NONRANDOM SEGREGATION OF CHROMOSOMES IN DROSOPHILA MALES[1]

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CHROMOSOMES which for some reason remain unpaired during prophase I of meiosis (univalents) are frequently not included in any of the meiotic products. In many organisms their loss has been shown to result from failure to align on the metaphase plate, from "lagging" on the anaphase spindle, or from misdivision of the centromere. Where there are two or more univalents their inclusion into a nucleus is usually at random; where two homologues are unpaired, disjunctional and nondisjunctional segregation would have equal expectations.

In order to explain the array of frequencies of gamete types formed by a male *Drosophila melanogaster* carrying a deficient X chromosome along with a normal Y, GERSHENSON (1933) and later SANDLER and BRAVER (1954) assumed meiotic loss of unpaired chromosomes. It will be shown in this paper that in fact there is no chromosome loss (an observation also made by COOPER [1964]) and that the behaviour of univalents has revealed some previously unsuspected properties of meiosis in the Drosophila male.

In both of these studies cited above, the X chromosome used was derived as a crossover product from a female having a different scute (*sc*) inversion in each of the X chromosomes. Both $In(1)sc^4$ and $In(1)sc^8$ have similar distal breakpoints; their proximal breakpoints, in the basal heterochromatin, are positioned such that the crossover chromosome $Ins(1)sc^4\text{-}sc^8$, carrying the distal region of $In(1)sc^4$ and the proximal region of $In(1)sc^8$, is deficient for a considerable portion of the basal heterochromatin. This chromosome, the $sc^4\text{-}sc^8$X, thus lacks most of the region of the X which is normally involved in pairing with the Y chromosome (COOPER 1959). The expectation that this chromosome might frequently fail to synapse with the Y at meiosis is supported by the observation of SANDLER and BRAVER that a high proportion of the gametes formed by these males are nondisjunctional (nullo and XY). The unusual feature of their results was that the complementary classes in both disjunctional and nondisjunctional gametes were not recovered in equal frequencies: the recovery of the X was approximately double that of the Y, and the nullo gametes were in great excess of the XY class. The experiments excluded any explanation in terms of viability and the conclusion was reached that, in primary spermatocytes in which the X and Y were unpaired at metaphase I, some meiotic loss occurred during

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anaphase I. Since the total recovery of the Y chromosome was considerably less than that of the sc^4-sc^8X, SANDLER and BRAVER further assumed that the univalent Y had a greater tendency to be lost than did the X. Analysis of the data suggested that the Y was lost from some 42% of the cells in which synapsis had not been achieved, whereas the X was not lost in any significant frequency.

Subsequently ZIMMERING (1963) has shown that the frequencies of gamete types obtained from a sc^4-sc^8 male are changed considerably, if the male is raised at 18° rather than at 25°C. At 18° the complementary classes, of both disjunctional and nondisjunctional gametes, approach equality. Even though the overall frequency of nondisjunctional gametes is reduced to less than half the 25° value, ZIMMERING indicated that it was unnecessary to invoke any change in the frequency of synapsis, and that the results could be interpreted solely on the basis of the assumption that meiotic loss of the Y is markedly reduced at the lower temperature. His argument that pairing is unchanged rests on the observation that a specially constructed chromosome containing the basal region of the X and both arms of the Y (X^PY^L·Y^S) also showed a reduced frequency of loss at 18°C, and in this case, since there is no pairing partner, the change in rate of loss is certainly independent of synapsis.

The present paper reports some combined cytological and genetic analyses of the meiotic behaviour of the sc^4-sc^8 male. It is shown that the sc^4-sc^8X frequently fails to synapse with the Y, but there is a negligible amount of loss of either of these univalents in the subsequent stages of meiosis. A striking property of the univalents is that their segregation at first anaphase is highly non-random. As a general rule, both the X and Y proceed to the same pole, the frequency of nondisjunction being directly comparable to the frequency of failure of synapsis. An interpretation of the array of gamete types is given in terms of meiotic drive.

MATERIALS AND METHODS

SANDLER and BRAVER used a Y chromosome which carried the wild-type allele for yellow body colour (y^+Y, or sc^8Y, of MULLER 1948) thereby enabling the Y to be followed throughout the crosses so that a complete genetic analysis could be made directly. This and several other marked Y chromosomes were used in the present studies with the X chromosome, *Ins(1)*sc^4-sc^8, y. The other Y chromosomes were: YB^S, carrying the dominant marker Bar (of Stone) on the tip of Y^L (BROSSEAU and LINDSLEY 1958); Yw^+, with the wild-type allele of white on Y^S (BROSSEAU, NICOLETTI, GRELL and LINDSLEY 1961); B^SYy^+, with Bar on Y^L and y^+ on Y^S (BROSSEAU 1958). In all crosses, individual males were mated with three females for two three-day broods. The females carried either free or attached-X chromosomes, homozygous for y.

