PATERNAL LOSS (*PAL*): A MEIOTIC MUTANT IN *DROSOPHILA MELANOGASTER* CAUSING LOSS OF PATERNAL CHROMOSOMES[1,3]

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ABSTRACT

The effects of a male-specific meiotic mutant, *paternal loss* (*pal*), in *D. melanogaster* have been examined genetically. The results indicate the following. (1) When homozygous in males, *pal* can cause loss, but not nondisjunction, of any chromosome pair. The *pal*-induced chromosome loss produces exceptional progeny that apparently failed to receive one, or more, paternal chromosomes and, in addition, mosaic progeny during whose early mitotic divisions one or more paternal chromosomes were lost. (2) Only paternally derived chromosomes are lost. (3) Mitotic chromosome loss can occur in homozygous *pal*+ progeny of *pal* males. (4) Chromosomes differ in their susceptibility to *pal*-induced loss. The site responsible for the insensitivity *vs.* sensitivity of the *X* chromosome to *pal* mapped to the basal region of the *X* chromosome at, or near, the centromere. From these results, it is suggested that *pal*+ acts in male gonia to specify a product that is a component of, or interacts with, the centromeric region of chromosomes and is necessary for the normal segregation of paternal chromosomes. In the presence of *pal*, defective chromosomes are produced and these chromosomes tend to get lost during the early cleavage divisions of the zygote. (5) The loss of heterologous chromosome pairs is not independent; there are more cases of simultaneous loss of two chromosomes than expected from independence. Moreover, an examination of cases of simultaneous somatic loss of two heterologs reveals an asymmetry in the early mitotic divisions of the zygote such that when two heterologs are lost at a somatic cleavage division, almost invariably one daughter nucleus fails to get either, and the other daughter nucleus receives its normal chromosome complement. It is suggested that this asymmetry is not a property of *pal* but is rather a normal process that is being revealed by the mutant. (6) The somatic loss of chromosomes in the progeny of *pal* males allows the construction of fate maps of the blastoderm. Similar fate maps are obtained using data from gynandromorphs and from marked *Y* chromosome (nonsexually dimorphic) mosaics.

A systematic attack on the genic control of meiosis in *D. melanogaster* began with the work of SANDLER *et al.* (1968) and LINDSLEY *et al.* (1968). Sev-

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eral successful searches for mutants that disrupt meiosis (meiotic mutants) have been reported (SANDLER *et al.* 1968; SANDLER 1971; BAKER and CARPENTER 1972) and the effects of many of these, as well as previously known meiotic mutants, have been examined in detail (DAVIS 1969; DAVIS 1971; ROBBINS 1971; HALL 1972; CARPENTER 1973; PARRY 1973; CARPENTER and BAKER 1974; CARPENTER and SANDLER 1974; WRIGHT 1974; reviewed by BAKER and HALL 1975; SANDLER and LINDSLEY 1974). From the genetic, and in some cases cytological, analysis of the abnormal chromosome behavior in these mutants, it has been possible to infer the functions that are specified in the wild-type alleles of these loci in insuring a normal meiosis.

This paper concerns the characterization of a meiotic mutant, *paternal loss* (*pal*).

TECHNICAL

pal is a second-chromosome, ethyl-methanesulfonate-induced, meiotic mutant (*mei-W5* of SANDLER 1971). Salivary preparations revealed no abnormalties on the *pal* second chromosome. A preliminary mapping with respect to *Sp J Pin* L^2 (for a full description of markers and chromosomes used in this study, see LINDSLEY and GRELL 1968) placed *pal* approximately halfway between *Sp* and *J* (163 unselected chromosomes tested). For a precise localization 130 recombinants between *Sp* and *J* were selected from *Sp* + *J*/+ *pal* + females and tested for the presence of *pal*; the results were + *pal J* = 15, + + *J* = 43, *Sp pal* + = 51 and *Sp* + + = 21. This places *pal* at 35.7 on *2L* assuming the standard map positions for *Sp* and *J*. (It should be noted, however, that in this mapping, the *Sp-J* map distance was 9.1 (8670 offspring) as compared to a distance of 19 units from their standard positions. A control cross of *Sp* + J/+ + + females gave a *Sp–J* distance of 9.3 units (7771 offspring).)

pal is complemented by the second chromosome region 27C–31E inserted into the *Y* in *T(Y;2)B231* and by second chromosome deficiencies for regions 27D–28C, 28D–29F, 30F–31CD, and 31CD–31DE in segmental aneuploids derived from the *Y;2* reciprocal translocations *A171* + *B66*, *B104* + *A145*, *L52* + *G20*, and *G20* + *J166*, respectively (LINDSLEY and SANDLER *et al.* 1972). Other deficiencies in the region 27D–31E were either inviable or sterile. This localizes *pal* to either region 28C–28D or 29F–30F of the salivary chromosome map.

The meiotic effects of *pal* have been examined for temperature sensitivity at 18°, 25° and 28° and no alteration in the frequencies or types of abnormal chromosome behavior were found.

BASIC CHARACTERISTICS OF *pal*

Sex and fourth chromosomes: The effect of *pal* on the meiotic behavior of the sex and fourth chromosomes was examined in crosses of y/y^+Y; *pal/pal*; spa^{pol}/spa^{pol} males to *y pn*/*y pn*; *C(4)RM*, *ci* $ey^R/0$ females. In this cross, nondisjunction of both the sex and fourth chromosomes is detectable. The products of regular segregation and nondisjunction at meiosis I are in principle equally recoverable. Because of their erratic viability, the haplo-*4* Minute progeny that result from

half of all the products of regular fourth chromosome disjunction were not recorded in these, or any other, crosses in which they were observed. The results of this cross (Table 1, cross 1) show that *pal* causes loss of both sex and fourth chromosomes; 17.4% of the progeny did not receive a paternal fourth chromosome and 2.4% did not receive a paternal sex chromosome. For both chromosome pairs the data reveal little, if any, excess over background in the frequency of diplo-exceptional sperm. Thus, *pal* causes chromosome loss but little, if any, nondisjunction.

In crosses to free *X* females, (Table 1, crosses 1–3), nondisjunction at the second meiotic division would give rise to nullosomic sperm that would be recoverable as well as diplo-*X* and diplo-*Y* sperm that would not be detected. (Diplo-*X* sperm result in triplo-*X* zygotes which die and diplo-*Y* sperm result in male progeny that are indistinguishable from the regular male progeny.) The occurrence of second division nondisjunction was detectable in a cross of *pal* males to attached-*X* females that allows the recovery and detection of diplo-*X* sperm. Only two diplo-*X* sperm were recovered (Table 1, crosses 4,5) as compared to 417 nullo-*XY* sperm, showing clearly that sex chromosome nondisjunction at the second meiotic division is very rare in *pal* males and cannot account for the previous recovery of only nullo-*XY* sex chromosome exceptions. Thus the defect in *pal* results in loss, but not nondisjunction, of both the sex and fourth chromosomes.

In addition to producing exceptions that failed to receive one, or more, paternal chromosome, *pal* also causes somatic loss of the sex chromosomes. For example, in the progeny of *pal* males crossed to free-*X* females (Table 1, cross 1) there were 3.4% gynandromorphs (*XX-X0*) and 0.7% y^+Y mosaic (*XY-X0*) progeny.

Table 1 also reveals that not all chromosomes are equally affected by *pal*. For example, in cross 1 the frequency of sperm that are nullo-*4* (0.174) is much greater than the frequency of sperm that are nullo-*XY* (0.024). Similarly, the frequency of somatic loss of an *X* chromosome (0.034) is greater than the frequency of somatic loss of a y^+Y chromosome (0.007).

These data also show that the loss of sex and fourth chromosomes is not independent in *pal* males. Specifically there is a 1.4–2.1-fold excess of sperm that failed to receive both a sex and a fourth chromosome over the number expected if these heterologs were being lost independently (Table 1, crosses 1,4).

Second and third chromosomes: The effect of *pal* on second and third chromosome behavior was examined in crosses of homozygous *pal* males bearing normal autosomes by *XXY* attached-autosome-bearing females (either $+/+/B^sY$; *C(2L)RM,dp*; *C(2R)RM,cn* or $+/+/B^sY$; *C(3L)RM,ri*; *C(3R)RM,sr*). In such females, the *Y* chromosome frequently segregates from both attached autosomes, resulting in the production of X/B^sY; *0*; *0* and *X*; *C(AL)RM;C(AR)RM* ova in approximately equal frequencies (GRELL 1970). In a cross of free autosome males by such females, the only progeny that survive are those that result from the union of a gamete that is disomic for the autosome in question from one sex with a gamete that is nullosomic for that chromosome from the other sex. Thus, while it is possible to determine if nondisjunction or loss of the major autosomes is

TABLE 1

Sex and fourth chromosome behavior in males

Crosses are of y/y^+Y; spa^{pol}/spa^{pol} males of the indicated second chromosome constitution by *y pn/y pn; C(4)RM,ci ey^R/0* females (crosses 1–3) or by *C(1)RM,y pn v/Y; C(4)RM,ci ey^R/0* females (crosses 4–5).

