EXCHANGE AND NONDISJUNCTION OF THE X CHROMOSOMES IN FEMALE DROSOPHILA MELANOGASTER[1]

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BRIDGES (1916) observed that nondisjunction in normal XX females resulted in two classes of exceptional female progeny: "regular primary exceptions" which carried a noncrossover strand from each of the maternal X chromosomes, and "equational primary exceptions" which carried a crossover and a noncrossover strand from among the four chromatids of the maternal tetrad and were, as a consequence, homozygous for some loci that were heterozygous in the mother. The regular exceptions were considered to result from a failure of the reductional division followed by a normal equational division in tetrads in which no exchange had occurred. Equational exceptions were explained as resulting from exchange tetrads in which there was a failure of sister centromeres to separate at second division anaphase.

BRIDGES' studies were made before results from attached-X chromosomes established that the centromere of the X-chromosome is at the end opposite the *y* locus (ANDERSON 1926). An examination of BRIDGES' equational exceptions with this point in mind reveals an inconsistency. The sequence of meiotic events postulated by BRIDGES to account for equational exceptions is diagramed in Figure 1; it can be seen that the loci homozygous in the equational exceptions that were heterozygous in the mother should, in the main, be proximally located. In fact, however, the majority of BRIDGES' equational exceptions were homozygous for distal loci while still heterozygous for more proximal markers, suggesting first division nondisjunction. However, no exceptions bearing complementary crossover products are recorded. This pattern of homozygosis was also obtained by STURTEVANT (1929) for equational exceptions recovered from *Drosophila simulans* females homozygous for claret. He noticed decreasing frequencies of homozygosis moving to the right on the X chromosome. The *ca* of *D. simulans*, located on the third chromosome, increases the frequency of exceptional males and females to 50 percent of the progeny recovered.

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This inconsistency was also noted by MORIWAKI (1938) who concluded that the equational exceptions described by BRIDGES resulted from failure of disjunction at first division anaphase. The experiments reported below were undertaken to expand BRIDGES' observations in order to determine whether, in fact, nondisjunction occurs at the second meiotic division and, further, to determine the nature and frequency of crossover events preceding nondisjunction. All the exceptional daughters of females heterozygous for well marked X chromosomes were collected and their genotypes determined. The results of this analysis indicate that the vast majority (and very probably all) of X chromosome nondisjunction occurs at the first meiotic division, and further, that nondisjunction may occur in tetrads having either no, one, or more than one exchange. It will, however, also be shown that tetrads undergoing nondisjunction have an abnormal tetrad distribution in that double exchange tetrads are considerably more frequent than tetrads of rank one which are about as frequent as those of rank zero. These observations will be considered in light of recent theories concerning the behavior of chromosomes during meiosis.

Rate and distribution of nondisjunction events: Exceptional females were collected from three matings: (1) *y* females from the cross of *y/y sc cv v f car* females by *sc cv v f car*/Y males; (2) *y* non-Bar females from the cross of *y/y sc cv v f car* females by YSX·YL, *In(1)EN y B*/0 males and (3) non-Bar females from the cross of *y ec* sn^3 *wy/cv v sd car* females by Muller-5 (*Ins(1)* sc^{SIL} sc^{sR}, *S*, w^a *B*)/Y males. Descriptions of the markers used can be found in BRIDGES and BREHME (1944). In control crosses, the map distances for the regions involved were found to be: from Crosses 1 and 2, *sc–cv* = 10.2 units, *cv–v* = 23.6 units, *v–f* = 20.9 units, *f–car* = 8.3 units; from Cross 3, *y–ec* = 4.0 units, *ec–cv* = 8.7 units, *cv–*sn^3 = 6.8 units, sn^3*–v* = 13.2 units, *v–wy* = 9.6 units, *wy–sd* = 8.9 units and *sd-car* = 11.5 units. The existence of any secondary exceptions (from XXY mothers) was made unlikely by testing the patroclinous males from Crosses 1 and 3 and the regular brothers of exceptional females from Cross 2 for fertility. The genotypes of the exceptions obtained were determined by scoring their male progeny. It should be noted that exceptional females from Cross 2 were XX rather than XXY as in the other two crosses. As a consequence, frequencies of crossing over and nondisjunction found for these exceptions are directly comparable with those of their mothers. A few exceptional females whose mothers carried newly arisen spontaneous lethals are excluded from the following analyses and are treated separately below.