For cytological analysis, testes of newly emerged males were dissected in saline and transferred to aceto-orcein. Squashes of the spermatocytes were examined with phase optics. Slides were made permanent in Euparal after removal of the coverslip by the dry ice technique.

RESULTS

Males of the constitution y sc^4-sc^8/YB^S produced a distribution of gametes (Table 1, lines 1, 2) similar to that reported for sc^4-sc^8/y^+Y males by SANDLER and BRAVER. The overall frequency of nondisjunction is higher than in the y^+Y data but the discrepancy between the reciprocal types is of the same order in

both cases; this is also true for the excess of X over Y chromosomes. Sib males crossed to free X or attached-X females yielded similar patterns of gamete formation (Table 1) so that differential viability probably has an insignificant effect on the frequencies. This was further demonstrated by egg counts in the crosses involving free X females; hatchability of experimental progenies was found to be as great as that of controls.

Cytological examination of meiosis, in males which were sibs to those used in the genetic crosses, failed to offer any support to the notion of loss of unpaired chromosomes. In the analysis it was possible to identify the sc^4-sc^8X and the Y at most stages of meiosis: metaphase I cells could be classified as to whether these chromosomes were paired or unpaired, and at anaphase I the behaviour of both the X and Y was usually quite evident. Second division cells are particularly suitable for observation and at all stages from early metaphase to late anaphase an unequivocal decision as to complement of sex chromosomes could be made in the majority of cells. A high proportion of all observed cells (ca. 90%) were suitable for scoring and it is felt that the introduction of bias in the results due to selective scoring was largely avoided.

TABLE 1

Progeny from crosses involving sc^4-sc^8 *males*

Particulars of crosses	Gametes formed by male				Total progeny	Proportion of disjunctional gametes bearing the X chromosome	Proportion of nondisjunctional gametes bearing no sex chromosome
	X	Y	0	XY			
sc^4-sc^8/YB^S × y (free X)* (0 months)†	0.438	0.181	0.367	0.014	7,539	0.703	0.976
sc^4-sc^8/YB^S × y (attached-X)* (0 months)	0.431	0.162	0.385	0.022	517	0.726	0.948
sc^4-sc^8/YB^S × y (free X)* (4 months)	0.597	0.277	0.134	0.010	2,037	0.676	0.932
sc^4-sc^8/YB^S × y (free X) (outcrossed)	0.517	0.215	0.252	0.016	5,296	0.706	0.938
sc^4-sc^8/YB^S × y (attached-X) (outcrossed)	0.507	0.217	0.260	0.016	2,547	0.700	0.942
sc^4-sc^8/B^SYy+ × y (free X)*	0.636	0.316	0.042	0.006	5,733	0.668	0.884
sc^4-sc^8/B^SYy+ × y (attached-X)*	0.607	0.331	0.057	0.005	3,781	0.647	0.915

* These data were obtained from crosses in which the male parents were sibs to males used in cytological analysis (see Table 2).
† Time from synthesis of stocks to sampling.

TABLE 2

Cytological data collected from sc^4-sc^8 *males with various marked Y chromosomes*

Chromosome constitution of male	Metaphase I		Anaphase I		Metaphase II and anaphase II			
	Paired	Unpaired	Disjunctional	Non-disjunctional	X	Y	0	XY
sc^4-sc^8/y+Y	42	19	44	9	71	72	26	21
sc^4-sc^8/YB^S* (0 months)†	51	34	23	10	96	83	71	67
sc^4-sc^8/YB^S (2 months)	87	39	54	20	43	37	13	15
sc^4-sc^8/YB^S* (2 months)	..	..	..	.	24	25	5	6
sc^4-sc^8/B^SYy+*	89	5	24	—	106	107	10	9
sc^4-sc^8/Yw+	85	44	38	14	161	159	76	81

* These data were collected from sibs of males used to obtain genetic data (see Table 1).
† Time from synthesis of stocks to sampling.

