*INTERCHROMOSOMAL EFFECTS AND SEGREGATION**

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Among the major unsolved problems of meiosis is the so-called "interchromosomal effect," or apparent rise in crossing over that occurs within one pair of homologous chromosomes when crossing over is suppressed in heterologous pairs by means of inversions.[1] Thus suppression of crossing over in either or both of the large autosomal pairs of female *Drosophila melanogaster* is apparently accompanied by an increase in crossing over in the X chromosomes. Since crossover X chromosomes very rarely (frequency $\leqslant 0.0001$) fail to segregate, and since nondisjunctional X chromosomes are derived almost exclusively from noncrossover pairs,[2] it would be expected that the suppression of crossing over in autosomes would be accompanied by a *decreased* rate of nondisjunction of X chromosomes. Sturtevant (1944),[3] however, has made the unexpected and remarkable discovery that heterozygous autosomal inversions may greatly *increase* the rate of nondisjunction of X chromosomes. Sturtevant's observation will now serve as the point of departure for a new investigation and interpretation of interchromosomal effects.

Hypothesis

As an example of the interchromosomal action on nondisjunction, X chromosomes of the constitution *sc, In dl-49 v, In* B^{M1}/y^2w^av, give about 0.3–0.6 per cent primary nondisjunction. However, when *Ins Cy*$(2L + 2R)$ are made heterozygous in chromosome-2, these two X chromosomes undergo from 4.5 to 6.5 per cent primary nondisjunction.

Our hypothesis to account for such effects is this: (1) If a pair of chromosomes is heterozygous for a sizable structural rearrangement, then the homologues pair with difficulty, presumably owing to a conflict of pairing tendencies along the chromosomes, as, for example, to each side of break points. Nevertheless, if but one chromosome pair of a set is structurally heterozygous, bivalent formation is essentially normal in frequency; hence so also is segregation. This notion is common to most genetic thinking today. However (2), when two different pairs of chromosomes are structurally heterozygous, they may pair as homologous sets *or* as nonhomologous complexes. In the former case normal segregation results. In the latter, "nondisjunction" of one or more chromosomes may occur by dissociation of the complex of nonhomologous partners to give randomly directed univalents, or the multivalent complex may give aneuploid segregants. For the present it is unimportant whether the nonhomologous pairing is assumed to occur euchromatically, heterochromatically, or both euchromatically and heterochromatically. The significant and new assumption is that nonhomologous pairing will occur under conditions of complex structural heterozygosity.

This general hypothesis predicts, then, that there will be a production of *dominant lethals* (by the formation of aneuploid oöcytes unrestorable to euploidy by normal sperm) when the X chromosomes and one autosomal pair are both structurally heterozygous; that an increase in dominant lethals in excess of that to be expected

from O-egg by Y-sperm fertilizations will occur; and that autosomal nondisjunctions (at least in principle) shall be demonstrable; finally, in the presence of structurally homozygous X chromosomes, structural heterozygosity of both autosomes should give a large increase in dominant lethals *without* an accompanying increase in primary nondisjunction of the X chromosomes. As will be shown, results so far bear out all these predictions.

EXPERIMENTS

Seventeen stocks of inversions have been cytologically analyzed in preparation for the experiments. Except for one,[4] all showed the rearrangements with limits the same, or closely similar to, those previously recorded.[5] These were made up in heterozygous combinations, eggs were collected, and their hatching or nonhatching was scored. Adult progenies were reared from aliquots in order to shorten the duration of each experiment. The results of these experiments are set forth in Table 1.

TABLE 1

CORRELATION OF PRODUCTION OF DOMINANT LETHALS (DOM. L.) WITH (1) OPPORTUNITIES FOR NONHOMOLOGOUS ASSOCIATION AND (2) OCCURRENCE OF NONDISJUNCTION OF THE SEX CHROMOSOMES

References in text are by item row and column number, e.g., F5, K9, etc. Single experiments are A + B, C + D, E + F, G + H + I + J, and K + L + M + N. In F8 no *Cy L*[4] exceptional ♀ ♀ appeared, despite *5L*[4] and *7* + exceptional ♀ ♀; this *Cy L*[4] class appears to be inviable in the experiment.

