G* females (Table 10, line 5, *vs.* lines 4, 6, and 10). In the females carrying all three inversion chromosomes, crossing over is effectively eliminated, just as in *c(3)G*. Yet

very few double exceptions are produced (too few to imply any significant tendency for *X–2* nonhomologous segregation). And in fact the vast majority of all ova recovered (which must be nondisjunctional for chromosome *2* because of the *C(2L)RM*; *C(2R)RM* male testers employed) are nullo-*2*. This high degree of chromosome loss implies rather poor stability of chromosome associations, either because of poorly mediated associations early in meiosis or eventual destruction of them. *c(3)G* females, though defective in crossing over and disjunction, are able to carry out nonhomologous chromosome associations more effectively than females made defective by other means. Once, for example, *X-2* associations are brought about in *c(3)G*, they seem often able to remain long enough to have segregational consequences, without a great degree of chromosome loss. Thus, to compare nonhomologous segregations in *c(3)G* to the extreme case of *FM6/+; SM1/+* females is misleading. For the meiotic mutant females are capable of mediating a rather high degree of directed chromosome behavior.

c(3)G-MEDIATED NONDISJUNCTION IN *XXY* FEMALES

COOPER (1948) presented a model to explain the meiotic behavior in *XXY* Drosophila females (which have higher *X* nondisjunction than *XX* females), whereby the two *X*'s and the *Y* form a trivalent in a fraction of meioses. When this occurs, the two *X*'s always segregate from the *Y*. In the remaining meiocytes, the *Y* would not associate with the *X* chromosomes, which disjoin at anaphase I. The trivalent configurations are thus said to determine a special kind of meiotic disjunction.

GOWEN (1933) found that the presence of a *Y* chromosome in $c(3)G^{17}$ females influences chromosome behavior. These effects have been further examined. *X*-, *Y*-, and fourth-chromosome segregations were assessed in $y/y/y^{+}Y$; *c(3)G* females and, as controls, in $c(3)G^{+}$ females, all crossed to *y B/Y*; *C(4)RM*, $ci\ ey^{R}/0$ males. The controls are in agreement with previous studies: *XXY* females produce .04 *X*-exceptional gametes (Table 11, column 1—a frequency fifty times greater than for *XX* females, cf. Table 1 and BRIDGES 1916). For 314 of 316 sex chromosome exceptions, the *X*'s disjoined from the *Y*. *XXY* females heterozygous for an *X* chromosome inversion, *In(1)dl-49*, show a fifteen fold increase in *XX*-from-*Y* separations (Table 11, column 2, cf. STURTEVANT and BEADLE 1936, and COOPER 1948). Finally, *dl-49/y/Y* females heterozygous for the third-chromosome multiple inversion *TM2* show a decrease in *XX-Y* separations of nearly 20% (Table 11, column 3 *vs.* column 2, cf STURTEVANT 1944).

Fourth-chromosome nondisjunction occurs in .01 to .02 of meioses in *XXY*; $c(3)G^{+}$ females (at least a fifteen-fold higher rate than for *XX* females. cf. Table 1). This interchromosomal effect is a clear case of nonhomologous segregation in that the vast majority of fourth-chromosome exceptions (551 of 596) arose from *Y*; nullo-*4* or nullo-*Y*; diplo-*4* ova (Table 11, columns 1, 2, and 3), that is, cases where *4*'s disjoined from the *Y*.

In *XXY*; *c(3)G* females, total gametic *X* nondisjunction is .54 and .51 for $c(3)G^{17}$ and $c(3)G^{68}$ respectively (Table 11, columns 4 and 5). These are in