Data on the cytology of YB^S males are given in Table 2 (line 1). GERSHENSON's postulate that the heterochromatic deficiency of the sc^4-sc^8X would interfere with its synaptic properties is borne out by these data. In many primary spermatocytes the X and Y were not associated in a bivalent and were often displaced from the metaphase plate (Figure 1). Where a bivalent was formed, the pairing was always between the distal regions of the arms of the X and the short arms of the Y—this configuration is attributable to the transposition (by *In* sc^4) of the small segment of the heterochromatic pairing region present in this chromosome. In many of the bivalents only one X chromatid was associated with the Y, perhaps providing further evidence of a reduced synaptic potential of the X. Another distinction between the properties of the sc^4-sc^8X and a complete X is that anaphase movement of the sc^4-sc^8/Y association tends to be precocious with respect to that of the autosomes (Figure 2) whereas the opposite generally prevails in regular stocks. Wherever there was precocious separation, the cell was scored as an anaphase since this avoided any confusion of these cells with those in which the X and Y were univalents at metaphase (Figure 3). In only two of the hundreds of AI cells examined was there lagging which could lead to meiotic loss. Anaphases were all classifiable as having disjunctional (Figure 4), or nondisjunctional (Figure 7) sex chromosome separations, so that with absolute regularity an X pole was produced as a sister of a Y pole, and a nullo pole as a sister of one containing both the X and Y. Nullo cells have a single mode of origin at anaphase I—nondisjunction. The frequencies of cell types at MII and AII are consistent with the data from first division in that the number of X cells (Figure 5) equaled the number of Y cells (Figure 6), and the nullo cells (Figure 8) were matched by their XY reciprocals (Figure 9). Examination of entire cysts provided evidence that all products of the first meiotic division completed meiosis and that the various cell types have their origin in the manner indicated above.

For example, one cyst in which all cells were in MII had 10 X, 9 Y, 5 nullo and 6 XY cells. Presumably two cells were out of synchrony or were lost in preparation of the slide, one being a Y and the other a nullo cell. No irregularities of any type were noted in the secondary spermatocytes. Spermiogenesis was also normal, sperm bundles at all stages of development having a full count of 64.

The same characteristics of meiosis were found in males carrying the y^+Y (Table 2, line 1), these being comparable to the stock used by SANDLER and BRAVER and by ZIMMERING in their experiments. Stocks which had other marked Y chromosomes with the sc^4-sc^8X also had genetic and cytological properties similar to the descriptions above: data on the doubly marked Y are in Table 1, lines 6 and 7, and in Table 2, line 5; data for Yw^+ are in Table 2, line 6. Of particular note is the low level of nondisjunction in the case of the doubly marked Y. Pairing efficiency of the sc^4-sc^8 chromosome may be influenced by the amount and distribution of X chromatin on the Y. DR. K. W. COOPER has obtained data on meiosis of sc^4-sc^8 males with various Y chromosomes, which are similar to the results reported here (personal communication to DR. E. NOVITSKI 1955).

Frequencies of nondisjunction: The genetic data show that the frequencies of nondisjunctional gametes vary over a wide range extending from 40% in one cross with YB^S male to 6% with the B^SYy^+ (Table 1). A direct parallel is found in the cytological data (Table 2). Regardless of the magnitude of nondisjunction, there is good agreement between estimates derived from progeny counting and from cell analysis in each of the experiments where this was attempted (Table 3). Yet a significant difference between the cytological and genetic data exists: contrasting to the equality of reciprocal classes within both categories which exists in the cytological scores, the genetic determinations have marked inequalities. The extent of the discrepancies between X and Y and between 0 and XY remains relatively constant in the various crosses and appears to be independent of the amount of nondisjunction. The proportion of disjunctional gametes carrying the X chromosome and the proportion of nondisjunctional cells which are nullo are given in Table 1.

The independence of the inequalities in reciprocal classes and the overall proportion of nondisjunction is adequately shown in the successive sets of data for the YB^S males (Table 1, 2). The cytological data are relatively few and have overlapping confidence limits at the 95% level, but since they parallel the genetic data, which differ significantly in the successive experiments, it may be assumed that they are representative of the actual meiotic situation. When the stock was first synthesised some 60% of primary spermatocytes had X/Y bivalents; two months later (stock maintained by mass transfer) synapsis was scored in 70% of cells and after four months, 85% of gametes were disjunctional. When these males were outcrossed and the stock reestablished, disjunctional gametes constituted 70% of the total. Presumably the probability of synapsis had increased with time, perhaps by some form of autoselection of modifiers, and when the background genotype was changed the initial level was again approached. The significant point is that throughout these changes in pairing, the excesses of X over Y and of 0 over XY remained essentially unchanged.