Second chromosomes of males	Constitution of male gametes producing recovered progeny: Nonmosaic progeny *X,4*	*Y,4*	*0,4*	*XY,4*	*X,0*	*X,44*	*Y,0*	*Y,44*	*XY,0*	*XY,44*	*0,44*	*0,0*	*XX,4*	Mosaic progeny* *X,4*	*X,0*	*Y,4*	*Y,0*	Total
														X X-X 0 mosaics		*X Y-X 0* mosaics		
1. *pal/pal* observed	18785	14637	749	76	3892	15	3074	5	5	0	2	246	—	662	144	98	18	42,408
expected†	18732	14624	823	69	3948	12	3083	9	14	0	1	173	—	665	140	96	20	42,409
2. *pal/SM1*	13353	9529	130	47	82	6	88	5	1	0	1	1	—	1	0	0	0	23,244
3. +/+	2973	2758	6	4	7	5	4	3	1	0	2	0	—	0	0	0	0	5,763
														$\overline{XX}$ *X-$\overline{XX}$ 0* mosaics		$\overline{XX}$ *Y-$\overline{XX}$ 0* mosaics		
4. *pal/pal* observed	1981	4843	283	10	400	8	747	0	2	0	0	134	2	68	11	42	9	8,461‡
expected†	2022	4731	353	10	365	2	854	5	2	0	0	64	2	—	—	43	8	8,461
5. +/+	1396	2941	3	0	1	3	1	2	0	0	0	0	0	0	0	0	0	4,347

Second chromosomes of males	Frequency of exceptions: nullo-*XY*§	*XY*§	*nullo-4*§	*44*§	*X X-X 0* mosaics¶	*X Y-X 0* mosaics¶	$\overline{XX}$ *Y-$\overline{XX}$ 0* mosaics¶
1. *pal/pal*	23.5	1.9	174.0	0.5	34.2	6.5	
2. *pal/SM1*	5.7	2.1	7.4	0.5	0.07	0.0	
3. +/+	1.4	0.9	2.1	1.7	0.0	0.0	
4. *pal/pal*	48.8	1.4	152.3	0.9	—		9.0
5. +/+	0.7	0.0	0.5	1.1	—		0.0

* Progeny exhibiting somatic loss of a sex chromosome. Genotypes are of progeny. A "—" separates different parts of mosaics.
† Calculated assuming independence of sex and fourth chromosome behavior.
‡ Not counting *XX/X-XX/0* mosaics.
§ Exceptions per 10^3 progeny.
¶ Exceptions per 10^3 progeny that received the chromosome lost somatically.

occurring in *pal* males, it is not possible to determine the rate. These crosses were carried out both using single males (1 ♂ and 3 ♀♀/vial) and *en masse* (15 ♂♂ and 45 ♀♀/quarter pint bottle). The results did not differ significantly and have been pooled (Table 2); an analysis of these data is presented in Table 3. Both nullo-*A* and diplo-*A* exceptional sperm (measured as progeny per male) are recovered more frequently from *pal/pal* and *pal/SM1* males than they are from +/+ males. Moreover, although homozygous and heterozygous *pal* males produce equivalent frequencies of diplo-*A* exceptional sperm, nullo-*A* sperm are recovered significantly more frequently from *pal/pal* males than they are from *pal/SM1* or +/+ controls. Thus *pal* causes loss of the major autosomes. Since diplo-*A* exceptions are produced more frequently by *pal/pal* and *pal/SM1* males than +/+ males, it may be the case that *pal* causes some nondisjunction of the major autosomes. However, if this is the case, then *pal* is a complete dominant mutant with respect to its effect on nondisjunction and an almost fully recessive mutant with respect to its induction of chromosome loss. Alternatively, the increase above background in nondisjuncion in *pal/pal* males and their *pal/SM1* sibs may be due to some other locus in the stock.

These crosses also reveal that the somatic loss of chromosomes (*X* and *4*) caused by *pal* is more frequent in progeny derived from second or third chromosome exceptional sperm than it is among progeny derived from mono-*2* mono-*3* sperm. Thus, somatic loss of the *X* chromosome occurs in approximately 3.4–6.5% of the zygotes derived from mono-*X*,*2* and *3* sperm (Tables 1, 6), in 16.1% of the zygotes derived from mono-*X*,*3*, nullo-*2* sperm, and in 16.0% of the zygotes derived from mono-*X*,*2*, nullo-*2* sperm. Similarly, fourth chromosome loss was observed in only 1.7–3.2% of the progeny derived from second and third regular sperm (Table 7), but occurred in 14.5% of the progeny derived from mono-*3*,*4* nullo-*2* sperm, and in 8% of the progeny derived from mono-*2*,*4* nullo-*3* sperm. The rates of *X* and fourth chromosome somatic loss are also higher among progeny derived from diplo-*2* or diplo-*3* sperm than they are among progeny derived from mono-*2*,*3* sperm.

In summary, when homozygous in males, *pal* can cause the loss of any chromosome pair so as to produce progeny that did not receive one, or more, paternal chromosomes. In addition, *pal* can cause the somatic loss of chromosomes in the male's progeny. That chromosomes differ in their sensitivity to the defect caused by *pal* is exhibited by their different frequencies of loss. Finally, the behavior of heterologs is positively correlated in that: (1) simultaneous losses of two chromosomes are more frequent than expected from independence; and (2) when the loss or non-disjunction of a major autosome has occurred, a subsequent somatic loss of both sex and fourth chromosomes occurs more frequently than in those cases where the major autosomes have segregated normally. A discussion of these two observations will be reserved until a later section.

TIME OF *pal*$^+$ FUNCTION

The above data demonstrate that the *pal*$^+$ gene product is required at least germinally in males for normal chromosome segregation. In order to understand

TABLE 2

Disjunctional behavior of second and third chromosomes

Crosses are of y/y^+Y; —/—, +/+; spa^{pol}/spa^{pol} males bearing the indicated free second chromosomes by either +/+/B^sY; *C(2L)RM,dp; C(2R)RM,cn;* +/+; +/+ females (crosses 1–3) or +/+/B^sY; +/+; *C(3L)RM,ri; C(3R)RM,sr;* +/+ females (crosses 4–6).*

Male gametes:	*X,0*	*Y,0* or *0,0*	*X,AA*	*Y,AA* or *0,AA*	*X,AA*	*Y,AA* or *0,AA*	*X,0*	*Y,0* or *0,0*	*X,0*	*X,AA*		
Female gametes:	*X,AA*	*X,AA*	*XY,0*	*XY,0*	*X,0*	*X,0*	*XY,AA*	*XY,AA*	*X,AA*	*XY,0*		
Second chromosome of male	Second chromosome data								Gynandromorphs		Number of ♂ parents	Total progeny
1. *pal/pal*	96(18)†	216(30)	98(10)	95(10)	2	2	0	2	27(6)	9(1)	682	622
2. *pal/SM1*	42	31	58	43	0	0	0	0	0	0	314	174
3. +/+	10	16	21	21	2	0	0	0	0	0	450	70
	Third chromosome data											
4. *pal/pal*	64(5)	71(7)	26(2)	35(4)	0	1	4	0	17(1)	1	769	238
5. *pal/SM1*	27	25	13	20	0	0	0	0	0	0	349	85
6. +/+	14	13	9	8	0	0	1	0	0	0	495	45

* Triploid, intersex, triploid-intersex mosaic, and superfemale progeny not recorded.
† Numbers in parenthesis are *4 4–4 0* mosaics.

TABLE 3

Analysis of data presented in Table 2 on the disjunctional behavior of the second and third chromosomes

Paternal second chromosomes	Autosomal exceptions			# ♂ parents	Autosomal exceptions per 100 ♂ parents			$\left(\frac{\text{\# nullo exceptions}}{\text{\# diplo exceptions}}\right)$	$\left(\frac{\text{\# nullo exceptions/\# diplo exceptions}}{\text{\# diplo exceptions in } SM1/pal \text{ control}}\right)$
	nullo	diplo	total		nullo	diplo	total		
	Second chromosome data								
1. *pal/pal*	395	227	622	682	57.9	33.3	91.2	1.74	2.42
2. *pal/SM1*	73	101	174	314	23.2	32.2	55.4	0.72	1.00
3. +/+	26	44	70	450	5.8	9.8	15.6	0.59	0.82
	Third chromosome data								
4. *pal/pal*	169	69	238	769	22.0	9.0	31.0	2.45	1.55
5. *pal/SM1*	52	33	85	349	14.9	9.5	24.4	1.58	1.00
6. +/+	28	17	45	495	5.7	3.4	9.1	1.65	1.04

the nature of the function specified by *pal*+ it is necessary to know if the wild-type gene product is required at other times during the life cycle. Therefore the effect of *pal* on female meiosis and on the mitotic cell divisions that produce the adult cuticle was examined.

The disjunction of *X* and fourth chromosomes as well as recombination on the *X* chromosome was monitored in homozygous *pal* females. The disjunction of the *X* and fourth chromosomes is normal in homozygous *pal* females (Table 4). The frequency of recombination in homozygous *pal* females is slightly less than that observed in heterozygous *pal* controls (Table 5). The reduction in recombination is most severe in the distal region (86% of the control) and least severe proximally (98% of the control). A tetrad analysis (Table 5) showed that, relative to the control, there is an increased frequency of no exchange and single exchange tetrads and a decreased frequency of double exchange tetrads in homozygous *pal* females. These differences have been observed in all other crosses of homozygous *pal* females in which recombination was examined (unpublished data). This differential reduction in recombination is similar to that observed in a number of female-specific meiotic mutants (see e.g., review by BAKER and

TABLE 4

Sex and fourth chromosome behavior in females

Crosses are *y/y*; —/—; spa^{pol}/spa^{pol} females by $Y^{S}X{\cdot}Y^{L}$, *In(1)EN, v f B/0*; *C(4)RM,ci* $ey^{R}/0$ males.

Second chromosome of females	Constitution of female gametes producing recovered progeny									
	X,4	*X,44*	*X,0*	*XX,4*	*0,4*	*XX,0*	*XX,44*	*0,0*	*0,44*	Total
1. *pal/pal*	4,227	0	2	4	1	0	0	0	0	4,234
2.* +/+	15,824	5	8	0	4	2	0	0	1	15,844

* Data from BAKER and CARPENTER (1972).

TABLE 5

Recombination in females

Crosses are of y^2 *cv v f car/y + + + +*; —/—; spa^{pol}/spa^{pol} females by $Y^SX{\cdot}Y^L$, *In(1)EN, v f B/0; C(4)RM, ci* $ey^R/0$ males. Regions are *y(1) cv (2) v (3) f (4) car.*

Progeny	2nd chromosome genotype of females		Map distances, region	2nd chromosome genotype of females	
	pal/pal	*pal/+*		*pal/pal*	*pal/+*
B/+ ♀	3323	3464	1	11.92 (0.859)*	13.87
Males			2	21.72 (0.877)	24.77
NCO	1953	1916	3	17.96 (0.932)	19.27
SCO 1	363	428	4	6.31 (0.975)	6.47
SCO 2	780	891	sum	57.91 (0.899)	64.38
SCO 3	594	614	Tetrad distribution		
SCO 4	200	173	E_0	0.059	0.031
DCO 1,2	25	34	E_1	0.733	0.662
DCO 1,3	77	108	E_2	0.197	0.294
DCO 1,4	19	31	E_3	0.010	0.011
DCO 2,3	59	92			
DCO 2,4	32	64			
DCO 3,4	5	14			
TCO 1,2,3	1	3			
TCO 1,2,4	3	1			
TCO 1,3,4	0	1			
TCO 2,3,4	1	0			
Total ♂ ♂	4102	4382			

* Map distance relative to that in *pal/+* control cross.