TABLE 11

Disjunction in XXY *females*

Constitution of ova producing recovered progeny	Sex and third chromosome constitutions 1 $\frac{X}{X};\frac{+}{+}$	2 $\frac{dl\text{-}49}{X};\frac{+}{+}$	3 $\frac{dl\text{-}49}{X};\frac{TM2}{+}$	4 $\frac{X}{X};\frac{c(3)G^{17}}{c(3)G^{17}}$	5 $\frac{X}{X};\frac{c(3)G^{68}}{c(3)G^{68}}$	6 $\frac{dl\text{-}49}{X};\frac{c(3)G^{17}}{c(3)G^{17}}$	7 $\frac{dl\text{-}49}{X};\frac{c(3)G^{68}}{c(3)G^{68}}$
$\frac{X}{Y}$							
X;4	7570	3261	3252	1194	860	1067	847
XY;4	6729	2972	2400	766	646	803	578
XX;4	161	2542	1425	471	265	505	304
Y;4	146	2706	1476	480	259	456	287
XXY;4	1	—	—	5	33	5	36
0;4	1	1	5	116	130	51	109
X;44	121	141	46	302	189	180	161
X;0	—	3	3	169	261	71	181
XY;44	1	—	1	95	114	65	81
XY;0	95	87	22	169	153	119	123
XX;44	3	17	4	117	55	60	41
XX;0	1	11	8	40	41	29	32
Y;44	2	12	3	70	55	36	33
Y;0	1	12	5	78	69	54	51
XXY;44	—	—	—	6	32	14	29
XXY;0	—	—	—	2	14	6	17
0;44	—	—	1	38	43	17	34
0;0	—	—	—	164	144	47	81
Total	14832	11765	8651	4282	3363	3585	3025
X chromosome nondisjunctions per 10^2 ova	4.2	62.1	50.6	54.1	50.6	52.6	51.7
XX-from-*Y* segregations per 10^2 ova	4.2	62.1	50.5	42.8	33.0	46.9	36.7
Fourth chromosome nondisjunctions per 10^2 ova	1.5	2.0	1.0	30.0	36.0	19.8	29.0
44-from-*Y* segregations per 10^2 ova	1.5	1.7	0.8	16.0	15.6	11.8	14.0

Such females had their *X* chromosomes marked with *y*, their *Y* chromosome marked with y^+, and their fourth chromosomes marked with spa^{pol}/spa^{pol}. The *dl-49* inversion used (columns 2, 3, 6 and 7) was *In(1)dl-49, y fa*^{n}. *TM2* is a third-chromosome multiple inversion (column 3) described in Table 10. The *XXY* females were tested by crossing to *y B/Y; C(4)RM, ci ey*^{R}*/0* males. In such crosses, sex-chromosome exceptions (from *XX*, *Y*, *XXY*, or nullo-*XXY* eggs) are recovered relatively half as frequently as sex-chromosome regulars or fourth-chromosome exceptions; so the gametic nondisjunction frequencies (at the bottom of each column) were estimated by doubling the number of sex-chromosome exceptions then calculating frequencies from these corrected numbers. The recoveries of *XXY* ova are no doubt underestimated, since such eggs are recovered as *XXYY* females, which are poorly viable.

creases (compared to *XX*; *c(3)G* females) in *X* nondisjunction of 67% for *c(3)G*^{17} and of 29% for *c(3)G*^{68} (cf. Table 1). The frequencies in *XXY*; *c(3)G* females are of course much lower than would be expected if an *XXY* trivalent formed in all *c(3)G* meioses, followed by obligatory *XX*-from-*Y* disjunction.

One striking aspect of these experiments is that this is the only case in which nondisjunction is greater in *c(3)G*^{17} than in *c(3)G*^{68}. Moreover, the nondisjunction in *XXY*; *c(3)G*^{17} females is higher in a very specific way: Cases where all sex chromosomes or no sex chromosomes move to a pole (*XXY* and nullo-*XXY* ova) amount to about .11 of ova in *c(3)G*^{17}, about .17 in *c(3)G*^{68}. But cases of *XX*-from-*Y* separation are more frequent in *c(3)G*^{17} than in *c(3)G*^{68}, i.e. .43 *vs.* .33. For both mutant alleles, the distributions of sex chromosome ova types are not in agreement with expectations based on random distribution of the two *X*'s and the *Y* at the first meiotic division, in spite of the fact that the overall nondisjunction frequencies are about .5. The departures from such expectations are in the direction of a tendency for the two *X*'s to separate from the *Y*; and the departure is greater for *c(3)G*^{17}.