Among a sample of 45,112 female progeny from Cross 2, 26 (1/1735) were matroclinous exceptions. This agrees well with the rate of 1/2000 reported by BRIDGES. The rates of nondisjunction for Crosses 1 and 3 were estimated to be approximately the same, although large progeny counts were not made. It may also be noted that the rate of nondisjunction is no higher among the progeny of exceptional (XX) females than among the progeny of normal females. Thus a sample of 36 XX exceptions recovered from Cross 2 were mated to y^+ males and treated exactly like their parents. Of these exceptions, 33 produced no exceptions, and three yielded one exception each among a total of 6,380 female progeny. Both

the overall rate of nondisjunction and its distribution suggest no differences from those of the newly synthesized heterozygotes.

The distribution of 41 matroclinous exceptions from a sample of 531 matings in Cross 2 (females cultured singly) yielding approximately equal total numbers of progeny shows that the nondisjunctional events that produced them were meiotic, i.e., they arose independently of each other. Of these matings, 494 yielded no exceptions, 34 yielded one exception, two yielded two exceptions and one mating yielded three exceptions. The observed distribution is in agreement with expectations based on the Poisson series. From this, there is no reason to doubt the meiotic origin of exceptions.

Evidence for first division nondisjunction: Primary exceptions (those carrying two noncrossover homologous strands) and exceptions carrying complementary crossover strands must always result from first division nondisjunction. Equational exceptions (those carrying a crossover strand and a noncrossover strand, or noncomplementary crossover strands) can come from nondisjunction at either the first or second division. These alternative methods of producing equational exceptions are represented diagrammatically in Figures 1 and 2. Figure 1 represents a single exchange tetrad with a normal reductional division and failure of sister centromeres to disjoin at the second division. Figure 2 represents a similar tetrad undergoing nondisjunction at the first division followed by a normal equational division. Second division exceptions (as in Figure 1) would be of two types depending on which strands fail to segregate: those homozygous for proximal markers on one chromosome or those homozygous for proximal markers on the other chromosome. First division nondisjunction (as in Figure 2), however, would

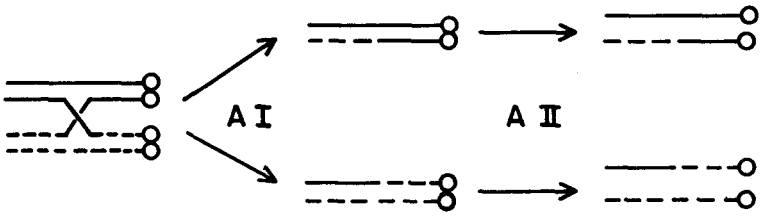

FIGURE 1.—A single-exchange tetrad with a normal reductional division and failure of sister centromeres to disjoin at the second division. The expected exceptions are discussed in the text.

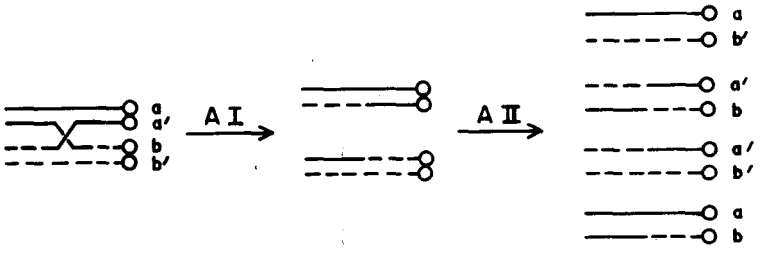

FIGURE 2.—A single-exchange tetrad undergoing nondisjunction at the first division followed by a normal equational division. The expected exceptions are discussed in the text.