HALL 1975). Since the locus responsible for the recombinational defect associated with the *pal*-bearing second chromosome has not been mapped, it is not clear if this effect is due to *pal* or an unrelated female meiotic mutant. The similarity of the effect to that of known female-specific mutants leads me to suspect that it is due to a second mutant. Thus, with the possible exception of a very weak effect on recombination, *pal* does not affect meiotic chromosome behavior in females.

The effect of *pal* on chromosome segregation in somatic cells was examined by crossing heterozygous *pal* males (y/y^+Y; *pal/SM1*; spa^{pol}/spa^{pol}) and females (*y/y*; *SM1/pal*; spa^{pol}/spa^{pol}) and scoring their homozygous *pal* progeny for somatic chromosome loss. No somatic losses were observed of either the y^+Y chromosome (1377 homozygous *pal* male progeny) or an *X* chromosome (1611 homozygous *pal* female progeny). Thus, pal^+ is not required in somatic cells for normal chromosome segregation. Moreover, the occurrence of somatic losses in pal^+/pal^+ progeny of homozygous *pal* males (Table 2, cross 1) shows that the occurrence of somatic loss in the progeny of a *pal* male is not dependent on the progeny's genotype at the *pal* locus.

These experiments then suggest that pal^+ is only required at some stage in the male's germ line and that it is the male's genotype at the *pal* locus that determines the occurrence of somatic losses in his progeny.

PARAMETERS OF CHROMOSOME LOSS

Parental origin of chromosomes lost somatically: The observation of somatic chromosome loss in the progeny of *pal* males suggests two alternatives as to the nature of the abnormality caused by *pal* that leads to somatic chromosome loss. First, pal^+ could act in males to specify a product that is transferred extrachromosomally to the egg and is requisite for normal cleavage divisions. Alternatively, pal^+ could specify some component of the chromosomes themselves that is necessary for their normal inheritance and thus *pal* males would contribute defective chromosomes to the egg. These two alternatives should be distinguishable since, in their simplest forms, the first model predicts that both paternally and maternally derived chromosomes would be lost somatically, whereas the second model predicts that only paternally derived chromosomes would be lost.

The parental origin of *X* chromosomes lost somatically in the progeny of *pal* males was examined in a cross of y^+ *car*/y^+Y; *pal*/*pal*; spa^{pol}/spa^{pol} males to y/y; +/+; +/+ females (Table 6, cross 1). Of the 147 gynandromorphs (*XX-XO*) recovered, all had patches of phenotypically y tissue. The y tissue was invariably male when it encompassed structures that are sexually dimorphic. Thus, somatic loss of only the paternal *X* chromosome occurs in progeny of *pal* males. Although not indicated in Table 6, in eight of the 147 gynandromorphs (5.5%), the non-male tissues had some constellation of the characteristics normally associated with superfemales (e.g., rough eyes, upturned posterior scutellars, shorter malformed wings, and twisted third legs) and were therefore probably superfemale-male mosaics (*XXX-X0*) resulting from somatic nondisjunction of the paternal *X* chromosome. Such mosaics have been observed in all crosses involving *pal* males at similar, or lower, frequencies. With respect to the progeny of *pal* males that have lost the y^+Y chromosome (e.g., Table 1, crosses 1,4; Table 6, crosses 1,2), this loss must perforce be of a paternal chromosome as that is the only source of a y^+Y chromosome in these crosses.

The somatic loss of fourth chromosomes in progeny of *pal* males was looked for in a cross of *pal* males carrying the attached-fourth chromosome *C(4)RM*, *ci* ey^R/O by females bearing free fourth chromosomes marked with spa^{pol}. Somatic loss of the paternally-derived, compound-fourth chromosome gives rise to tissue that has the *Minute* phenotype associated with monosomy for the fourth chromosome. If the haplo-*4* patch includes eye tissue, that tissue will be phenotypically spa^{pol}. Somatic loss of the maternal fourth chromosome gives rise to diplo-*4* (i.e., not *Minute*) tissue that should express the recessive markers *ci* ey^R on the paternal chromosome when eye or wing tissue is included in the diplo-*4* patch. The results of this cross (Table 7, cross 1) show that somatic loss of fourth chromosomes does occur in progeny of *pal* males and that only paternally derived chromosomes are lost. To confirm this result, crosses were carried out in which the fourth chromosome constitutions of the parents were reversed. These experiments show that the spa^{pol} chromosome is lost somatically when it is derived from a *pal* father (Table 7, cross 2) and the *C(4)RM*, *ci* ey^R is not lost when it is maternally derived (Table 7, cross 3). It should be noted that the estimates of the

TABLE 6

Parental source of sex chromosomes loss somatically and nonindependence of somatic loss of sex and fourth chromosomes

Cross 1: *car/y+Y; pal/pal; spa^{pol}/spa^{pol}* males by *y/y; +/+; +/+* females. Cross 2: *y/y+Y; pal/pal; spa^{pol}/spa^{pol}* males by *C(1)RM,y pn v/O; +/+; +/+* females.

	Constitution of male gametes producing recovered progeny										
	X,4	*Y,4*	*0,4*	*X,4*			*Y,4*			*0,4*	
	Nonmosaic progeny			Mosaic progeny*							
Cross				*XX,44-X0,44*	*XX,44-XX,40*	*XX,44-X0,40*†	*XY,44-X0,44*	*XY,44-XY,40*	*XY,44-X0,40*†	*X0,44-X0,40*	Total
1. observed	2066	2003	61	140	67	7	24	58	4	2	4431
expected‡	2067.0	1997.3	61.1	142.5	65.9	4.5	26.1	63.7	0.8	1.9	4430.8
					X0,44-X0,40		$\overline{XX}Y$,44-XX0,44	$\overline{XX}Y$,44-XXY,40	$\overline{XX}Y$,44-$\overline{XX}$0,40†	$\overline{XX}$0,44-$\overline{XX}$0,40	
2. observed	4476	4040	522	—	157	—	91	106	25	17	9434
expected‡	4483.2	4012	521.6	—	149.8	—	112	134	3.7	17.4	9433.7

	Frequency of exceptions			
	nullo-*XY*§	*XX-X0* mosaics¶	*XY-X0* mosaics¶	*44-40* mosaics¶
1.	14.2	64.5	13.4	31.1
			$\overline{XX}$/Y-$\overline{XX}$/0 mosaics¶	
2.	57.1	—	27.2	32.1

* Losses were of paternally derived chromosomes. Genotypes are of progeny. The maternal member of each chromosome pair is listed first. A "-" separates different parts of a mosaic.

† See text for full description of mosaics that arose from loss of both a sex and fourth chromosome.

‡ Calculated assuming independence of sex and fourth chromosome behavior.

§ Exceptions per 10^3 progeny.

¶ Exceptions per 10^3 progeny that received the paternal chromosome in question.

TABLE 7

Parental source of fourth chromosomes lost somatically

Cross 1: *y pn/y+; pal/pal; C(4)RM,ci ey^R/0* males by *y/y; +/+; spa^{pol}/spa^{pol}* females. Cross 2: *y/y+Y;* pal/pal; *spa^{pol}/spa^{pol}* males by *pn/pn; +/+; +/+* females. Cross 3: *y/y+Y; pal/pal; spa^{pol}/spa^{pol}* males by *y pn/y pn; C(4)RM,ci ey^R/0* females.

Fourth chromosomes of parents		Nonmosaic progeny	Fourth chromosome mosaic progeny			Total	Mosaics/ 10^3 progeny
♂	♀		*4-4.4-0*	*4-4.0-4*	*4-4.0-0*		
1. *4/0 (ci ey^R)*	*4/4 (spa^{pol})*	3972	0*	69†	—	4041	17.1
2. *4/4 (spa^{pol})*	*4/4 (+)*	1894	—	—	75‡	1969	38.1
3. *4/4 (spa^{pol})*	*4/0 (ci ey^R)*	11227	—§	0	—	11227	0.0

* Indicated mosaics plus *4/0* exceptions.

† Forty-three flies had some head tissue haplo-*4* (Minute) and some eye tissue *spa^{pol}*; 25 flies had no head tissue haplo-*4* (Minute) and no eye tissue *spa^{pol}*; 1 fly had some head tissue haplo-*4* (Minute) and no eye tissue *spa^{pol}*.

‡ No eye tissue *spa^{pol}*.

§ Not distinguishable from *4/0* nonmosaic exceptions.

frequencies of somatic fourth chromosome loss obtained from these crosses are minimum estimates because the *Minute* phenotype used to detect the mosaics could only be reliably scored in the major head and thoracic bristles; haplo-*4* patches that did not encompass these structures would have been missed.

These experiments are consistent with the second model, namely that *pal+* specifies a product necessary for the inheritance of normal chromosomes. Thus, in *pal* males defective chromosomes are produced which tend to get lost during the embryonic divisions of their progeny. However, one important qualification should be noted with respect to this conclusion. The first mitotic division of the Drosophila embryo is gonomeric (HUETTNER 1933) (i.e., the parental chromosome sets remain separate during the first zygotic cleavage division). Thus, if all loss occurs at the first mitotic division in the progeny of *pal* males, the data showing that only paternal chromosomes were lost would also be consistent with a slightly modified form of the first model: that *pal+* specified a product that was inherited extrachromosomally by the zygote, and functioned for only that region of the gonomeric first mitotic division that contained the paternally derived chromosomes. To inquire whether this is a valid alternative, one may determine at which of the embryonic nuclear divisions loss occurs.