If *XX*-from-*Y* segregation is viewed as a type of disjunction, and not nondisjunction, these results are consistent with the fact that *c(3)G*^{68} has repeatedly exhibited a more defective meiosis than has *c(3)G*^{17} (i.e. higher overall frequencies of nondisjunction—Tables 1, 5, and 6—and more chromosome loss—Table 2). *c(3)G*^{68} may be viewed as carrying out *XXY* trivalent associations which are less stable than those in *c(3)G*^{17}; such that, in the former, the trivalents are initially formed less often, or fall apart in higher frequency, resulting in fewer *XX-Y* separations, but more cases of *XXY-0* nondisjunction. However, if *XXY* trivalents are a type of nonhomologous pairing (since the *Y* is not strictly speaking a homolog of the *X*'s in these females), then it would seem that *XXY*; *c(3)G*^{68} females should show more *XX-Y* separations than *XXY*; *c(3)G*^{17} (cf. Table 7). They do not.

In summary, two *X* chromosomes tend to disjoin from the *Y* chromosome in *c(3)G* meioses, and differently for the two alleles of *c(3)G*. Thus, as in the case of homologous nondisjunction and nonhomologous segregations, these females are capable of effecting directed chromosome disjunction.

It should be that the amount of *XX-Y* separation in *c(3)G* is less than what is possible in *XXY; c(3)G*$^{+}$, because, in the former, the major autosomes must be able to interfere with *XXY* trivalent formation via nonhomologous pairing. The prediction is confirmed, in that *dl-49/y/Y; c(3)G*$^{+}$ females show 45% more *XX-Y* separation than do *c(3)G*^{17} females and 88% more than do *c(3)G*^{68} females. In *dl-49/y/Y*; *c(3)G*$^{+}$ virtually all sex chromosome exceptions (5300/5301) are the result of *XX-Y* disjunction. The autosomal interactions with the sex chromosomes in *XXY*; *c(3)G*—which are presumed to cause relatively low levels of *XX-Y* disjunction and high degrees of *XXY-0* nondisjunction—may be analogous to those which occur in *dl-49/y/Y*; *TM2/+* females, in which the extent of *XX-Y* separation is reduced and the degree of *XXY-0* nondisjunction is increased (both in comparison to *dl-49/y/Y* females without *TM2*). The effects of chromosomes *2* and *3* in *c(3)G* are, however, much greater than in the case of *TM2/+* females (e.g. *XXY-0* nondisjunction in *dl-49/y/Y; TM2/+*, while

increased, is only 6/2927 total sex chromosome exceptions), because, in the latter, the second chromosomes are usually not available to disrupt the behavior of the sex chromosomes.

These conclusions now enable one to explain why *XX*-from-*Y* separations are less frequent in $c(3)G^{68}$ than in $c(3)G^{17}$. The extent of nonhomologous segregation among the *X* chromosomes and second chromosomes, or among the *X*'s and thirds, is greater in $c(3)G^{68}$ than in $c(3)G^{17}$ (cf. Table 7). Thus, *X-2*, *X-3* pairings, in meioses of *XXY*; $c(3)G^{68}$ females would—more often than in *XXY*; $c(3)G^{17}$—prevent the formation of *XXY* trivalents.

The meiotic behavior of chromosome *4* is also affected in *XXY; c(3)G* females. In comparison with *XX*; *c(3)G*, fourth-chromosome nondisjunction in $c(3)G^{17}$ is increased by 67%, and in $c(3)G^{68}$ by 35% (Table 11, columns 4 and 5—compare to Table 1). These increases are ostensibly not the result of *Y-4* nonhomologous pairings and segregation, since only about half of the fourth chromosome exceptions—for either mutant allele—are cases of *4*-from-*Y* disjunction (Table 11).