result in four types of exceptional progeny. Assuming independent segregation of the two dyads, four classes would be found with equal frequency: (1) exceptions carrying two noncrossover chromosomes (primary exceptions), (2) exceptions carrying complementary crossover strands, (3) exceptions carrying crossover strand a′ and noncrossover strand b′ (equational exceptions), and (4) exceptions carrying crossover strand b and noncrossover strand a (equational exceptions). The equational exceptions would be homozygous for distal markers. In addition, whatever the frequency of single exchanges, equational exceptions would appear twice as frequently as exceptions carrying complementary crossover strands. Actually a larger proportion of equational exceptions would occur in the experiments reported here because exceptions carrying complementary crossover products of an exchange in the unmarked *car*–centromere region would be classified as primary exceptions while equational exceptions (the proximal homozygotes discussed below) resulting from such an exchange would be detected as such.

A similar analysis of multiple exchange tetrads yields predictions analogous to those for single exchange tetrads. Following multiple exchange, nondisjunction at the second anaphase division will yield equational exceptions homozygous for proximal loci while nondisjunction at the first anaphase division will yield equational exceptions homozygous for distal loci. A schematic representation of exceptions expected from anaphase I nondisjunction following two-strand, three-strand, and four-strand double exchange is presented in Figure 3. It can be seen by summing the exceptional classes that equational exceptions should appear twice as frequently as reductional exceptions carrying complementary crossover products. In summing, exceptions that carry complementary crossover products as well as noncomplementary crossover products and which are equational exceptions (i.e., homozygous for some loci) are classified as exceptions carrying complementary crossover products. This convention is followed throughout this report.

From the three experimental crosses, a total of 149 female exceptions were recovered and the genotypes determined. The results, summarized in Table 1, are in agreement with the expectations derived above for nondisjunction occurring at the first meiotic division. In the first place, most equational exceptions are homozygous for distal rather than proximal markers: 49 are homozygous for markers to the left of *car* but remain heterozygous for *car* (the most proximal

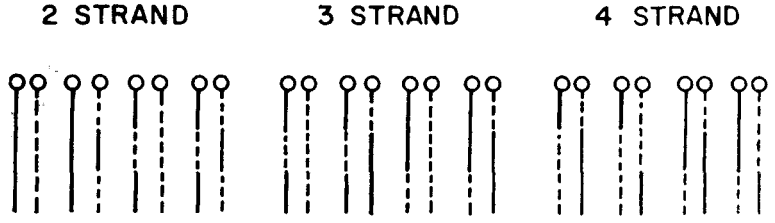

FIGURE 3.—Exceptions expected from anaphase I nondisjunction following two-strand, three-strand and four-strand double exchange.

TABLE 1

Distribution of 149 exceptions recovered from three experimental crosses

Cross	Class A	Class B	Class C	Class D	Totals
1	15	4	12	1	32
2	33	22	31	8	94
3	16	. .	6	1	23
Totals	64	26	49	10	149

Cross No. 1 = *y/y sc cv v f car* ♀ ♀ × *sc cv v f car* ♂ ♂

Cross No. 2 = *y/y sc cv v f car* ♀ ♀ × XY, y B/0 ♂ ♂

Cross No. 3 = *y ec sn³ wy/cv v sd car* ♀ ♀ × Muller-5 ♂ ♂

Class A = regular exceptions; Class B = exceptions bearing complementary crossover strands; Class C = equational exceptions homozygous for distal markers, and Class D = equational exceptions homozygous for proximal markers.

marker), while only ten are homozygous for the *car* locus. In addition, the observed ratio of exceptions bearing complementary crossover products to equational exceptions (distal homozygotes) is 26 to 49, which is in close agreement with the expected 1 to 2 ratio. This suggests that crossover-bearing exceptions do arise from exchange tetrads as diagramed in Figure 2 and that the dyads segregate independently of each other at anaphase II.