	Constitution			Egg Counts			Adult Counts			
					%	%		Exceptions		Per Cent
	X/X	II/II	III/III	No.	Hatch	Dom. L.	No.	♀	♂	XX-O
Item	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)		(9)
A	*dB*/+	+/+	+/+	5,248	91.3	..	4,210	7	6	0.6
B	*dB*/+	*Cy*/+	+/+	6,499	76.6	14.7	4,033	40	43	4.1
C	*dB*/+	+/+	+/+	4,439	95.7	..	4,593	5	7	0.5
D	*dB*/+	*Cy*/+	+/+	5,258	81.9	13.8	3,933	12	52	5.2
E	*sA*/+	+/+	+/+	5,480	94.0	..	4,503	2	4	0.3
F	*sA*/+	*Cy*/+	+/+	3,771	81.8	12.2	2,170	12(24?)	33	4.1(5.1?)
G	*dB*/+	+*/+	+*/+	3,883	97.7	..	1,896	0	1	0.1
H	*dB*/+	*dp*/+	+*/+	3,537	61.4	36.3	3,106	88	81	10.3
I	*dB*/+	+*/+	*P*/+	2,775	82.1	15.6	4,057	136	98	10.9
J	*dB*/+	*dp*/+	*P*/+	3,904	50.8	46.9	2,518	141	161	21.4
K	+/+	+/+	+/+	3,041	96.6	..	4,568	1	1	0.09
L	+/+	*Cy*/+	+/+	3,268	93.7	2.9	7,707	1	0	0.03
M	+/+	+/+	*C*/+	3,413	87.1	9.5	5,875	0	0	...
N	+/+	*Cy*/+	*C*/+	3,608	71.4	25.2	3,709	0	0	...
Total				58,124			56,878	485	487	

X-Chromosomes: + = *y*[2]*w*[a]*v*; *dB* = *sc*, *In dl-49 v*, *In B*[M1]; *sA* = *In sc*[7], *In AM*. 2-Chromosomes: + = wild-type sequence, no markers; +* = wild-type sequence, marked by *Bl*; *Cy* = *In Cy*(2*L* + 2*R*), *L*[4]; *dp* = *Ins dp*(2*LR*). 3-Chromosomes: + = wild-type sequence, no markers; +* = wild-type sequence, marked by *R Ly*; *C* = *Ins C*(3*LR*), *D*; *P* = *Ins P*[ra](3*L* + 3*R*).

RESULTS AND CONCLUSIONS

1. Whether structurally heterozygous (Table 1, items A, C, E, G) or not (K), it is clear that nondisjunction of X chromosomes is negligible (0.09–0.6 per cent) when the pairs of major autosomes are structurally homozygous.

2. When X's are structurally homozygous, but one (L, M) or both (N) major autosomes are structurally heterozygous, the X chromosomes likewise segregate normally, and their nondisjunction rate (0.0–0.03 per cent) is no greater than when the autosomes are both structurally homozygous (K; XX-O, 0.09 per cent [see Table 1]).

3. However, nondisjunction of structurally heterozygous X's is vastly increased when either major autosome is structurally heterozygous (compare AB, CD, EF, and GHI).

4. Furthermore, when two different structural rearrangements of X that give equal frequencies of secondary disjunction are employed (*In sc*^{7}, *In AM* and *In dl-49*, *In B*^{m1} both give approximately 80 per cent X'X-Y)[6], then the rate of primary nondisjunction is raised to a similar degree by the same autosomal structural heterozygote (compare AB and CD and EF).

5. The degree to which structurally heterozygous X's undergo primary nondisjunction is evidently a function of the particular heterozygous combination employed within the autosome and not of the autosome involved (cf. AB and CD with GH).

6. The nondisjunction of the structurally heterozygous autosome (A*i*/A) is accompanied by the production of dominant lethals (col. 6). It is very significant that the excess of dominant lethals over the corresponding control rate cannot be accounted for by dying OY zygotes (which are to be estimated as one-quarter the frequency of nondisjunction [col. 9]). This is readily seen by comparing columns 6 and 9.