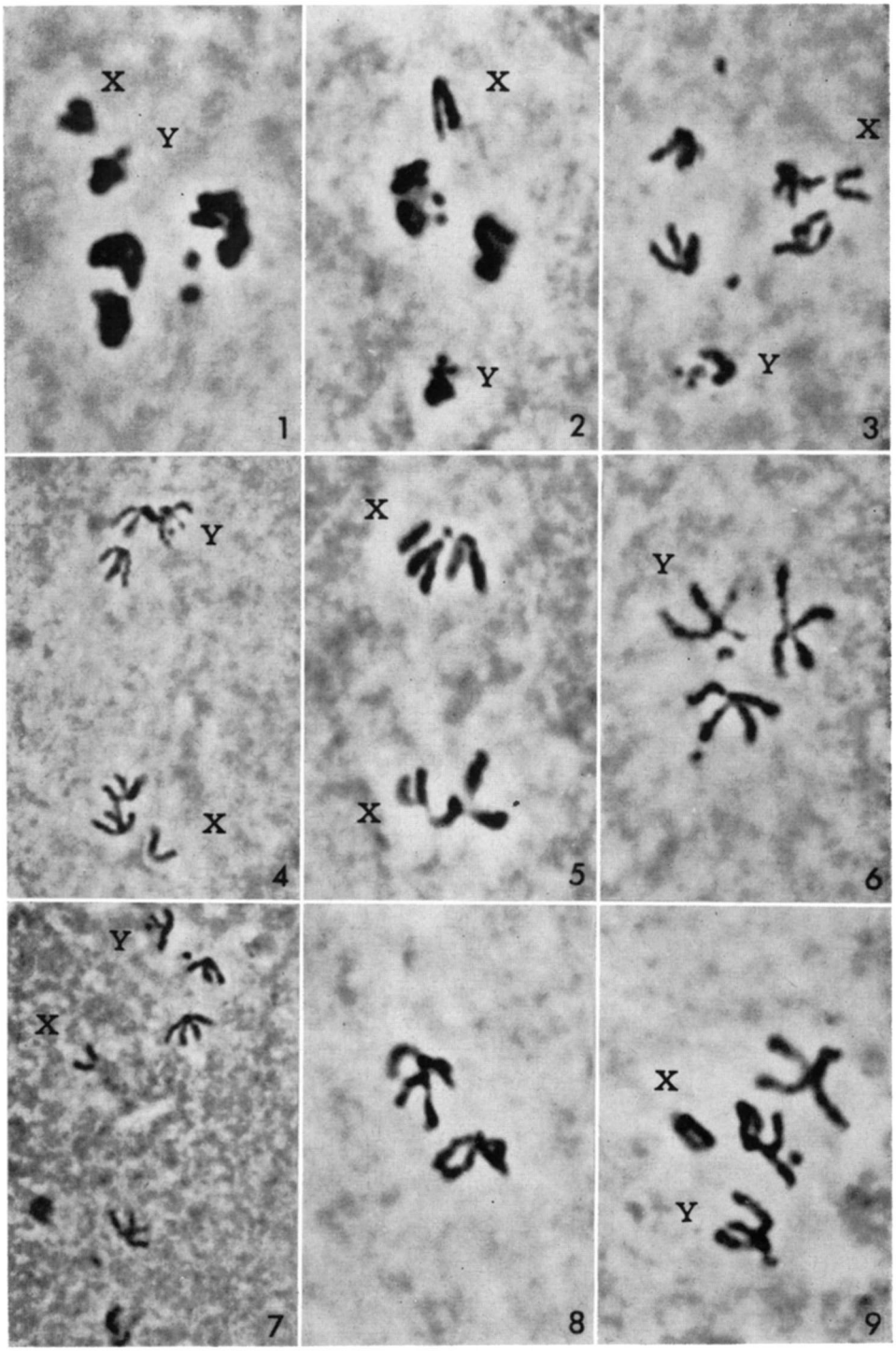
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TABLE 3

Frequencies of synapsis and nondisjunction

Chromosome constitution of male	Proportion of MI cells with unpaired X and Y	Proportion of nondisjunction scored at AI, MII, and AII	Proportion of nondisjunction scored by progeny counts
sc^4-sc^8/y+Y	0.311	0.230	....
sc^4-sc^8/YB^S (0 months)†	0.400	0.423	0.381
sc^4-sc^8/YB^S (2 months)	0.310	0.264	....
sc^4-sc^8/YB^S (4 months)	....	0.183	0.144
sc^4-sc^8/B^SYy+	0.053	0.074	0.062
sc^4-sc^8/Yw+	0.341	0.319	....