The ten exceptions homozygous for the *car* locus can be explained as resulting from tetrads with a crossover between *car* and the centromere prior to first division nondisjunction. From Figures 2 and 3 it is seen that a single crossover between a marker and the centromere will result in exceptions homozygous for that marker (or its wild-type allele) assuming nondisjunction at anaphase I, and thus the number of such homozygotes among all exceptions should give an estimate of the map distance between the most proximal marker and the centromere. From the data presented here that distance is 6.7 map units ($= 10/149 \times 100$). This is fairly close to the known *car–bb* distance of 3.5 map units (BRIDGES and BREHME 1944) which is approximately the *car*–centromere distance, since crossing over between *bb* and the centromere is very infrequent. It seems reasonable, therefore, to conclude that the *car* homozygotes all arose from anaphase I nondisjunction preceded by an exchange in the *car*-centromere region.

Thus, from these data, the majority of primary and equational exceptions originate from first division nondisjunction and therefore, no distinction exists between the nondisjunctional event that gives rise to primary as contrasted with equational exceptions, because both types can result from identical exchange tetrads.

Exchange and nondisjunction: The frequencies of tetrads of the different ranks (referred to as exchange frequencies) that yield exceptional females can be calculated from formulae derived in ways similar to those employed by WEINSTEIN (1936) to compute exchange frequencies among regular progeny. From Figure 2 it can be seen that of the exceptions from single exchange tetrads, one fourth will carry two noncrossover strands, one half will carry a noncrossover strand and a crossover strand and one fourth will carry complementary crossover strands. For double exchange tetrads (Figure 3), in the absence of chromatid interference,

one sixteenth of the exceptions will carry noncrossover strands, one eighth will carry a noncrossover strand and a single crossover strand, one eighth will carry complementary single crossover strands, one fourth will carry a noncrossover strand and a double crossover strand, one fourth will carry two noncomplementary single crossover strands, one sixteenth will carry complementary double crossover strands, and one eighth will carry a single crossover strand and a strand with a complementary single crossover and a noncomplementary single crossover. Exceptions from noexchange tetrads will all carry two noncrossover strands. The analysis, extended to triple exchange tetrads, is represented by the following equations. E_0, E_1, E_2 and E_3 represent the frequency of zero-, single-, double- and triple-exchange tetrads, respectively.

n_0 = two noncrossover strands = $E_0 + 1/4E_1 + 1/16E_2 + 1/64E_3$
n_1 = a noncrossover strand and a single crossover strand = $1/2\,E_1 + 1/8E_2 + 1/32E_3$
n_2 = complementary single crossover strands = $1/4E_1 + 1/8E_2 + 3/64E_3$
n_3 = a noncrossover strand and a double crossover strand = $1/4E_2 + 1/8E_3$
n_4 = two noncomplementary single crossover strands = $1/4E_2 + 1/8E_3$
n_5 = complementary double crossover strands = $1/16E_2 + 3/64E_3$
n_6 = a double crossover strand and a complementary single crossover strand = $1/8E_2 + 1/16E_3$
n_7 = a double crossover strand and a double crossover (one complementary) strand = $1/8E_3$
n_8 = a triple crossover strand and a complementary single crossover strand = $1/8E_3$
n_9 = a triple crossover strand and a complementary double crossover strand = $1/32E_3$
n_{10} = a double crossover strand and a noncomplementary single crossover strand = $3/16E_3$
n_{11} = complementary triple crossover strands = $1/64E_3$
n_{12} = a triple crossover strand and a noncrossover strand = $1/16E_3$

The genotypes and classifications of the 94 exceptions recovered from Cross 2 are presented in Table 2. The exchange frequencies are computed from Cross 2 only in order to insure homogeneity. Cross 2 yielded the most exceptions and these exceptions, being recovered as XX virgins, gave the most precise determination of the genotype of the exceptions. Six F_2 exceptions recovered from regular (*y/y sc cv v f car*) exceptions are included in these results. Classes n_3 and n_4 are considered together because it is not possible in the case of proximal homozygotes to determine if they carried a double crossover strand and a noncrossover strand or if they carried two noncomplementary single crossover strands. The expected frequency of each class is the same so that summing the two classes does not affect the computed exchange values. The observed classes are: $n_0 = 33$, $n_1 = 16$, $n_2 = 13$, $n_3 + n_4 = 23$, $n_5 = 3$, $n_6 = 5$, $n_7 = 1$, and $n_8 = n_{12} = 0$. The above equations were solved for the exchange frequencies and their variances are shown in Table 3.