Time of somatic chromosome loss: The time of *pal*-associated somatic chromosome loss may be determined if it is assumed that the loss of one of a pair of homologs at any particular mitotic division will result in an adult that has a monosomic patch of tissue whose size is reciprocally related to the cell division at which the loss occurred. For example, if one of the two daughter cells of the first mitotic division fails to receive a particular chromosome, one-half of the cells of the resulting adult should be missing this particular chromosome. Although it is not possible to examine all cells in a mosaic, it is feasible to determine what proportion of a selected subset of cells (in this study, the adult cuticle for which markers are available to determine cellular genotypes) are derived from a cell

in which loss occurred (see, e.g., STURTEVANT 1929; LEE, KIRBY and DEBNEY 1967; GARCIA-BELLIDO and MERRIAM 1968 for a discussion of these procedures). In order to circumvent errors that would result from differential limits on cell multiplication in different tissues, each region of the adult cuticle that is derived from one imaginal disk, or well-defined part of a disk, is scored as a single point. Thus, what is scored in a mosaic is the fraction of these parts that is derived from the cell in which loss occurred. In deriving estimates of the time of *pal*-associated somatic loss, the sets of landmarks (structures) of the adult cuticle listed in Table 13 were used. In determining the proportion of the structures in a mosaic that failed to receive a given chromosome, parts that received the chromosome were counted as zero, those that did not receive the chromosome as one, and those mosaic for the chromosome as one-half.

The data from the analysis of 128 *C(1)RM/Y-C(1)RM/0* mosaic progeny of y/y^+Y; *pal/pal*; spa^{pol}/spa^{pol} males crossed to *C(1)RM,y pn v/0*; +/+; +/+ or *C(1)RM, y pn v/Y*; +/+; *C(4)RM,ci* $ey^R/0$ females is presented in Figure 1a. The average fraction of nullo-y^+Y tissue in these mosiacs is 51.7%, suggesting that mean time of loss of the y^+Y chromosome is the first embryonic nuclear division. The rather wide variation in the amount of nullo-y^+Y tissue may be due to loss occurring at different times in the mosiacs. However, the distribution is roughly symmetrical about the mean whereas, *a priori*, late losses (small patches) and multiple losses (large patches) would not be expected with equal probability. Moreover, even if all loss occurs during just the first nuclear division a wide variance in patch size is to be expected since only a small fraction of the cells present at the blastoderm stage are represented by descendants in the adult cuticle (estimated to be 16% in *D. simulans*, GARCIA-BELLIDO and MERRIAM 1968). However, these considerations do not rule out the possibility that the occurrence of multiple losses within a single fly, as well as losses at later nuclear divisions, also contribute to the wide variation in the amount of mosaicism depicted in Figure 1a. Despite these uncertainties it seems likely that most somatic loss of the y^+Y chromosome in the progeny of *pal* males occurs at the first embryonic nuclear division.

A similar analysis of 111 *X/Y-X/0* mosaic progeny of X/y^+Y; *pal/pal* males crossed to *X*, *y/X*, *y* females is presented in Figure 1b. In these mosaics the average proportion of nullo-y^+Y tissue is 51.6% and the distribution is symmetrical, suggesting that in male as well as female progeny of *pal* males, the y^+Y chromosome is lost primarily at the first embryonic nuclear division.

The amount of male tissue in 389 *XX-X0* mosaics was analyzed to determine the time of *X* chromosome loss. The mosaicism in these flies was scored using either a y^+ paternal *X vs.* a *y* maternal *X*, or a y^+ w^+ sn^+ paternal *X vs.* a *y w* sn^3 maternal *X*, or a y^2 w^+ sn^+ paternal *X vs. y w* sn^3 maternal *X*. As neither the mean time of loss (i.e., average fraction of male tissue, Table 8) nor the variation in the amount of mosaicism differed substantially between the different series of *XX-X0* mosaics, they have been pooled for presentation here (Figure 1c). The average proportion of male tissue in these mosaics is 33.8%. This suggests that *X* chromosomes derived from *pal* males are often lost at stages later than the first embryonic nuclear division. The striking difference between

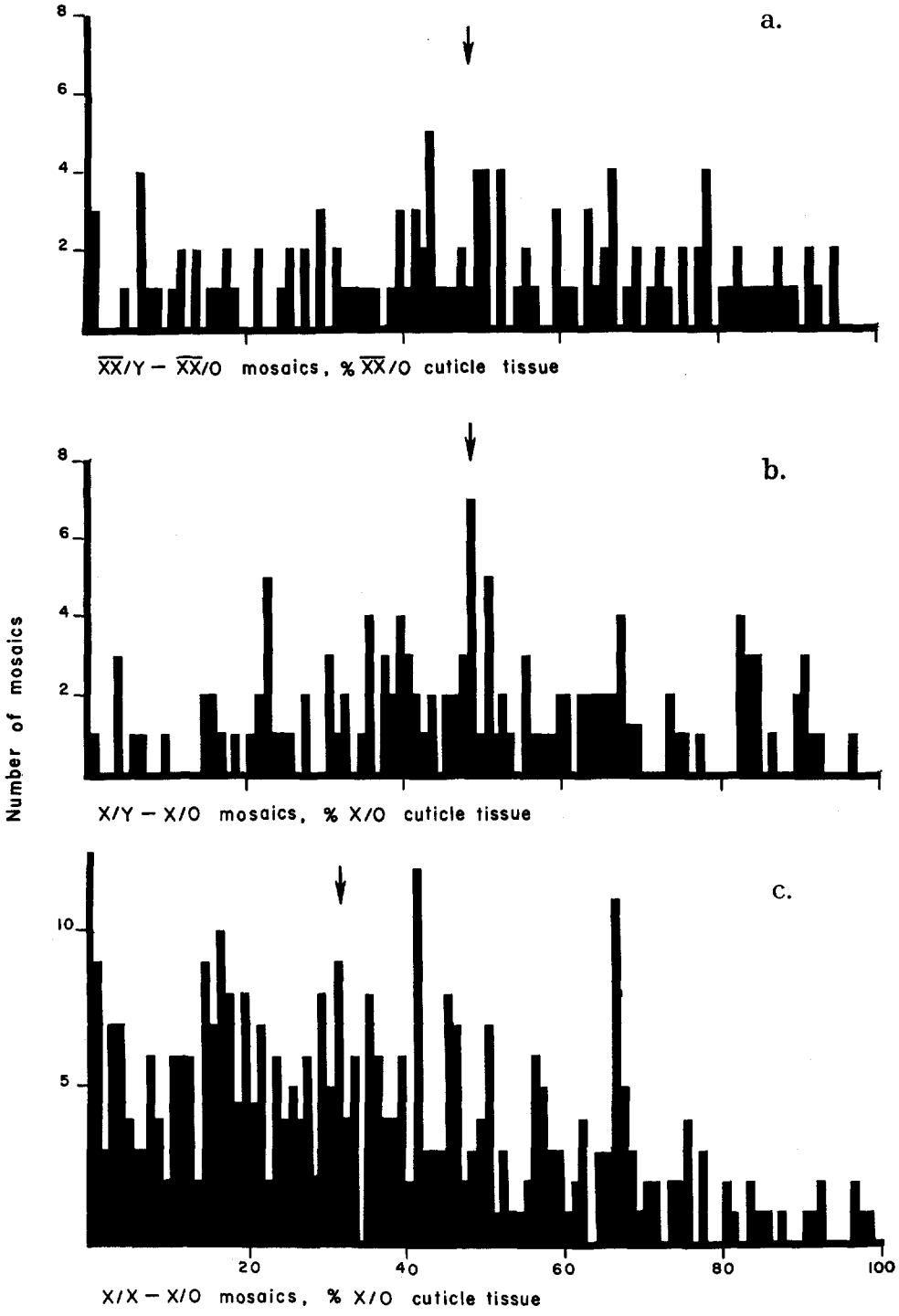

FIGURE 1.—Distribution of amount of monosomic cuticle tissue in *pal*-induced sex chromosomal mosaics. Arrow indicates mean.

TABLE 8

Amount of detected male cuticle in gynandromorphs using various markers

	Paternal *X* chromosome	Maternal *X* chromosomes	Average percent of cuticle that is male	Number of gynandromorphs
1	*car*	*y w sn*^{3}	37.9	44
2	*car*	*y*	32.8	157
3	*y*^{2} *v f car*	*y w sn*^{3}	36.5	30
4	*y*^{2} *v f car*	*y w sn*^{3} *car*	31.8	113
5	*pn*	*y w sn*^{3}	36.0	45
			33.8	Total = 389

these results and those obtained with respect to the time of loss of the y^+Y chromosome is probably real and not the result of selection against *X0* cells in *XX-X0* mosaics, since in *XX-X0* mosaics produced by other methods (*e.g.*, *ca*nd, *In(1)w*^{vC}), the average amount of *X0* tissue is nearly 50% (reviewed by HALL, GELBERT and KANKEL 1975).

In summary, the mean time of somatic loss of the *Y* chromosome is at the first embryonic nuclear division, whereas the *X* chromosome is lost at both the first and second (and perhaps subsequent) nuclear divisions. The possibility, suggested above, that *pal*$^+$ might specify an extrachromosomally inherited product that was required in only that portion of the first (gonomeric) mitotic division that contained the paternal chromosomes is not supported by the finding that *X* chromosomes can be lost at stages later than the first embryonic nuclear division. However, the alternative model, that *pal*$^+$ specifies a product that is required for the inheritance of normal chromosomes, is consistent with these results. Moreover, since the mean time of loss of both the *X* and *Y* chromosomes is early, it must be the case that defective chromosomes either have a very high probability of loss per mitotic division and are thus quickly eliminated or else that they are rendered stable very early in zygotic development.

These conclusions are based on the study of chromosome behavior in the somatic cells that are the progenitors of the adult cuticle. Whether chromosomes were rendered stable in the germ line of progeny of *pal* males was also examined. Virgin $\overline{XX}Y$-$\overline{XX}0$ progeny of *pal* males (Table 6, cross 2) were crossed to $\overline{XY}$,*y B/0*; *pal*$^+$/*pal*$^+$ males to determine whether the y^+Y chromosome that had been lost somatically in these females would also be lost in these females' sons. A total of 95 y^+Y mosaic females were tested in this manner and, of these, 30 transmitted the y^+Y to some of their sons. Of the 1,241 sons that received the y^+Y chromosome, none were mosaic. This result, plus the finding that most somatic chromosome loss in progeny *pal* males occurs at the early mitotic divisions of the zygote, suggests that the defect that causes the loss of chromosomes inherited from *pal* males is no longer operative after some early point in the development of the zygote.