† Time from synthesis of stocks to sampling.

Synapsis and nondisjunction: In all of the cytological analyses completed in the present study, the frequency of nondisjunction as scored at AI, MII, and AII is of the same order as the frequency of failure of pairing at MI (see Table 3). Again this relationship holds over a wide range of values. Apparently when the X and Y are unpaired, there is a high probability that their subsequent anaphase movement will be to the same pole. Other direct evidence of nonrandom movement of univalents has been obtained in males carrying a bobbed-deficient X and a normal Y (MORIZOT and PEACOCK, in manuscript). Here the frequency of nondisjunction, both cytologically and genetically, approaches 70%. Even if the X and Y were unpaired in *every* primary spermatocyte the maximum proportion of nondisjunctional products expected on the basis of random chromosome segregation is 50%. The degree of nonrandomness is actually greater than this argument would demand since clear evidence of X/Y bivalent formation was obtained in some 30% of MI cells.

DISCUSSION

The principal findings of the present experiments may be summarised as follows: (1) The sc^4-sc^8X often fails to synapse with its Y homologue at MI. The probability of synapsis appears to be dependent upon the particular Y chromosome which is present, the background genotype and on external factors such as culture temperature. (2) When the X and Y are unpaired their anaphase

FIGURE 1.—MI, X and Y univalents on the same side of the metaphase plate. FIGURE 2.—Precocious anaphase separation of the sex chromosomes. FIGURE 3.—Early AI, X and Y chromosomes unpaired. FIGURE 4.—AI, disjunctional distribution of sex chromosomes. FIGURE 5.—AII, X cell. FIGURE 6.—MII, Y cell. FIGURE 7.—AI, nondisjunctional distribution of sex chromosomes. FIGURE 8.—MII, nullo cell having no sex chromosomes. FIGURE 9.—MII, both the X and the Y present.

movement is highly nonrandom, both usually proceeding to the same pole. Thus the frequency of MI pairing approximates that of AI disjunctional segregation, and failure of synapsis is equivalent to AI nondisjunction. (3) At the completion of meiosis reciprocal gamete types, of both disjunctional and nondisjunctional classes, occur in equal numbers. Furthermore, spermiogenesis appears to be normal with all 64 members of a sperm bundle reaching maturity. (4) There is no significant zygotic death associated with the system. (5) Cytological and genetic determinations of the proportion of nondisjunctional gametes are in agreement. (6) The frequencies of recovery of reciprocal gamete types are not equal, and in fact have characteristic discrepancies.

Meiotic drive: The puzzle emerging from these findings concerns the differences in relative frequencies of complementary classes of gametes in the two methods of analysis. Restrictions to any hypothesis are imposed by the close agreement of the two techniques in their measures of total disjunction and nondisjunction and by the knowledge that neither sperm nor zygotic mortality is present. The oriented movement of univalents provides a key to an explanation when considered with the premise that some sperm are regularly nonfunctional. Such a possibility was first postulated by NOVITSKI and I. SANDLER (1957) in their interpretation of the gametic array produced by a male carrying a translocation between the X and chromosome 4. PEACOCK and ERICKSON (1965) have shown that there is a class of sperm which fail to participate in the successful fertilization of an egg. This class amounts to half of the total sperm production. On the basis of their findings with Segregation-Distorter (SD) these authors further proposed that an intracellular differentiation exists in the primary spermatocyte such that one pole of the anaphase spindle ultimately leads to the formation of two functional sperm, the other pole yielding nonfunctional sperm. The mechanism of segregation distortion was suggested to be an orientation of the second chromosome bivalent such that the SD-bearing chromosome was almost always included in the nucleus at the "functional" pole. The nonrandom segregation of univalents suggests a possible relationship between the sc^4-sc^8 and SD systems.