The most striking feature of these exchange frequencies is the decided deficiency of single, as compared with double, exchanges. This is in contrast with exchange frequencies calculated from regular progeny. In the tetrads giving rise to regular progeny in Cross 2, the exchange frequencies were $E_0 = 4.6$ percent, $E_1 = 65.7$ percent, $E_2 = 28.7$ percent and $E_3 = 1.0$ percent. The excess of doubles is also shown by the fact that among exceptions middle markers are homozygous more frequently than are distal markers. From Table 2, the frequencies of homo-

TABLE 2

Genotypes and classifications of 94 exceptions recovered from Cross 2
(y/y sc cv v f car ♀♀ × *XY*, y B/*0* ♂♂)

Class	Genotype	Number	Class	Genotype	Number
n_0	00000	33	n_3+n_4	00000	2
	11111			10001	
n_1	00000	2	n_3+n_4	01111	2
	01111			11111	
n_1	10000	1	n_3+n_4	00000	2
	11111			11011	
n_1	00000	3	n_3+n_4	11000	3
	00111			00011	
n_1	11000	1	n_3+n_4	11100	1
	11111			00111	
n_1	00000	5	n_3+n_4	00110	2
	00011			11111	
n_1	00000	1	n_3+n_4	00000	3
	00001			11000	
n_1	11110	1	n_3+n_4	11100	1
	11111			00001	
n_1	00000	1	n_3+n_4	11110	2
	00000			00111	
n_1	11111	1	n_3+n_4	00000	1
	11111			11100	
n_2	10000	3	n_5	01100	1
	01111			10011	
n_2	11000	6	n_5	00100	2
	00111			11011	
n_2	11100	4	n_6	11100	1
	00011			10011	
n_3+n_4	01100	2	n_6	00100	3
	11111			00011	
n_3+n_4	00000	1	n_6	11110	1
	10011			11001	
n_3+n_4	10000	1	n_7	01100	1
	00011			10111	

Following the convention of LEDERBERG the markers are symbolized by: 0=maternal markers (="+") and 1= paternal markers (= *sc cv v f car*). The markers are read from left to right, according to their position on the chromosome. Thus, $\frac{00000}{11111}$ = *y/y sc cv v f car*, a regular primary exception, and $\frac{11000}{11111}$ = *y sc cv / y sc cv v f car*, an equational primary exception. No symbol for *y* is given.

TABLE 3

The values for the frequencies of tetrads of different ranks based on 94 exceptions recovered from Cross 2. The no-exchange class* $= 1 - (E_1 + E_2 + E_3)$. *Equations are in text*

Exchange rank	Frequency	Variances
no-exchange (E_0)	.2597	.....
single exchange (E_1)	.2453	.00576
double exchange (E_2)	.4755	.00516
triple exchange (E_3)	.0195	.00048

* These are maximum likelihood estimates arrived at by a machine program kindly provided by Dr. E. Novitski of the University of Oregon. This program, written for the IBM 1620, requires only the input of the raw data and the maximum likelihood formulation; in its execution, it takes the necessary partial derivatives and makes successive approximations by the Newton-Raphson method and gives the final estimates within any desired accuracy along with the variances of those estimates.

zygosis are $sc = 22.4$ percent, $cv = 26.6$ percent, $v = 33.0$ percent, $f = 18.1$ percent and $car = 8.5$ percent.

This unusual distribution of exchange frequencies cannot be ascribed to peculiarities of the X chromosomes used in these experiments. Crossing over in female parents was measured by scoring the regular male progeny, and for all experiments the distributions of crossing over were normal. It was also noted that female parents yielding one or more exceptions did not differ noticeably in crossing over from female parents producing no exceptions. From Cross 2, exchange and crossing over were measured in regular (i.e., *y/y sc cv v f car*) exceptions. These values were not significantly different from those of their regular mothers. Finally, nondisjunctional tetrads do not involve preferential crossover regions. That is, crossovers carried by exceptions are not clustered in any region. The proportion of recombinants by regions among all recombinants as measured in strands from regular daughters and in strands from exceptional daughters are presented in Table 4. The recombinant percentages for each region are approximately equal in both female classes.

