INDUCED CHANGES IN FEMALE GERM CELLS OF DROSOPHILA. IV.
DEPENDENCE OF INDUCED CROSSOVER-LIKE EXCHANGES
IN OOCYTES AND OOGONIA UPON X-RAY INTENSITY¹

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A number of studies have shown that in *Drosophila* (see HERSKOWITZ 1953 for references) the rate of exchanges between exactly homologous loci, crossovers, depends upon sex and other genotypic factors, age of female, stage in gametogenesis, temperature, nutrition, and degree of hydration (IVES, FENTON, YOST and LEVINE 1953; LEVINE 1955). For recent data and a review of induced crossing over see WHITTINGHILL (1955). The effect of temperature on crossover rate has been interpreted as being due to a modification of the spontaneous crossover process, and the effect of X-rays on such exchanges has been similarly explained on the basis of four lines of evidence. (1) The X-ray effect is apparently a direct one, in that it seems both to increase linearly with dosage (PARKER 1948) and to be independent of radiation intensity (WHITTINGHILL 1951). (2) The cells and the cell stages affected by X-rays and temperature are similar (for example, when adult females are treated no clear and consistent effect on crossover-like exchange frequency was noted in eggs first laid, but one appeared in later-laid eggs). (3) The pattern of change in the frequency of crossovers along the length of a chromosome is similar for X-rays, age and temperature, the effect being greatest closest to the centromere (MULLER 1925, 1926). (4) There is no greater tendency, following X-ray treatment, for lethals to be associated with points of crossing over than of non crossing over (PATTERSON and SUCHE 1934; FRIESEN 1937). If the induced crossover-like exchanges were due to breakages occurring at random at breakable places along the chromosome they frequently would be expected to occur between nearby but not homologous loci—causing the recombinant strands, properly called “pseudocrossovers” (a term suggested by H. J. MULLER), to have small duplications and deficiencies, the latter often acting as recessive lethal mutations. Because the frequency of recessive lethal mutations declines in successive eggs laid after irradiation (KING 1952) while the effect on crossover-like exchanges is known to increase and reach a peak in eggs laid later, this also has argued in favor of the exchanges in later laid eggs being between homologous loci, e.g. crossovers.

It became desirable to retest the effect of X-ray intensity on crossover and crossover-like exchanges in oocytes and oogonia since the earlier work had not employed as great an intensity difference as was used recently in demonstrating that half-translocations were intensity dependent (HERSKOWITZ and ABRAHAMSON 1956a). It was also apparent from the half-translocation work that one might obtain, amongst

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eggs first laid, exchanges between homologous chromosomes which would appear to be crossovers but which would be, in reality, pseudocrossovers or half-translocations following multiple chromosome breakages. It may be mentioned in this connection that, in the data given in some of the earlier papers of MAVOR and SVENSON (1924, 1925) and of others since that time (e.g. PARKER in discussion of paper by WHITTINGHILL 1955), crossover-like exchanges seemed to be increased by radiation in eggs laid within the first four days after treatment of the adult female (cells which, when irradiated, were oocytes presumed to be past the stage of spontaneous crossing over). However, the number of adults from such eggs were usually not sufficient, because of the high X-ray-induced egg mortality, to permit the conclusion that there was really an increase and it was assumed by most *Drosophila* workers (see MORGAN, BRIDGES and STURTEVANT 1925, p. 104-105) that there was no increase among eggs laid during the first five days after any treatment.

The present study was designed therefore to retest the effect of radiation intensity on the rate of crossover and crossover-like exchanges in eggs laid in successive periods with particular reference to the rate obtained among flies derived from the eggs first laid. The experiments will be discussed as to their bearing on the mechanism of action of X-rays in producing crossovers and pseudocrossovers. Some of the present results have been referred to earlier (HERSKOWITZ and ABRAHAMSON 1956b).