If the movements of the unpaired X and Y were associated with the proposed intracellular differentiation such that both were usually included in the "nonfunctional" pole, then nullo sperm would be recovered far in excess of XY sperm. An XY gamete would be functional only when both chromosomes had moved to the functional pole. The discrepancy between the numbers of X and Y gametes recovered would reflect a greater probability of the X being oriented toward the functional pole when these two chromosomes are associated in a bivalent. On this hypothesis only one of the two reciprocal products of each anaphase I separation would be recovered but this would not alter the proportion of disjunctional to nondisjunctional types. Thus all of the cytological and genetic data fit this interpretation. ZIMMERING's data on the temperature effect are also consistent with this explanation. He found that a reduction in temperature to 18°C halved the frequency of nondisjunction, with reciprocal classes approaching equality. If movement of chromosomes, both paired and unpaired, were random at this temperature then the above results would be expected. Preliminary cytological

data offer support—the proportion of nullo and XY cells at second division approximates half the frequency of MI synapsis failure. It is concluded that the sc^4-sc^8 system is a valid case of *meiotic drive* (SANDLER and NOVITSKI 1957) with a mechanism similar to that proposed for the T(1:4)B^S and SD systems. This scheme resolves the apparent contradiction between the inference of chromosome loss made on the basis of genetic data, and the absence of cytological confirmation of such loss in the meiotic divisions. Segregation of chromosomes into the nonfunctional class of sperm results, in effect, in the loss of these chromosomes.

Nonrandom movement of paired and unpaired chromosomes: Of the two univalents, the sc^4-sc^8 chromosome is structurally abnormal, having a large heterochromatic deficiency, but the Y is of normal composition (an unmarked Y behaves similarly to the marked Y chromosomes). Yet both of these chromosomes have oriented anaphase movement. The question arises, do all unpaired chromosomes show a polarized movement in the primary spermatocyte? Both SANDLER and BRAVER, and ZIMMERING commented on the puzzling difference in behaviour of the sc^4-sc^8 chromosome in X/Y and X/Y/Y males. With one Y chromosome the X showed no "meiotic loss" whereas in the presence of two Y's, the recovery of the X was greatly reduced. An examination of meiosis in a sc^4-sc^8/Y/Y male has shown, as GERSHENSON had predicted, that the Y chromosomes regularly form a bivalent with the X being unpaired. This contrasts with the trivalent found with a regular X and two Y chromosomes (COOPER 1949). At anaphase the sc^4-sc^8 univalent proceeds to a pole, and second division cells are mostly XY or X. The genetic and cytological results can be reconciled with an inference of preferred movement of the X to the nonfunctional pole. ZIMMERING's (1963) finding of a deficiency in recovery of an attached Y-partial X chromosome ($X^PY^{L\cdot}Y^S$), which had no homologue, also fits the notion of oriented segregation of univalents. The introduction of attached-XY chromosomes into Drosophila genetics (LINDSLEY and NOVITSKI 1950) has provided the opportunity for a univalent condition to be used regularly. In an XY/O male the univalent has a relatively high recovery but the nullo gametes characteristically occur in greater frequency (e.g., 11% and 24% deficiencies of the XY chromosomes [SANDLER and BRAVER, Table 4]). Thus although the discrepancy is smaller than in the other situations, the suggestion is that the univalent does not have random segregation. In general, unpaired chromosomes would appear to show polarized movement in the spermatocyte but the degree of nonrandomness is probably dependent on chromosome composition and structure, as well as on total genotype.

Nonrandom segregation from a bivalent may be sometimes dependent on a structural alteration of the chromosome (SD may be an example) but NOVITSKI and I. SANDLER have pointed out that this is not necessarily the case. In their experiments one of the high recovery chromosomes was a regular chromosome 4. The common factor was one of chromosome size—the chromosome recovered in high frequency from each bivalent was the shorter element. In this respect the situation is analogous to that documented for nonrandom disjunction in the female (NOVITSKI 1951). The sc^4-sc^8 chromosome has both structural change

and reduced size: on present evidence nothing can be said of their relative importance.

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SUMMARY

Genetic analyses of *Drosophila melanogaster* males carrying an X chromosome with a large heterochromatic deficiency ($Ins(1)sc^4$-sc^8), and one of several different Y chromosomes, have shown that there are characteristic discrepancies between reciprocal classes of both disjunctional and nondisjunctional gamete types. The excess in recovery of X over Y and of 0 over XY holds over a wide range of values of total nondisjunction. Cytological analysis has revealed that the sc^4-sc^8X frequently fails to synapse with its Y homologue, but that there is no meiotic loss of either of the unpaired chromosomes. The univalents exhibit nonrandom movement at anaphase I, both generally moving to the same pole. Strict equality of the reciprocal cell types is found at the second division of meiosis. An inference is made that this system is a case of meiotic drive based on nonrandom segregation of the X and Y chromosomes, from both the bivalent and univalent conditions, into functional and nonfunctional classes of sperm.

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