Similarly, there is no reason to ascribe the results obtained to either chromatid interference or preferential recovery of crossover strands since any nonrandomness among strands in crossing over or recovery would be expected to result in a nonrandom distribution of exceptions among the expected classes. For example, with negative chromatid interference more exceptions bearing complementary double crossover strands (Class n_5) would be expected relative to the other classes

TABLE 4

Proportions of recombinants among all recombinants as measured in strands from regular daughters and in strands from exceptional daughters recovered from Cross 2

Region	Regular daughters	Exceptional daughters
sc–cv	.16	.20
cv–v	.37	.34
v–f	.33	.36
f–car	.13	.10

of double exchange exceptions. However, the observed number of exceptions in each class agrees closely with the number expected from the exchange frequencies computed on the assumptions of no chromatid interference and of independent recovery of crossover strands.

Spontaneous lethals and nondisjunction: In the course of these experiments, five events were noticed where exceptional progeny were recovered from females heterozygous for a newly arisen, spontaneous, sex-linked lethal mutation. In each case, the position of the lethal was determined by scoring the male progeny. Each of the five lethals was of independent origin. Of approximately 70 tested sisters of lethal-bearing females, none carried the lethal. The lethals were not localized on either chromosome or at any one locus. These results are summarized in Table 5. The exceptional progeny listed are not included in the previous analyses. However, it is obvious that the inclusion of these few exceptions would not demonstrably alter the results obtained.

That such lethals are somehow correlated with nondisjunction is suggested since exception-producing females carry lethals more often than would be expected from a random distribution of spontaneously occurring lethal mutations. Moreover, three of the lethal-bearing females produced more than one exceptional daughter. The exceptions in each cluster, however, carried nonidentical crossover (or noncrossover) strands (Table 5). No exceptions were recovered among the progeny of tested lethal-bearing exceptions. Mutants that increase the frequency of primary nondisjunction in females have been reported, but none of these were noted to be lethal (GOWEN 1939; LEWIS and GENCARELLA 1952; SAFIR 1920; SPIELER 1963; STURTEVANT 1929). It is interesting to note that in the only case mentioned where crossing over was followed, that of claret in *D. simulans*, equational exceptions, i.e., crossover exceptions, increased proportionately to primary exceptions (STURTEVANT 1929). That crossing over among exceptions associated with these mutants is normal is also observed here.

TABLE 5

Summary of five cases of spontaneous lethals recovered from female parents

Experiment number	Location of lethal and parental chromosome	Matroclinous exceptions recovered	Patroclinous exceptions
2	near *sc*+	*y/y sc cv v f car* *y sc cv/y v f car* 2 (wild type) sterile	7
2	near *v*+	*y sc cv v/y cv v f car*	. .
2	near *v*	*y/y cv v f car* 1 (wild type) sterile	1
3	between *wy* and *sd* on *sd* chromosome	*y ec sn³ wy/cv v sd car* *y ec sn³ v sd car/cv wy* 1 (*cv v*) sterile	. .
3	near *y*+ (tip of X)	*y ec sn³ wy/cv v sd car* . .	. .

DISCUSSION

In postulating mechanisms to explain primary nondisjunction, the following characteristics must be taken into consideration: (1) Nondisjunction results from a failure of the reductional division. (2) At least in nondisjunction of structurally normal chromosomes, exceptions may result from exchange tetrads. (3) An excess of patroclinous males over matroclinous females is observed (MORGAN, BRIDGES and STURTEVANT 1925). A slight excess of patroclinous males was also noticed in the experiments reported here despite the fact that in Crosses 1 and 3 exceptional males had low viability, and in Cross number 2 attached-XY-bearing sperm are recovered less frequently than nullo-XY sperm (SANDLER and BRAVER 1954). (4) There is an unusual distribution of exchange frequencies to be accounted for.