Loss before the first zygotic mitosis: The chromosome losses that produce exceptions which failed to receive one, or more, paternal chromosomes could, *a*

priori, result from loss during the premeiotic (gonial) mitoses, at either meiotic division, or zygotically in the progeny of *pal* males at or before the first mitotic division. That at least some of these exceptions result from postfertilization loss is shown by the observation that their frequency is dependent on the female parent. Thus, in crosses of *pal* males to *C(1)RM,y pn v/0* females, the frequency of *XX0* exceptions is more than twice as great (11% *vs.* 6%) as in crosses of males from the same stock to other females (Table 9). That the increased frequency of XX0 exceptions in the cross to *C(1)RM,y pn v/0* females is real is suggested by the observation that somatic loss of the y^+Y chromosome is also increased (3–5-fold) in this cross (Table 9). Furthermore, the increased loss observed in this cross was reproducible in crosses done over a year apart. (The data in Tables 9 and 6 are the sum of these two experiments.)

This result that the female parent can influence the frequency of nullo-paternal *XY* exceptions, shows that some, if not all, such exceptions are the result of the loss of paternal chromosomes in the zygote.

CHROMOSOME-SPECIFIC FACTORS INFLUENCING LOSS

The frequencies of loss for different chromosomes are not the same (Table 10), suggesting that chromosomes differ in some way in their sensitivity to the *pal* defect.

The investigation of the causes of the differential sensitivity of chromosomes to the *pal* defect was facilitated by the discovery of an *X* chromosome (which happened to carry the marker *pn* and will be referred to as the "pn chromosome") that was lost less frequently than other *X* chromosomes. *X*-chromosome, somatic loss (*XX-XO* mosaics) normally occurs at a frequency of 4% to 6% among the female progeny of *pal* males crossed to free-*X*-bearing females; in similar crosses of *pal* males bearing the *pn* chromosome only 1% of such mosaics are found (Table 11). Furthermore, exceptions that failed to receive a paternal sex chromo-

TABLE 9

Maternal effect on frequency of loss of paternal chromosome

Crosses of y/y^+Y; *pal/pal*; spa^{pol}/spa^{pol} males to indicated females.

	Female parent	Frequency of exceptions, percent		Total
		nullo-*XY**	y^+Y mosaic†	
1.‡	$\overline{XX}$,*y pn v/0*; +/+; +/+	11.2	2.49	9,434
2.§	$\overline{XX}$,*y pn v/Y*; +/+; *C(4)RM,ci* $ey^R/0$	6.88	0.90	8,461
3.¶	*y pn/y pn*; +/+; *C(4)RM,ci* $ey^R/0$	5.29	0.65	42,408

* Calculated using all flies of the same sex as the nullo-*XY* exceptions as the denominator.
† Calculated using all flies that had received the y^+Y (i.e., had some y^+ cuticle tissue) as the denominator.
‡ Data from Table 6, cross 2.
§ Data from Table 1, cross 4.
¶ Data from Table 1, cross 1.

TABLE 10

Frequencies of loss of sex and fourth chromosomes caused by pal

Chromosome	Frequency somatic loss	Frequency nullo exceptions
X*	0.034	0.024
y^+Y*	0.007	
4†	0.038	0.174
$\overline{44}$‡	0.017	——

* Data from Table 1, cross 1.
† Data from Table 1, cross 1 and Table 7, cross 2.
‡ Data from Table 7, cross 1.

some also occur at a lower frequency among the progeny of *pal* males carrying the *pn* chromosome. Since the frequencies of nullo-4 and *Y*-mosaic exceptions obtained from males with the *pn* chromosome do not differ from those observed with *pal* males with other *X* chromosomes (Table 11), it must be that the difference between the *pn* chromosome stock and other *pal* stocks is restricted to the *X* chromosomes. Cytological preparations of salivary chromosomes and larval ganglion chromosomes revealed no abnormalities in the *pn* chromosome. Genetic tests for translocations involving the *pn* chromosome were negative. In order to map the site responsible for the difference between the *pn* and other *X* chromosomes, females heterozygous for the *pn* chromosome and a y^2 *v f car* chromosome that had normal levels of loss when inherited from a *pal* father were constructed. Forty-two unselected *X* chromosomes were recovered in male progeny, scored for *v*, *f*, and pn^+ car^+ (*pn*, *pn car*, and *car* could not be distinguished and y^2 was not scorable because the males carried a y^+Y) and stocked (the stocks were *recombinant* X/y^+Y; *pal/SM1*; spa^{pol}/spa^{pol} males by *C(1)DX,y f* bb^-/y^+Y; *pal/SM1*; spa^{pol}/spa^{pol} females). To determine the frequency of somatic loss of these *X* chromosomes, 10 males from each stock were mass mated to *y w* sn^3 *car*/*y w* sn^3 *car*; *C(4)RM,ci* $ey^R/0$ females. This cross also allowed the determination of the genotype of the *X* chromosome recombinants with respect to y^2, *pn* and *car* (y^2 and pn^+ were assumed to be inseparable). The results of these tests showed that the property of high *vs.* low frequency of somatic *X* chromosome loss did segregate (Table 12). As there is no sharp dividing line between high and low frequencies of *X* chromosome somatic loss, mapping with respect to the *X* chromosome markers was done by (1) taking all chromosomes with >4% somatic loss(the frequency of somatic loss of the nonrecombinant y^2 *v f car* chromosome) as exhibiting high loss and the rest as low (Table 12, mapping A); and (2) taking only those *X* chromosomes with >6% somatic loss as high and those with <4% loss as low (Table 12, mapping B). Both mapping procedures placed the site responsible for high *vs.* low loss proximaly to *car*. Thus, the relative insensitivity of the *pn* chromosome to *pal* is the result of a difference between this chromosome and other *X* chromosomes that is located in the basal region of the *X* chromosome. Taken together with the earlier results, these data

TABLE 11

Sex and fourth chromosome behavior in (1) pn *males that have a low frequency of* X *chromosome misbehavior and in (2)* y² v f car *males with typical chromosome behavior*

Crosses are of *X/y+Y; pal/pal; spa^{pol}/spa^{pol}* males bearing indicated *X* chromosome to *y w sn^{s} car/y w sn^{s} car; C(4)RM,ci ey^{R}/0* females.

	Constitution of male gametes producing recovered progeny										
	Non-mosaic progeny						Mosaic progeny				Total
							XX-X0 mosaics		*XY-X0* mosaics		
X chromosome of male	*X,4*	*Y,4*	*0,4*	*X,0*	*Y,0*	*0,0*	*X,4*	*X,0*	*Y,4*	*Y,0*	
1. *pn*	2072	1178	12	246	220	4	19	4	7	2	3764
2. *y² v f car*	2054	1423	36	309	243	15	95	13	6	2	4196

	Frequency of exceptions			
	nullo-*XY**	nullo-*4**	*XX-X0* mosaics†	*XY-X0* mosaics†
1. *pn*	4.2	12.7	9.8	6.3
2. *y² v f car*	12.1	13.9	43.7	4.7

* Exceptions per 10^3 progeny.
† Exceptions per 10^3 progeny that received the sex chromosome in question.

TABLE 12

Mapping of the site responsible for the difference in behavior of the pn *and* y² *v f car chromosomes in* pal *males*

Data are from 42 unselected recombinants between these two chromosomes; tested as described in text.

I. Frequency of *XX-X0* mosaics in the 42 tested recombinants

Percent *XX-X0* mosaics	Number recombinants	Percent *XX-X0* mosaics	Number recombinants	Percent *XX-X0* mosaics	Number recombinants
0.0–1.0	11	4.0–5.0	1	8.0– 9.0	4
1.0–2.0	8	5.0–6.0	3	9.0–10.0	2
		6.0–7.0	1	>10.0	5
2.0–3.0	3	7.0–8.0	2		
3.0–4.0	2				

II. Segregation of sensitivity-insensitivity to loss with respect to *X* markers

Genotype of recombinants	Segregation of high-low loss site with respect to *X* markers: Mapping A*, # recombinants High	Mapping A*, # recombinants Low	Mapping B†, # recombinants High	Mapping B†, # recombinants Low
y² + *v* *f* *car*	8	0	7	0
+ *pn* + + +	2	14	1	14
+ *pn* *v* *f* *car*	5	1	5	0
y² + + + +	0	5	0	5
+ *pn* + *f* *car*	1	0	1	0
y² + *v* + +	0	2	0	2
+ *pn* + + *car*	2	0	1	0
y² + *v* *f* +	0	2	0	2

III. Map distances

Interval	Mapping A	Mapping B
y²–v	26	24
v–f	7	8
f–car	10	10
car–site‡	7	3

* High = ≥4% *X/X-X/0* mosaics; Low = <4% *X/X-X/0 mosaics*.
† High = ≥6% *X/X-X/0* mosaics; Low = <4% *X/X-X/0* mosaics.
‡ Site responsible for difference in somatic loss frequency of *pn* and *y² v f car* chromosomes.

suggest, as the most straightforward hypothesis, that *pal*+ acts in male meiosis to specify a product that is a component of, or interacts with, the centromeric region of chromosomes and whose action is required during meiosis for the inheritance of chromosomes that will segregate normally during the following zygotic nuclear divisions.

NON-INDEPENDENCE OF CHROMOSOME LOSS

Heterologs are not lost independently in the presence of *pal*: there are more nullo-*XY*, *nullo-4* double exceptions than would be expected from independence (Table 1, crosses 1,4).

To determine if the somatic losses of heterologs were also more frequent than expected from independence, the somatic loss of the *Y* and fourth chromosomes

were examined in a cross of y/y^+Y; *pal/pal*; spa^{pol}/spa^{pol} males by $XX,y\ pn\ v$; +/+; +/+ females. Somatic loss of the y^+Y chromosome in the regular (y^+) female progeny of this cross was detected by the appearance of y cuticle patches, and somatic loss of the fourth chromosome by the appearance of *Minute* bristles, indicative of haplo-*4* tissue. The results of this cross (Table 6, cross 2) show that the somatic loss of the *Y* and fourth chromosome is positively correlated; 25 progeny that lost both a *Y* and a fourth chromosome somatically were observed, whereas only 3.7 such progeny would be expected if the somatic loss of these heterologs were independent.