MATERIAL AND METHODS

Drosophila melanogaster was used in this study. Virgin females were collected, aged 4-8 days, and were either not irradiated or treated with X-rays while motile and well aerated, at 20 ma at a peak of 200 kv with 1 mm Al filtration. After this they were placed without additional etherization into pint milk bottles containing culture medium and an excess of males. The parents were transferred to new bottles periodically.

In both Experiments I and II the females were $y \cdot Dp\ sc^{v1}\ y^+/y^2\ v\ f\ car$ (the duplication, $Dp\ sc^{v1}\ y^+$, is attached beyond the centromere of an X chromosome having otherwise a normal structure and containing the genes y and sc^+ in their usual distal position), and the males $Y^+/y^2\ v\ f\ car$ (except for a small group which was $Y^+/y\ ct^6\ f\ car$). The dosage of about 2940r was given either in a concentrated treatment in two minutes five seconds at 1404r/min, or in a protracted treatment at 23r/min in 16 irradiations each eight minutes long with 20-minute stops between successive irradiations (requiring seven hours seven minutes to deliver). In both experiments the number of females per bottle was ten for the control, 40 for the concentrated and 32 for the protracted series. In Experiment I the duration in days for successive broods was 2, 1, 2, 3, 3, 3, and in Experiment II 2, 1, 1, 1, 3, 3, 3.

The numbers and phenotypes of all F_1 flies were determined after periodically removing them from the bottles. Each bottle was scored through the 18th day from the time parents were introduced, at which time very few or no flies were eclosing.

The temperature following treatment was 25-27°C throughout the experiments.

RESULTS AND DISCUSSION

Table 1 gives the frequencies of exchange between car^+ and y^+ among 45,537 flies scored in Experiment I and 87,560 flies scored in Experiment II in different broods of

TABLE 1
Frequency of exchanges between car^+ and y^+ among F_1 for different treatments

	Brood 1	2	3a	3b	4	5	6	Total
	Days 1-2	3	4	5	6-8	9-11	12-14	
Experiment I								
Unirradiated (control) (4 bottles/brood)								
No. F_1	1645	1144	1707		2792	2002	2222	11,512
Percent exchanges	3.5	3.2	3.2		2.2	1.8	1.5	
Protracted dose (5 bottles/brood)								
No. F_1	1191	2044	2941		4070	3691	4562	18,499
Percent exchanges	4.4	4.2	3.8		3.2	3.7	5.9	
Concentrated dose (5 bottles/brood)								
No. F_1	988	1162	2343		3269	3535	4229	15,526
Percent exchanges	5.2	5.5	5.3		6.1	7.4	9.2	
Experiment II								
Unirradiated (control) (10 bottles/brood)								
No. F_1	7211	2904	2331	1799	5725	5171	5067	30,208
Percent exchanges	3.1	3.2	3.4	2.4	2.2	1.7	2.1	
Protracted dose (9 bottles/brood*)								
No. F_1	3749	1880	2123	2823	6072	6538	6143	29,328
Percent exchanges	4.6	3.6	3.9	3.5	3.7	4.1	5.9	
Concentrated dose (10 bottles/brood)								
No. F_1	2621	1398	1574	2720	6259	6766	6686	28,024
Percent exchanges	6.3	7.8	5.3	5.2	5.3	7.2	8.1	

* Except in broods 3a and 3b where there were eight.

eggs oviposited following the different treatments. In every brood in both experiments, the control rate of exchange was lowest, the one for the protracted irradiation was intermediate, and that for the concentrated irradiation highest. A decrease in crossover frequency in the control series as the female parents aged, long ago established by BRIDGES (1915) and confirmed by PLOUGH (1917) and others, was found here also.

For those bottles in Experiment I in which $Y^+/y^2 v f car$ males were used as parents, exchanges involving the $v-f$ and the $f-car$ regions were scored as well as those between car^+ and y^+ . These data are presented in table 2. For the $f-car$ region the protracted and concentrated doses gave higher values than the control in broods 2, 4, 5, 6, while for the $v-f$ region broods 2, 5, 6 and 2, 4, 5, 6 were higher in the protracted and concentrated treatments, respectively, than in the control. These data are consistent with those of MULLER (1925, 1926) and of later workers in that the greatest effect on "crossovers" is found in the region tested which lies closest to the centromere.