The diagrams in Figures 2 and 3 illustrating nondisjunction at the first meiotic division are purely schematic and make no assertion regarding the actual forces involved in preventing separation of the homologues. Furthermore, the experimental evidence for first division nondisjunction, in its most general sense, is simply evidence for the failure of the reductional division. It may be, for instance, that nondisjunction represents a few cases in which the equational division precedes the reductional division, followed by failure of the homologous X-chromosome strands to separate at the second division. This sequence would be formally indistinguishable from a reductional first division. Such a sequence could result from sister centromeres dividing prematurely at the first division. At the second division, the free half-dyads might segregate independently of each other, yielding one quarter nullo-X gametes, one half single-X gametes and one quarter diplo-X gametes. The observed excess of patroclinous males could be accounted for by assuming meiotic loss of the chromatids at the second division. It is clear that both exchange and no-exchange exceptions could originate through such a sequence, but it is not clear what would then account for the observed exchange frequencies.

Several model systems have been suggested by earlier workers to explain nondisjunction under normal or special conditions. BRIDGES (1916) suggested that nondisjunction resulted from homologous strands intertwining with each other to such a degree that they were unable to separate from each other at the reductional division. BRIDGES' model can account both for exceptions carrying crossover strands and for the excess of patroclinous males since the entanglement could result in either nondisjunction or in anaphase-I bridgelike complexes. The latter could result in nullo-X eggs being formed with a corresponding increase in the numbers of patroclinous males.

STURTEVANT and BEADLE (1939) suggested that primary exceptions recovered from XX females could arise by a failure of metaphase pairing, that is by an occasional failure of homologous strands to pair with resulting independent segregation of each unpaired homologue (nonconjunction). Independent segregation of such unpaired homologues would yield one quarter nullo-X eggs, one half single X eggs and one quarter diplo-X eggs. Exceptions recovered from such XX eggs would characteristically carry noncrossover strands. SANDLER and BRAVER

(1954) have further suggested that such asynapsis could lead to meiotic loss of one or both unpaired dyads with resultant production of more patroclinous males (from nullo-X eggs) than matroclinous females (from XX eggs). However, since it is now evident that the majority of exceptions originate from exchange tetrads, to account for the observed excess of patroclinous males by meiotic loss would necessitate assuming a higher frequency of loss among a smaller number of asynaptic tetrads.

The bimodal distribution of exchange frequencies calculated above suggests that both BRIDGES' and STURTEVANT's models may be operating to cause nondisjunction in normal diplo-X females. The exceptions arising from no-exchange tetrads could be due to failure of metaphase pairing as postulated by STURTEVANT. What BRIDGES postulated as chromosome entanglement might be occasional unresolved chiasmata formed by crossing over which would give rise to the exceptions carrying crossover strands. This would suggest that entanglement should be more frequent among multiple rank tetrads and could account for the increase in double exchanges relative to single exchanges among exceptions. However from such a relation, an increase in triple exchanges among exceptions would also be expected, but this has not been observed.

Moreover, the high estimate of E_0 need not imply nonconjunction among a share of the tetrads giving rise to exceptions. In the first place, STURTEVANT and BEADLE (1936) and COOPER (1945) have pointed out that segregation is regular even in situations with high values of E_0. Also, it is evident that regular segregation of normal chromosomes without exchange is possible for the reason that there are far too many noncrossover strands recovered in regular progeny to come from nonconjunction because nonconjunction would be expected to produce exceptional eggs 50 percent of the time, which would give rise to many more patroclinous males and matroclinous females than are observed. Finally, it has been shown here that synapsed tetrads (detected genetically as exchange tetrads) can undergo nondisjunction.