Experiments performed with *dl-49/y/Y*; *c(3)G* females provide a possible explanation for the effects of the *Y* on the fourth chromosomes. As is observed for *c(3)G* females without a *Y* chromosome, or $c(3)G^{+}$ females with a *Y* chromosome, *X* chromosome inversion heterozygosity affects chromosome behavior. *In(1)dl-49/y/Y* females homozygous for either mutant allele of *c(3)G*, show increased *XX-Y* separation in comparison with females having both *X* chromosomes in normal sequence (Table 11, columns 6 and 7 *vs.* 4 and 5 respectively). These statistically significant increases—about 7% for $c(3)G^{17}$ and 11% for $c(3)G^{68}$—are qualitatively similar to that observed in $c(3)G^{+}$ females. However, in the mutant females, (a) the increases are not as great, (b) the overall proportions of sex chromosome exceptions remain unchanged, and (c) there are still appreciable frequencies of *XXY-0* ova. For the fourth chromosomes, the effect of *X*-chromosome inversion heterozygosity is to virtually *abolish the increases in nondisjunction induced by a Y chromosome*. The data in Table 11 reveal that fourth-chromosome nondisjunction in either *dl-49/y/Y*; $c(3)G^{17}$ or *dl-49/y/Y*; $c(3)G^{68}$ (columns 6 and 7) is nearly the same as in *XX* females (cf. Table 1)—but substantially lower than in *XXY* females without the inversion (columns 4 and 5).

These results imply that (1) the structural integrity of euchromatic chromosome sequences can be an important factor in determining chromosome behavior in *c(3)G* meiosis (the same conclusion derived from inversion experiments in *XX; c(3)G* females); (2) the *Y* chromosome, in *XXY; c(3)G*, can disrupt the the behavior of the fourth chromosome by pairing nonhomologously with them (as occurs in *XXY; c(3)G*$^{+}$)—but, though fourth chromosome nondisjunction is increased via this disruption by a nonhomolog, the associations are not stable enough to lead to *4*-from-*Y* segregations; (3) introduction of *X*-chromosome inversion heterozygosity in *XXY; c(3)G* females leads to more *XXY* trivalents, such that the *Y* chromosome is *less often free* to pair with and disrupt the behavior of the fourth chromosomes; (4) therefore, in all kinds of *c(3)G* females

(with and without a *Y*, with and without inversions), the fourth chromosomes are able to pair nonhomologously with other elements, but not in a manner stable enough to lead to specific kinds of separations from the other chromosomes (Table 7). This hypothesis explains, for instance, the substantial increases in fourth-chromosome nondisjunction in *SM1/+; c(3)G* (Table 9) as an increase in second chromosome–fourth chromosome nonhomologous pairing which further disrupts the ability of the *4*'s to pair with and separate from one another. Also, the nonindependent behavior of the *X* and fourth chromosomes in *c(3)G* (Table 4) may well be due to *X-4* nonhomologous pairings, the results of which are that the *X*'s sometimes interfere with fourth-chromosome disjunction, and vice versa; but these interactions do not lead to nonhomologous segregations.

DISCUSSION

Some investigators who have reported on the properties of $c(3)G^{17}$ have concluded, or strongly implied, that the mutant affects meiosis by directly disrupting exchange. SMITH and KING (1968), confirming the result of MEYER (1964), reported that there is no synaptonemal complex in $c(3)G^{17}$ oocytes, and concluded that $c(3)G^{+}$ is directly concerned with the construction of the complex along paired homologous chromosomes. Thus, $c(3)G^{+}$ would be directly involved in crossing over, since the synaptonemal complex is presumed to mediate that process in higher organisms (MOSES 1968, 1969). SMITH and KING also argued that the complex influences chromosome segregation by helping to "position" homologs such that they are properly oriented toward the first meiotic division poles. Thus, $c(3)G^{17}$ females, without the complex, would have defective segregation. WATSON (1969) presented evidence for the hypersensitivity of $c(3)G^{17}$ oocytes to the induction of chromosome damage by ionizing radiations. He concluded that the meiotic mutant directly disrupts exchange (being deficient in an enzyme necessary for recombination)—by analogy with recombination-deficient, radiation-sensitive mutants in *E. coli* (see, for example, HOWARD-FLANDERS and BOYCE 1966).

Neither of these conclusions is necessarily correct. Crossing over between homologous chromosomes requires not only the breakage and reunion events, but also the successful establishment of certain preconditions. For instance, in the absence of recognition of homologous chromosomes for one another, or in the absence of synapsis of these homologs, crossing over cannot occur. Thus, appealing to the logic of blocks in a pathway allows the possibility that *c(3)G* disturbs a precondition to crossing over. It is not difficult to imagine, for example, how improper homologous recognition could lead to both an absence of crossing over and meiotic nondisjunction. Such a defect could also explain why there is no synaptonemal complex in *c(3)G* oocytes, since its construction along bivalents must require the juxtaposition of homologs. Further, asynapsis of homologous chromosomes could result in radiation hypersensitivity if proper synapsis promotes the repair of induced chromosome defects (as discussed in general terms by THOMPSON 1962).