An examination of the patterns of mosaicism in the 25 progeny that were mosaic for both the *Y* and fourth chromosomes (Table 6, cross 2) revealed that the patches of haplo-*4* and nullo-*Y* tissue were nearly always coincident. Thus, 23 mosaics had only nullo-*Y* haplo-*4* and *Y*-bearing diplo-*4* tissues, indicating that one daughter cell of the division in which the losses occurred had received neither a *Y* nor a fourth chromosome whereas the other daughter cell had received both a *Y* and a fourth chromosome. One of the two remaining mosaics had *Y*-bearing diplo-*4* tissue, nullo-*Y* diplo-*4* tissue and nullo-*Y* haplo-*4* tissue, indicating loss of the fourth chromosome in the cell lineage in which loss of the *Y* chromosome had previously occurred. The final mosaic contained *Y*-bearing diplo-*4* tissue, nullo-*Y* diplo-*4* tissue, and *Y*-bearing haplo-*4* tissue.

To further examine the nonindependence of somatic loss, $y^+\ car/y^+Y$; *pal/pal*; spa^{pol}/spa^{pol} males were crossed to y/y; +/+; +/+ females and the incidence of somatic loss of the $X + 4$ and $Y + 4$ chromosome pairs in their progeny monitored (Table 6, cross 1). These data are much less numerous, and it is therefore not possible to demonstrate that the somatic loss of the $X + 4$, and $Y + 4$ chromosome pairs are positively correlated. However, in both instances the number of simultaneous somatic losses of heterologs observed was greater than the number expected from independence. The number of simultaneous somatic losses (observed:expected) were 7:4.5 for $X + 4$ loss, and 4:0.8 for $Y + 4$ loss. Furthermore, the double somatic losses of the sex and fourth chromosomes in this cross are again primarily coincident: in six of the sexen *X* and fourth chromosome double mosaics there were only *X/0*; *4/0* and *X/X*; *4/4* tissues, and in three of the four *Y* and fourth chromosome double mosaics there were only *X/Y*; *4/4* and *X/0*; *4/0* tissues.

This finding—that the patches of tissue derived from the loss of a sex and a fourth chromosome in a fly are nearly always coincident—means that not only are the two heterologs lost at the same cell division, but moreover, that they are not lost independently of one another with respect to the poles of this division. That is, if loss were independent, there would be equal frequencies of mosaics with coincident patches of monosomic tissue and mosaics with reciprocal patches of monosomic tissue (i.e., diplo-sex chromosomes, mono-*4* and mono-sex chromosomes, diplo-*4*). The rarity of the latter type of mosaic suggests that the early mitotic divisions of the zygote are asymmetric, as least in progeny of *pal* males.

INTERPRETATION

The experiments presented above have demonstrated the following properties of *pal*. (1) When homozygous in the male germ line (meiosis?) *pal* causes an elevated incidence of loss of all chromosome pairs. (2) Since the maternal genotype can influence the frequency of exceptions that appear not to have received one or more paternal choromosomes, it must be the case that at least some, and conceivably all, such exceptions arise from loss of paternal chromosomes in the zygote at, or before, the first mitotic division. (3) In addition, somatic loss of paternal sex chromosomes occurs during the early zygotic nuclear divisions of progeny of *pal* males and results in mosaic progeny. Somatic loss of the fourth chromosome also occurs. (4) Different chromosomes are lost with different probabilities in the progeny of *pal* males. These results suggest that pal^+ is required at meiosis in males for the normal inheritance of paternal chromosomes during the early zygotic nuclear divisions of their progeny.

Although a great many mechanisms can be envisaged that will lead to chromosome loss (e.g., defective centromeric regions, defective spindle apparatus, faulty chromosome replication, chromosome breakage, etc.), the choice among these possibilities in the case of *pal* is sharply restricted by several observations. Thus, it was shown that different chromosomes are not lost with the same probability in the progeny of *pal* males and, in the case examined, the difference resides at or near the centromere. This strongly suggests that the function specified by pal^+ is concerned in some manner with chromosome movement.

There are two general classes into which functions involved with chromosome movement can be divided: those that specify part of the cytoplasmic apparatus concerned with disjunction ("spindle apparatus"), and those that ensure the proper structure and functioning of the chromosomal elements that mediate disjunction.

That pal^+ specifies a component of the spindle apparatus is rendered unlikely by the observations that somatic chromosome loss in the progeny of *pal* males can occur later than the first zygotic nuclear division and its occurrence is restricted to paternal chromosomes. At the second zygotic division, the parental chromosome sets are no longer separated as they are during the gonomeric first division and thus it seems likely that a defect in the spindle apparatus at the second and subsequent divisions would affect maternal as well as paternal chromosomes. It is possible to imagine, however, that (1) the paternal and maternal chromosome sets normally differ in some manner; (2) this difference renders the maternal chromosomes insensitive to a defective component of the spindle apparatus that is contributed to the zygote by *pal* males; (3) the centromeric region of a paternal chromosome determines the frequency with which it will get lost in a cell with a defective spindle apparatus; and (4) the pal^+ specified paternal component of the spindle apparatus functions only during the first few (possibly only the first two) mitotic divisions of the zygote. Although this model is consistent with the observations on chromosome behavior in *pal* males reported here, there are, to the best of my knowledge, no independent data available that support the occurrence of the processes assumed to exist by this model.

The report of HUETTNER (1933) that centrioles are inherited only through the sperm (and, thus, a candidate for the site of *pal* action under this model) is brought into serious question by the failure to observe centrioles with the electron microscope in mature spermatids of a number of insect species (PHILLIPS 1970).

An alternative model, and the one that I favor since it requires fewer *ad hoc* assumptions, is that *pal*$^+$ functions during male meiosis and specifies a product that is a component of, or interacts with, the centromeric region of chromosomes. In *pal* males this function is abnormal and, as a result their progeny inherit chromosomes with defective centromeric regions that consequently have some probability of being lost. It should be noted that such a defect may be in either the structure of the centromere itself or in some property of the adjacent centric heterochromatin. That is, in *D. melanogaster* centromeric regions of different chromosomes differ in "strength" as measured by the behavior of anaphase bridges (NOVITSKI 1955) and these differences in kinetic activity are attributable to the constitution of the heterochromatin adjacent to the centromere (LINDSLEY and NOVITSKI 1958). Moreover, these normal differences in the kinetic activity of centromeric regions of various chromosomes suggest a possible reason for the chromosome-specific frequencies of loss observed in *pal* males.

There are several possible modes by which defective chromosomes could be produced in *pal* males. Most directly, since centromere behavior at meiosis I is unique (sister centromeres orient to the same pole and remain held together throughout the first meiotic division) it is reasonable to expect loci to exist that function only during meiosis to control the behavior of centromeric regions. In fact, mutants are known in the tomato (CLAYBERG 1959) and in *D. melanogaster* (DAVIS 1971) that appear to be in loci whose functions are to hold sister centromeres together between the first and second meiotic divisions. Thus it is possible that *pal*$^+$ specifies a product that is directly involved in ensuring the normal functioning of centromeric regions. The possibility of a more indirect mechanism for *pal*-induced chromosome loss is suggested by the demonstration in a number of plant species that chromosomes which are univalent at meiosis I frequently lag during this division as well as the subsequent reductional division and, in addition, often give rise to isochromosomes and telocentrics by misdivision of the centromere. The resulting iso- and telochromosomes in turn tend to lag or to be lost in the subsequent mitotic divisions of the embryo (e.g., RHOADES 1940; DARLINGTON and JANAKI-AMMAL 1945; STEINETZ-SEARS 1966). Thus, a defect in meiosis I of *pal* males such that chromosomes sense themselves as being univalent at this division could account for the observed loss at subsequent divisions. It seems unlikely, however, that chromosome misbehavior in *pal* males is the result of centromere misdivision, since tests for the production of new isochromosomes by *pal* males gave negative results (BAKER 1972). In addition, tests of five diplo-*4* and one diplo-*X* exceptional progeny of homozygous *pal* males showed that these exceptions all resulted from nondisjunction and not from the formation of isochromosomes.

In summary, it seems reasonable to suggest that *pal*$^+$ acts during meiosis I in males to specify a product that is necessary for the normal structure of centro-

meric regions during this division. In homozygous *pal* males, chromosomes with defective centromeric regions are produced. The chromosome loss observed in the progeny of *pal* males would then result from the inheritance of these defective chromosomes.

There are two aspects of nonindependence in the behavior of heterologous chromosome pairs in *pal* males that require consideration. Firstly, by examining the behavior of two chromosome pairs in *pal* males, it was shown that the simultaneous loss of heterologs is more frequent than would be expected from independence. Secondly, when the simultaneous somatic loss of marked *Y* and fourth chromosomes occurs, it is found that their loss is not independent with respect to the plane of the cell division in which the losses occur: almost invariably one daughter cell failed to receive both a *Y* and a fourth chromosome, whereas the other daughter cell received a normal chromosome complement. The latter result implies that the early mitotic divisions of the zygote are asymmetric, at least in the progeny of *pal* males.

These same two patterns on nonindependence were also observed in studies of the meiotic mutant claret (*ca*) in *D. simulans* (STURTEVANT 1929) and the homologous mutant (claret nondisjunctional, ca^{nd}), in *D. melanogaster* (DAVIS 1969). Both of these mutants act only in females and cause high frequencies of nondisjunction of all chromosome pairs at meiosis I, as well as the loss of maternal chromosomes during meiosis and the early zygotic nuclear divisions. The somatic loss of heterologs is positively correlated. Moreover, STURTEVANT (1929) found that among 27 cases in which somatic losses of both an *X* and a fourth chromosome had occurred, there were 21 cases in which the losses occurred at the same cell division and one daughter cell failed to receive both chromosomes, whereas the other daughter cell received the normal chromosome complement. In the other six cases, the clone of cells that was lacking a fourth chromosome was entirely within a larger clone of cells that had failed to receive an *X* chromosome. Thus, in these six cases the loss of heterologs also occurred in the same cell lineage in the zygote, although at different cell divisions. The same asymmetry is observed in cases of simultaneous *X* and *4* somatic loss in the progeny of ca^{nd} females (DAVIS, personal communication). At this time, it is not clear whether the primary lesion in ca^{nd} is in the spindle apparatus, as suggested by DAVIS (1969), or in the structure of the chromosome (BAKER and HALL 1975).