Thus, there is every reason to suppose that the two X chromosomes nearly always pair, usually cross over, and then, whether or not an exchange has occurred, may fail to disjoin. This, however, leaves unexplained the excess of patroclinous males and the bimodal tetrad frequency distribution. Regarding the latter point, at least, a model system in Drosophila does exist. Reversed acrocentric compound-X chromosomes(structurally similar to attached-X's but with the centromere subterminal instead of median) and reversed compound ring X chromosomes (structurally similar to attached-X's with the free ends attached to each other) both show an excess of zero-and double-exchange tetrads and a deficiency of singles (SANDLER 1954, 1957). These distributions do not involve an asynaptic class (SANDLER 1957). Whether any physical similarities exist between these compound chromosomes and free X tetrads that will undergo nondisjunction is unknown, but at least the compound cases show that bimodal tetrad frequency distributions can occur without an asynaptic class.

GRELL (1962a) has proposed a scheme whereby two kinds of pairing occur at meiosis: exchange pairing, which precedes crossing over, and distributive pairing,

which precedes disjunction. Successful exchange pairing accompanied by exchange is considered sufficient for distributive pairing which leads to regular disjunction. According to this view, for which there is additional more recent evidence (GRELL 1962b; ROBERTS 1962) nondisjunction occurs when failure of exchange permits nonhomologous distributive pairing to occur. Although the chromosomes utilized in the experiments reported here were all structurally normal, it is still possible, on this basis, to consider no-exchange tetrads resulting in exceptions as consisting of asynaptic X chromosomes. If nonhomologous pairing can occur between no-exchange X chromosomes and no-exchange autosomes, the low frequency of primary nondisjunction might be explained as corresponding to the low frequency of both no-exchange X tetrads and no-exchange autosomal tetrads occurring simultaneously in the same nucleus. In the absence of no-exchange autosomal tetrads, the chromosomes of a no-exchange X-tetrad would pair distributively with each other according to the GRELL hypothesis. However, nonhomologous distributive pairing would not account for the observed excess of patroclinous males, since in situations postulated to involve nonhomologous pairing no chromosome loss (or excess of patroclinous males) is observed (COOPER, ZIMMERING and KRIVSHENKO 1955; FORBES 1962). In addition, most of the exceptions recovered here arose from exchange tetrads. This must mean that exchange does not always lead to successful disjunction of homologues. It should be pointed out, however, that failure to disjoin takes place in a fraction of exchange tetrads that is nonrepresentative in that it involves more tetrads of rank two than of rank one. Whether the X chromosomes in these cases could, or do, pair distributively with nonhomologous chromosomes is a moot point. At any rate it is clear that the initial mechanism involved in secondary nondisjunction, or in primary nondisjunction involving structural heterozygosity in the chromosomal sets (i.e., failure of exchange leading to nonhomologous distributive pairing) is quite different from the initial mechanism involved in most of the primary nondisjunction reported here (i.e., failure of disjunction despite successful exchange). That the mechanisms are separate is also borne out by the observation that equational exceptions occur with approximately the same frequency in XXY and in XX females (BRIDGES 1916; STURTEVANT and BEADLE 1936).

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SUMMARY

A genetic analysis of exceptional daughters recovered from females heterozygous for markers covering the entire length of the X chromosome revealed that: (1) Nondisjunction is a meiotic event, i.e., there is no evidence of clustering. (2) The observations are consistent with the hypothesis that all exceptions result from failure of reductional separation of centromeres. (3) Exceptions arise from no-, one-, two- and three-exchange tetrads.

The half tetrads recovered among exceptions are not derived from the same population as the quarter tetrads recovered among regular progeny. Tetrad analyses by the method of WEINSTEIN (1936) making conventional assumptions leads to estimates of $E_0 = 4.6$ percent, $E_1 = 65.7$ percent, $E_2 = 28.7$ percent, and $E_3 = 1.0$ percent for the cells giving rise to regular progeny and $E_0 = 25.97$ percent, $E_1 = 24.53$ percent, $E_2 = 47.55$ percent and $E_3 = 1.95$ percent for oocytes giving rise to exceptional progeny. The latter distribution appears not to involve an asynaptic class but is similar to that observed in the reversed acrocentric and the reversed ring compound X chromosomes. It is probable that the origin of secondary exceptions according to the hypothesis of GRELL (failure of exchange leading to nonhomologous distributive pairing) is different from the origin of primary exceptions reported here (failure of disjunction despite successful exchange).

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