HINTON (1966) suggested that the effects of *c(3)G* might be understood in terms of R. GRELL's distributive pairing pool model (reviewed in 1969, and further elaborated in 1970), or with respect to NOVITSKI's chromocentral association model (1964). It is proposed here that the former model is best applied to *c(3)G* in regard to a direct elimination of exchange by the mutant, but that the latter scheme is applicable if *c(3)G* affects a precondition to exchange.

The distributive pairing pool model is the most elegant one proposed to deal with the disjunctional fate of nonexchange tetrads in Drosophila females. Briefly, Grell proposes that homologous chromosomes associate early in meiosis I, undergo exchange or not, and if not, go into a "distributive pool." For a population of meiocytes in normal females, the chromosomes in this pool would be four to five percent of *X* chromosomes and all fourth chromosomes. Such nonexchange chromosomes have a second opportunity to pair, but, now, association of elements is not based on homology, but rather on size similarity (R. GRELL 1969, E. GRELL 1970, MOORE 1970). Thus, for normal females, the two *X*'s (if they are in the pool) and the two *4*'s would pair with one another, insuring segregations from the distributive pool that would be the same as the results of segregations determined earlier (i.e. at the time of exchange). However, in abnormal situations, nonhomologous segregations—resulting from nonhomologous pairing in the distributive pool—would occur. For example, a *Y* chromosome (in *XXY* females) and a nonexchange second chromosome (resulting from, say, inversion heterozygosity) would pair in the distributive pool with high probability—because of the size similarity of these nonhomologous elements—and disjoin from each other.

The meiotic behavior of *c(3)G* seems explicable in the framework of the distributive pairing model. If one imagines that, in homozygous *c(3)G* females, homologous chromosomes associate, but exchange is eliminated because of the meiotic mutant, then all eight chromosomes would go into the distributive pool. Which elements would associate is now a very complex matter. Chromosomes *2* and *3* are very similar in size, so these elements could associate in an homologous pairwise fashion or in a nonhomologous manner. But the *X* chromosome is not very dissimilar in size from the major autosomes, so *X-2* and *X-3* nonhomologous pairings might also be expected to occur, though perhaps with lower probabilities than *2–2*, *3–3*, or *2–3* associations. The fourth chromosomes, much smaller than any of the other chromosomes, should not segregate nonhomologously from them in any appreciable frequency. The situation, already complex, becomes more so if one imagines that more than two elements can sometimes associate in the distributive pool, e.g. an *X* with two second chromosomes, two *X*'s with a *2* and *3*, and so forth. The precise array of gametes produced by *c(3)G* females in terms of this model—considering all eight chromosomes—is impossible to predict. However, at least qualitatively, there should be (a) a tendency for homologs (identical in size) to disjoin from each other, and (b) the possibility of nonhomologs disjoining from each other, such that there is a greater degree of second chromosome-third chromosome nonhomologous segregation than *X-2* or *X-3* nonhomologous segregations, which are in turn greater than any nonhomologous segregations involving chromosome *4*. These predictions are fulfilled, and

therefore, the general segregational behavior of chromosomes in *c(3)G* is consistent with the idea that the mutant simply eliminates exchange.

A corollary to the distributive pairing model is that the fourth chromosomes (always from nonexchange tetrads) always undergo distributive pairing. In this light, it is significant that, in *c(3)G*, fourth chromosome nondisjuunction is highly temperature sensitive (far more so than, at least, *X*-chromosome nondisjunction), just as is the degree of nonhomologous segregation for the nonexchange second and third chromosomes.