One possible explanation for the lack of independence in the disjunctional behavior of heterologs in the *ca* mutants (DAVIS 1969) and *pal* is that there exists a cell-to-cell heterogeneity in the conditions that lead to nondisjunction. Such a heterogeneity could exist either at the time these genes function (thus, some meiocytes would be more defective than others), or in the conditions present at the time losses and nondisjunctions occur (that is, a previously caused defect would be more or less likely to cause chromosome misbehavior as a function of the cellular environment in which the chromosomes found themselves). The first model would seem to be favored by the observations that, in all of these mutants, the probability of loss of a chromosome at one division is correlated with the behavior of heterologs at previous divisions. Thus, in the case of *pal*, somatic

losses of the *X* and fourth chromosomes are more frequent in cells in which a major autosome has previously nondisjoined or been lost than it is among cells in which the major autosomes segregate normally (Tables 1 and 2). Similarly, DAVIS (1969) noted that the frequency of somatic loss of the *X* chromosome in progeny of ca^{nd} females differed between ova that were diplo-*4*, mono-*4* and nullo-*4*. However, as DAVIS pointed out, this model predicts, in the case of ca^{nd}, a different array of gametes from that observed. For example, if nondisjunction, in the absence of loss, of the *X* and fourth chromosomes is considered, this model allows for an excess of *X-4* double exceptions above expectations from independence, but predicts equal frequencies of the four types of double exceptions (nullo-*X*, nullo-*4*; nullo-*X*, diplo-*4*; diplo-*X*, nullo-*4*; and diplo-*X*, diplo-*4* ova). However, the data exhibit marked deficiencies of those classes of ova that are simultaneously nullosomic for one chromosome pair and disomic for the other. This coincident recovery of identical disjunctional types for heterologous chromosomes is reminiscent of the asymmetry observed in cases where two heterologs are lost at the same somatic cell division. There it is almost invariably observed that, when two chromosomes are lost in one somatic cell division, one daughter cell fails to get either and the other daughter cell receives the normal chromosome complement.

There seem to be two possible explanations for this asymmetry. On the one hand, these mutants could either directly cause, or indirectly elicit, the occurrence of an assymetry that is not normal. Thus the assymetry would be the result of the nature of the defects caused by the mutants. For example, it is possible to imagine that the chromosomal material inherited from the parents is defective in a manner that leads to the orientation of all defective chromatids in a cell to one pole of the division; however, it is not easy to construct a plausible mechanism to bring this about. On the other hand, the observed asymmetry of somatic chromosome loss may be due to a normal asymmetry in the process of chromosome disjunction. The existence of such an asymmetry as a normal part of mitotic chromosome disjunction is perhaps supported by the finding of such an asymmetry in all three of these mutants. Evidence for a normal asymmetry in chromosome segregation that could lead to the results observed with these mutants has been presented in *E. coli* (JACOB, RYTER and CUZIN 1966), and in several eukaryotes (LARK, CONSIGLI and MINOCHA 1966; LARK 1967, 1969), where it has been suggested that DNA strands that are synthesized during one round of replication segregate to the same daughter cell at subsequent cell divisions. Evidence suggesting that DNA strands made at the same time do not segregate together at subsequent divisions has also been presented (HEDDLE *et al.* 1967). Nevertheless the asymmetry observed in somatic chromosome loss in the progeny of *pal* males and *ca* and ca^{nd} females is understandable if there exists a normal process in Drosophila that segregates at least the centromeric regions made in one division to the same pole at subsequent cell divisions (Figure 2).

APPENDIX

The utility of mosaics for studying problems in Drosophila development was first noted by STURTEVANT (1929), and they have subsequently been employed to approach a number of prob-

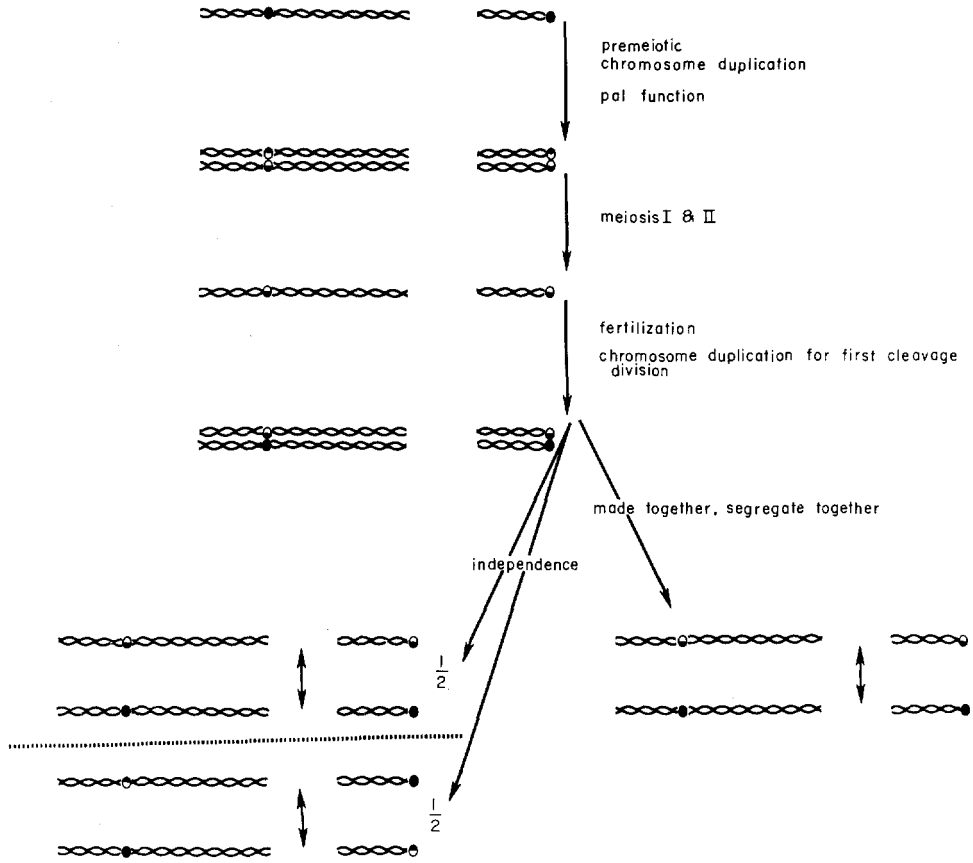

FIGURE 2.—Chromosome behavior during meiosis and the first cleavage division of the zygote. Depicted are the consequences of (1) independent segregation of heterologous centromeric regions made at the same time, and (2) segregation of heterologous centromeric regions made at the same time to the same pole at subsequent cell divisions. The latter mode of segregation provides a mechanism for generating the observed coincident pattern of loss of heterologous chromosomes derived from *pal* males. Centromeric regions defective due to *pal* are indicated as unshaded half-centromeres (O).

lems. Mosaic individuals have, for example, contributed greatly to our understanding of cell lineage relationships in development, the time, site, and nature of gene action, and the processes involved in determination and differentiation (for reviews see NOTHIGER 1972; GEHRING 1972; GARCIA-BELLIDO 1972; BRYANT 1974; POSTLETHWAIT and SCHNEIDERMAN 1973).

There are at present three genetic techniques available for generating mosaic individuals. These are: (1) somatic crossing over (STERN 1936; BECKER 1975); (2) unstable ring-*X* chromosomes (HINTON 1955; PASZTOR 1971); and (3) mutants that cause chromosome loss during the early cleavage mitoses (*ca*nd—DAVIS 1969; *mit*—GELBART 1974). (For a review of mosaic systems in Drosophila see HALL, GELBART and KANKEL 1975.) The mosaics generated by chromosome loss differ from those that arise from somatic crossing over in that chromosome losses can be generated at only the first few cleavage divisions (thus making mosaics with large patches), whereas somatic crossing over appears not to be inducible before blastoderm (thus only relatively small patches can be obtained).

The finding that *pal* causes the loss of paternally-derived chromosomes during the early

cleavage divisions of progeny of *pal* males makes available another method for producing mosaics *via* chromosome loss. Moreover, since all paternal chromosomes appear to be subject to somatic loss in the progeny of *pal* males, it is possible to use *pal* to make mosaics for any chromosome for which aneuploidy is compatible with survival. Although this limits mosaics for normal chromosomes generated by this method to the *X*, *Y* and fourth chromosomes, mosaics for regions of interest on the major autosomes can be generated by using appropriate rearrangements (e.g., free duplications or translocations) in *pal* males (HALL and KANKEL, personal communication; BAKER, unpublished results). While ca^{nd} and *mit* can be used in analogous ways to generate mosaics, ca^{nd} has the disadvantage of being relatively infertile and not all chromosomes are subject to *mit*-induced loss. As pointed out by GELBART (1974), *mit* does have the benefit for some uses that chromosome loss of both maternal and paternal chromosomes occurs in the progeny of *mit* females and thus it is not necessary to introduce a chromosome into a *mit* stock to cause its loss.

An analysis of such mosaics allows construction of fate maps of the embryo (GARCIA-BELLIDO and MERRIAM 1969). Since *Y* chromosome mosaics (either *X/Y-X/0* or *XX/Y-XX/0*) do not alter sex, a comparison of the fate maps constructed from such *pal*-induced mosaics to each other and to the fate map derived from *pal*-induced gynandromorphs permits us to inquire whether sex or sexual dimorphism alters embryological relationships. A comparison of these fate maps to those derived from unstable ring-*X*, ca^{nd} and *mit*-induced gynandromorphs allows us to determine whether the embryology is disturbed by the lesions used to induce loss.

From crosses involving *pal* males carrying a $y+Y$ by females having free-*X* chromosomes marked with *y*, drawings of 129 *X/Y-X/0* mosaic males representing 258 sides were obtained. Crosses of similar males to attached-*X*, *y pn v* females yielded 123 *XX/Y-XX/0* mosaic females (246 sides) whose patterns of *y* and + tissue were recorded. Drawings of *X/X-X/0* mosaics were made from crosses of *pal* males carrying a $y+$ $w+$ $sn+$ *X* chromosome to females bearing either *y X* chromosomes (149 gynandromorphs) or *y w* sn^3 *X* chromosomes (207 gynandromorphs) for a total of 712 sides. Sex chromosome mosaics that were simultaneously haplo-*4 Minute* mosaics have been excluded from these data since *Minute* tissue is at a growth disadvantage in mosaics MORATA and RIPOLL 1975; GARCIA-BELLIDO, RIPOLL and MORATA 1973).