TABLE 2

Exchange percentages for various regions of the X chromosome in those bottles in Experiment I in which mating was with Y^+/y^2 v f car males*

Region		Brood 1	2	3	4	5	6
		Days 1-2	3	4-5	6-8	9-11	12-14
<i>car</i> —centromere 3.5	C	3.6	3.7	3.7	2.1	2.0	1.4
	(Total F ₁)	(1314)	(972)	(1439)	(2253)	(1614)	(1836)
	D	4.5	4.1	3.8	3.2	3.6	6.0
	(Total F ₁)	(1156)	(1938)	(2737)	(3699)	(3383)	(4250)
	I	5.2	5.3	5.3	6.1	7.2	9.2
<i>f</i> — <i>car</i> 5.8	(Total F ₁)	(973)	(1115)	(2266)	(3078)	(3379)	(4066)
	C	6.7	3.4	4.9	3.5	2.6	2.7
	D	5.1	4.5	4.6	4.1	3.6	4.5
	I	3.8	4.8	4.2	4.0	4.3	5.5
	(Total F ₁)	(973)	(1115)	(2266)	(3078)	(3379)	(4066)
<i>v</i> — <i>f</i> 23.7	C	23.4	20.5	22.8	23.1	20.8	20.4
	D	21.3	21.8	21.9	21.5	21.4	24.0
	I	21.5	21.7	21.4	23.6	22.8	23.0
	(Total F ₁)	(973)	(1115)	(2266)	(3078)	(3379)	(4066)
	(Total F ₁)	(973)	(1115)	(2266)	(3078)	(3379)	(4066)

* No. bottles per brood was 2, 4 and 4 for the unirradiated (C), protracted (D), and concentrated (I) treatments, respectively. Italicized numbers are the standard crossover map distances.

FIGURE 1.—Induced frequencies of exchange between car^+ and y^+ in groups of eggs laid in different periods after concentrated (solid line) and protracted (broken line) treatments in Experiments I and II.

Figure 1 presents the induced frequencies of exchange (obtained by subtracting, from the rate after irradiation, the control rate for the same brood) between car^+ and y^+ in eggs laid in different broods in both experiments, using the data in table 1. Whenever an egg-laying period was longer than one day the middle time is used, for convenience, to represent the time at which all the eggs were oviposited.

That the present experimental results are due to either or both a differential delay in oviposition or differential resorption of oocytes in different treatments is extremely unlikely in view of a discussion by HERSKOWITZ (1957).

GENERAL DISCUSSION

The cells tested in these studies were, at the time of irradiation, oocytes, with chromosomes in tetrad condition, and oogonia. Figure 2 shows schematically the tetrads of the X chromosome and of an autosome as they might be arranged in the oocyte, indicating the relative positions of the yellow and carnation loci. There are

FIGURE 2.—Diagrammatic scheme of tetrads of the X chromosome (wavy lines) and of an autosome (straight lines) showing points of breakage or exchange (arrows) whereby *car*⁺ and *y*⁺ can change their linkage. Details are given in the General Discussion. ● = telomere, ○ = centromere. A letter and its prime (such as *a* and *a'*) represent identical positions on two different strands.