Several findings in the present investigation, however, indicate that the effects on meiosis of *c(3)G* are not fully comprehensible in terms of the elimination of exchange and the properties of the distributive pool. According to the model, two alleles which directly eliminate exchange should produce the same array of gametes. $c(3)G^{17}$ and $c(3)G^{68}$ must affect meiosis via a disruption of the same meiotic process, and females homozygous for either allele are indeed equally defective in crossing over. Yet they are quite different in their disjunctional behaviors by the criteria of nondisjunction frequencies, loss, and types of nonhomologous chromosome segregations. Moreover, the effects of the two mutant alleles are differentially sensitive to the effects of inversions; and chromosome behavior influenced by $c(3)G^{17}$ and $c(3)G^{68}$ is different in *XXY* females. The effects of inversion heterozygosity indicate, further, that it is not only chromosome size which can influence nonhomologous segregations. In summary, it would seem that, to explain the disjunctional differences regarding the two mutant alleles of *c(3)G* in terms of distributive pairing, necessitates the proposal that the meiotic mutants disrupt exchange and—at a later meiotic stage—differentially affect chromosome behavior in the distributive pool.

The model of SMITH and KING (1968)—whereby the simple absence of synaptonemal complexes is determinant for nondisjunction—would predict that $c(3)G^{17}$ and $c(3)G^{68}$ females should have the same amounts and patterns of nondisjunction. If it can be assumed that $c(3)G^{68}$ females have no complex, then this prediction fails.

c(3)G can be understood in terms of a defect at only one meiotic stage, if one postulates the disruption of an early event in meiosis, before crossing over (cf. GOWEN 1933, and SANDLER *et al.* 1968). NOVITSKI (1964) proposed a model which states that all chromosomes in Drosophila females associate at their centromere regions "in a chromocentral type of configuration prior to the time of synapsis and crossing over." This configuration facilitates the later synapsis of homologs. That is, bringing all chromosomes together at one place obviates the necessity for "long range pairing forces" involving each pair of homologs separately. Once in this advantageous position at the chromocenter, homologous chromosomes would achieve a "synaptic configuration," allowing both exchange and the eventual separation of homologs. A disruption of meiosis that disallowed —to some degree or completely—the achievement of homologous synapsis could allow chromocentral nonhomologous associations to become determinant for segregation.

It is proposed, then, that in *c(3)G* homozygotes, chromocenter formation is

normal. Moreover, from the results of the *XXY*; *c(3)G* experiments, it is submitted that the chromocenter involves all four pairs of chromosomes, even the fourth chromosomes. That is, though the *4*'s do not undergo nonhomologous segregations, they are involved in nonhomologous pairings. Once chromocenter formation is complete, it must be altered in such a manner that synapsis of chromosomes can begin. This process is totally absent in $c(3)G^{17}$ and in $c(3)G^{68}$. No synapsis, no synaptonemal complex formation, and no exchange occurs. The establishment of the chromocenter, however, is such that specific types of homologous and nonhomologous associations can be effected. That is, the *c(3)G* gene product is concerned—still at this early stage of meiosis—with stabilizing the overall associations among elements at the chromocenter. That *c(3)G* is involved in such hypothetical stabilizations is indicated by the different meiotic behaviors of $c(3)G^{17}$ and $c(3)G^{68}$ females. The differentially defective gene products, presumed to be produced under the control of these two different mutants, lead to stabilizations which are different among the various chromosomes, and thus, to arrays of ova types which are different on several grounds.

The suggestion has been made that nonhomologous pairing in Drosophila females concerns only the constitutive heterochromatin, localized near the centromeres of all chromosomes (SANDLER and NOVITSKI 1956, NOVITSKI 1964). It is tempting to propose that this is the case with respect to the determination of segregations in *c(3)G* females. That is, heterochromatic homologous and nonhomologous pairings would occur, but there would be no synapsis involving euchromatic chromosome segments. Consistent with this notion are the observations that crossing over can be induced in *X*-chromosome heterochromatic regions in $c(3)G^{17}$ females with ionizing radiations (ROBERTS 1969); but recombination cannot be so induced in euchromatic regions (WHITINGHILL 1938). However, it was found that heterozygosity for inversions with only euchromatic breakpoints—in either *XX* or *XXY* females—alters both the amounts and patterns of nondisjunction in *c(3)G* females. Thus, the proposal that chromocenter formation in *c(3)G* is mediated via heterochromatic pairings is not sufficient.

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