For each mosaic the phenotypes of a set of structures (landmarks) on the adult cuticle were recorded. The landmarks scored for the three types of mosaics are listed in Table 13. Also indicated in Table 13 are the frequencies with which each landmark was observed to be derived entirely from cells that did not have the paternal chromosome for which the fly was mosaic, as well as the frequency of mosaicism within each landmark. Within each type of mosaic the probabilities of different structures being monosomic are comparable. However, as noted above, the probability of a landmark being monosomic differs between cases of *Y* chromosome loss (0.48) and *X* chromosome loss (0.33).

The procedure used to transform such data into a two-dimensional map of the location, on the blastoderm surface, of the cells that are the progenitors of these landmarks has been recently described and the assumptions behind the procedure discussed (GARCIA-BELLIDO and MERRIAM 1969; HOTTA and BENZER 1972). The crucial assumptions are that: (1) orientation of the cell division at which loss occurs is random with respect to the surface of the egg; (2) loss occurred only once in the cell lineage of each mosaic; (3) daughter nuclei remain together during the preblastoderm divisions; (4) the site a nucleus occupies on the blastoderm determines its fate; and (5) there is no difference between the growth rates of cells of different genotypes in mosaics.

With these assumptions, the distance between two sites on the surface of the blastoderm is proportional to the frequency with which mosaic boundaries fall between them. To avoid assumptions about the spatial arrangement of sites on the blastoderm in order to determine the frequency with which they are separated by mosaic boundaries, it is assumed that if two landmarks in the adult differ in genotype, at least one (or a higher odd number of) mosaic boundaries fell between their progenitor cells in the blastoderm. Thus the metric used to measure distances is the frequency with which a pair of landmarks differ in genotype.

To obtain these frequencies for the three series of *pal*-induced mosaics, a computer program was employed that took all pairwise combinations of landmarks and tabulated the number of

TABLE 13

Structures scored in mosaics and the frequencies with which they are derived from monosomic and mixed cell populations

Structure*	Frequency of monosomy			Frequency of mosaicism		
	X/Y-X/0	*$\overline{XX}$/Y-$\overline{XX}$/0*	*X/X-X/0*	*X/Y-X/0*	*$\overline{XX}$/Y-$\overline{XX}$/0*	*X/X-X/0*
ar	.480	.399	.333	—†	—	—
pa	.473	.411	.323	—	—	—
or	.493	.374	.344	—	—	—
oc	.492	.403	.349	—	—	—
iv	.488	.374	.347	—	—	—
ov	.489	.382	.349	—	—	—
pv	.496	.407	.348	—	—	—
e	—	—	.207	—	—	.077
vb	.473	.409	.325	.000	.004	.000
w	.459	.482	.366	.142	.159	.093
l1	.463	.492	.348	.074	.049	.057
l2	.439	.514	.350	.028	.061	.045
l3	.512	.549	.358	.023	.041	.028
hu	.523	.509	.354	.015	.000	.010
asc	.500	.483	.366	—	—	—
psc	.499	.488	.367	—	—	—
adc	.489	.504	.353	—	—	—
pdc	.497	.496	.366	—	—	—
sp	.483	.535	.362	.016	.037	.017
apa	.477	.512	.342	—	—	—
asa	.458	.492	.346	—	—	—
anp	.458	.492	.346	—	—	—
ppa	.477	.525	.346	—	—	—
psa	.454	.491	.345	—	—	—
pnp	.442	.480	.350	—	—	—
ps	.458	.484	.346	—	—	—
t2	.517	.512	.382	.058	.045	.035
s2	.477	.498	.328	.008	.000	.014
t3	.519	.557	.399	.034	.044	.040
s3	.495	.506	.355	.003	.012	.007
t4	.569	.594	.394	.060	.037	.038
s4	.545	.533	.377	.012	.016	.009
t5	.556	.596	.401	.066	.053	.055
s5	.551	.559	.376	.008	.020	.009
t6	.565	.626	.404	.089	.028	.034
s6	—	.542	.384	—	.016	.000
t7	—	.598	.420	—	.008	.006
gt	.392	—	—	—	—	—
gs	.543	.407	.320	—	—	.087

* The abbreviations used are: adc, anterior dorsocentral bristle; anp, anterior notopleural bristle; apa, anterior postalar bristle; ar, arista; asa, anterior supra-alar bristle; asc, anterior scutellar bristle; e, eye; gs, genital sternite; gt, genital tergite; hu, humeral bristles; iv, inner vertical bristle; l1, first leg; l2, second leg; l3, third leg; oc, ocellar bristle; or, orbital bristle; ov, outer vertical bristle; pa, palp; pdc, posterior dorsocentral bristle; pnp, posterior notopleural bristle; ppa, posterior postalar bristle; ps, presutral bristle; psa, posterior supra-alar bristle; psc, posterior scutellar bristle; pv, post-vertical bristle; s2, etc., second abdominal sternite, etc.; sp, sternopleural bristles; t2, etc., second abdominal tergite, etc.; vb, vibrissae; w, wing.

† Indicates not scored.

times each pair of sites differed in genotype. Cases in which two landmarks differed in genotype were counted as one and cases in which one landmark was mosaic and the other not as one-half. The frequency with which each pair of landmarks was separated by a mosaic boundary was obtained by dividing this sum by the total number of comparisons. The distances thus obtained have been designated Sturtevant Units or Sturts (HOTTA and BENZER 1972) where one Sturt represents the probability that, among all mosaics in a series, two landmarks will differ in genotype 1% of the time.

In these constructions, the fate maps of the head, thorax, and abdomen were constructed separately and then positioned relative to each other by a few triangulations. One-half of the distance between homologous parts on the left and right halves of the fly was used to estimate the distance from that part to the midline. The set of points on the midline thus generated were connected to give the closed curves in Figure 3. This procedure, which uses, whenever possible, short distances to construct fate maps minimizes the errors that are introduced (1) by cases in which more than one mosaic boundary separates two landmarks (which are unrecognized since only the landmark's genotypes are scored) and (2) the approximation of the distance between two points on the curved blastoderm surface by a straight line (since the approximation of an arc between two points by a subtending straight line improves as the distance between the two points decreases).

The fate maps derived by this procedure are presented in Figure 3. The location of the structures on the blastoderm surface is consistent with the known embryology of Drosophila (POULSON 1950). The fate maps derived from *pal*-induced mosaics are also in agreement with fate maps produced from gynandromorphs caused by unstable ring-*X* loss (HOTTA and BENZER 1972) or the mutants *ca* (GARCIA-BELLIDO and MERRIAM 1969) and *mit* (GELBART 1974), suggesting that the embryological relationships are not disturbed by the lesions used to induce chromosome loss. Finally, the near identity of the fate maps derived from *pal*-induced *X/X-X/O*, *X/Y-X/O* and *XX/Y-XX/O* mosaics (Figure 3) demonstrates that the fate map of the blastoderm is independent of sex and sexual dimorphism.

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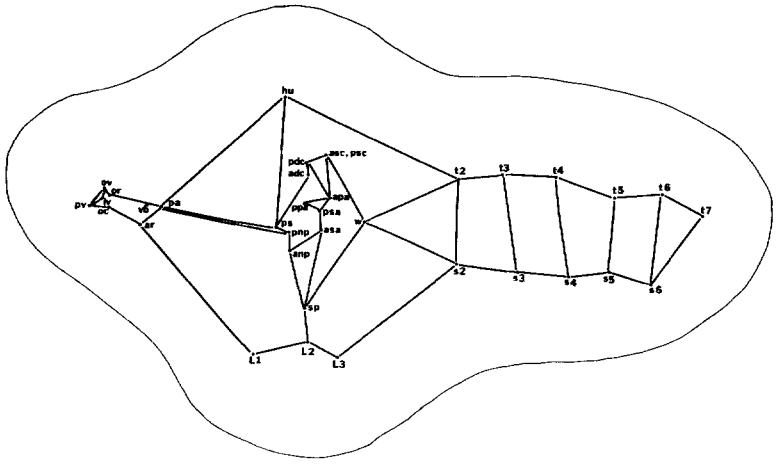
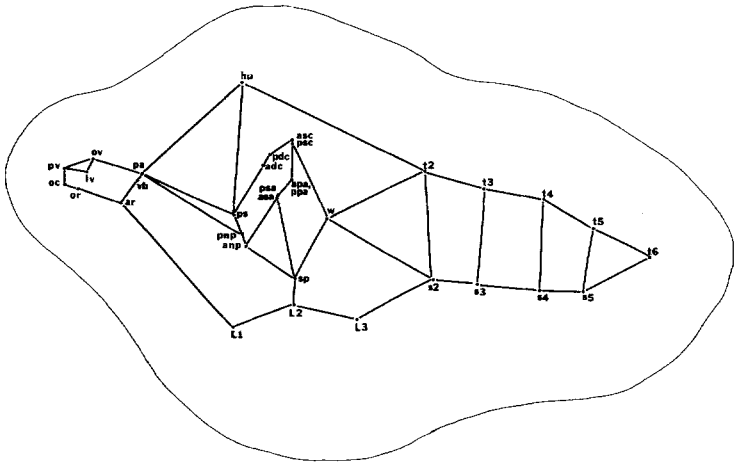


FATE MAP FROM $\overline{XX}/Y - \overline{XX}/O$ MOSAICS



FATE MAP FROM X/Y - X/O MOSAICS

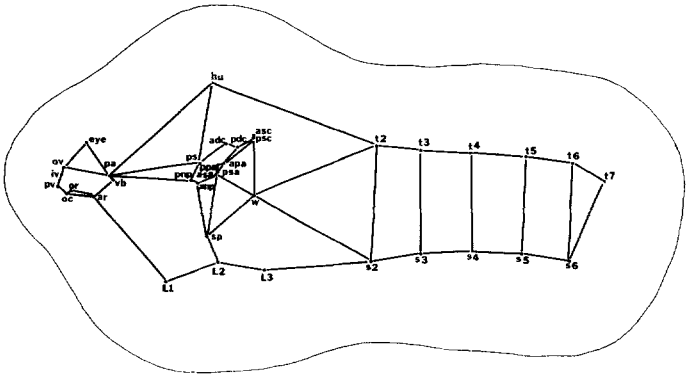


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FIGURE 3.—Fate maps of the blastoderm of male, female, and gynandromorphic embryos constructed from the indicated types of mosaics. Abbreviations as in Table 13.

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