7. Nor can the excess of dominant lethals be accounted for by increased crossing over *within* the heterozygous inversions in X, hence by a class of O-eggs produced by 4-strand doubles within inversions. This follows from the fact that male and female exceptions are approximately equal in number. Were such O-eggs produced in detectable numbers by 4-strand doubles, then the male exceptions should exceed the female exceptions, which they do not (col. 8).

8. The excess dominant lethals are probably produced by a number of factors, of which nondisjunction of autosomes is perhaps chief. Although it is possible that as few as 2.9 per cent dominant lethals may arise in eggs of *In Cy* (*2L* + *2R*) heterozygotes (Table 1, L6) by 4-strand double exchanges, it is highly unlikely that 9.5 per cent dominant lethals (M6) could be thus formed in *Ins C*(*3LR*) heterozygotes, possessing, as the bivalent does, 7–8 consecutive breaks along the midlength. The high frequency of dominant lethals in this case (M6) is held to be due in fair or even in chief part to primary nondisjunction of chromosome-3. The conclusion by Sturtevant and Beadle[2] that structural heterozygosity of X chromosomes does not affect their segregation probably cannot be transferred without reserve to statements about autosomes. Here the possession by an autosome of two limbs must greatly enhance the steric problems of pairing and conjunction in the structural heterozygote.

9. The over-all excess of dominant lethals is taken to come about, therefore, by autosomal nondisjunction that gives rise to aneuploid gametes possessing either A*i* A, or no-A, i.e., for one or both pairs of autosomes. Such gametes would yield lethal zygotes only and hence would seem to carry dominant lethals, for normal sperm complements could not restore their autosomal deficiency (or excess) to a viable combination. That at least some dominant lethals arise in this way has been proven by mating X*i*/X, *In Cy*(*2L* + *2R*)/+ by males heterozygous for *T*(2; 3), *rn; Gl; Sb*. From this cross, individuals that receive from their mother both, or neither, 2-chromosome can be recognized, since the *T*(2; 3), *rn* ♂ gives A^2A^2, A^3 sperm as well as no-A^2, A^3 sperm.[7] Such autosomal exceptions occur.

10. Finally, it is clear that a nonhomologous interaction is not limited to X*i*/X and A*i*/A and does not involve anything peculiar to X chromosomes, for A^2i/A^2, A^3i/A^3 also produce a large excess of dominant lethals (cf. Table 1, KLMN).

The foregoing results, therefore, demonstrate that the predictions from our hypothesis are in agreement with the experimental facts—namely, that dominant lethals are in fact produced when two or more pairs of major chromosomes are made structurally heterozygous, that these dominant lethals cannot be accounted for by 4-strand double exchanges within inversion loops, that nondisjunction of autosomes does occur, and that structural heterozygosity of both autosomes gives a large increase in dominant lethals without increasing the rate of primary nondisjunction of structurally homozygous X chromosomes. The postulated mechanism would tend to eliminate selectively from the class of viable zygotes those eggs which at meiosis had low-rank, or potentially low-rank, tetrads. Conversely, it would accordingly give an apparent increase in the proportion of recovered multiple exchanges, i.e., an "interchromosomal effect on crossing over."

SUMMARY

It has been proved for *D. melanogaster* that the interactions at meiosis between nonhomologous chromosomes that are structurally heterozygous result in the production of dominant lethals as well as of primary nondisjunction. Such interactions may occur between any two (or three) pairs of structurally heterozygous chromosomes and need not involve the X chromosomes. Not only does nondisjunction of X chromosomes occur but also nondisjunction of autosomes. It is shown that the preponderance of dominant lethals cannot be accounted for by the production of eggs deficient in sex chromosomes or by multiple-strand crossing over within inverted sequences of either X chromosomes or autosomes. A hypothesis that predicted these findings, and which will partially account for an interchromosomal effect on crossing over, is briefly described.

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[4] *Ins dp(2LR)* apparently includes also a genetically demonstrable, but cytologically invisible, translocation with chromosome 3.

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