several ways in which mature eggs bearing either *y*⁺ or *car*⁺, but not both, could be produced. One of these dominant markers could become a recessive mutant through gene mutation or become lost by deletion from the X chromosome by two or more breakages in the same strand, or *y*⁺ or *car*⁺ could be gained by reverse mutation or by an insertion, following multiple breakage, in one of the two strands not originally containing these genes. These events however are relatively rare so they will be neglected in the rest of the discussion. (By far the most frequent is deletion of the *y*⁺ which, if like that of *y*⁺ from an X chromosome containing *sc*⁸ in sperm, would have a frequency at 5000r of about 0.5 percent, see VALENCIA and MULLER 1949. However, the rate for *Dp sc*^{v1} *y*⁺ in irradiated oocytes might be lower.) There are

several other ways *car*⁺ and *y*⁺ may relatively frequently change their linkage in the present experiments (fig. 2). (1) A crossover may be produced between exactly homologous loci, either between *car*⁺ and the centromere (producing crossover strands by *a* joining to *b'* and *a'* to *b*), or, less frequently, between the centromere and the right hand telomere (producing *cd'* and *c'd* strands). (2) A pseudocrossover (exchange between nearby but non-homologous loci) could occur which would produce small deficiencies or duplications. If in figure 2 the right side of a breakage in one strand joined to the left side of a breakage in another strand and the two breakages involved both occurred on the same side of the centromere, eucentric rearrangement would result producing *a'f* and *eb'* or more rarely *ch* and *gd*, but if the breakages involved were on different sides of the centromere, one of the two strands produced would be dicentric (for example *c'f*) the other acentric (*d'e*)—the latter certainly and the former probably would not be capable of continued cellular transmission when included in the female pronucleus. Other pseudocrossovers would be those in which, in the diagram, the right side of a break joined to the right side of another break in another strand or a left side to a left side. Such joinings would produce, when the two breakages were on different sides of the centromere, for example, *ca'* (attached-X's) and *db'*, or *eg* (attached-X's) and *hf*, while when the breaks were on the same side of the centromere an acentric (*ea'*) and a dicentric (*fb'*) would be produced which would, like the other aneucentrics already mentioned, probably not be able to survive. (3) These two genes also would no longer be connected in any gamete containing a eucentric half-translocation which removed *y*⁺ from its linkage to *car*⁺. For by such a half-translocation one could obtain a gamete either carrying an unbroken *car*-containing chromosome (B) plus a broken autosome which was capped by a fragment containing *y*⁺ (*ih*), or a gamete carrying a broken *car*⁺-containing chromosome made eutelomeric by being capped by a broken piece of autosome (*c'k*) plus a normal autosome (A) from that tetrad.

The following discussion attempts roughly to estimate the contribution of crossing over, pseudo crossing over, and half-translocation to the induced exchanges. First will be considered exchanges in the eggs laid within the first four days of treatment, which were usually oocytes as far developed as metaphase I at the time of irradiation, and second exchanges in eggs laid six or more days after irradiation, which were usually early oocytes or oogonia at the time of treatment.

Both pseudo crossing over and half-translocation require one break in each of two different chromosome strands. Since the frequency of half-translocations (and also of recessive lethal mutations) is highest in the eggs laid the first days after irradiation and declines in eggs oviposited later (HERSKOWITZ 1954; HERSKOWITZ and ABRAHAMSON 1956a; ABRAHAMSON 1956) it is likely that pseudocrossover frequency follows the same pattern and that some of both types of mutations occurred in the first laid eggs in the present experiments. An estimate of the frequency of half-translocations induced by irradiation of the late oocytes in the present experiments can be obtained indirectly from data of another experiment. When females homozygous for *y sc⁵·Dp sc^{v1} y⁺* were irradiated with 4250r delivered intensely about 0.6 percent *y*⁺-deficient half-translocations and/or deficiencies of *sc^{v1} y⁺* were obtained among F₁ from eggs laid within four days of the irradiation (MULLER and HERSKOWITZ

TABLE 3
Incidence of half-translocations among y^+ -containing exchanges
(No. half-translocations/no. exchanges tested)

Treatment	Eggs laid on day(s)	
	1-4	5 and later
Unirradiated	0/22	0/40
Irradiated intensely	2/14	0/68

1956). Since the dose used in the present work was about 3000r, and half-translocation frequency is known to decline exponentially about as the $\frac{2}{3}$ power of the dose as the dose decreases (HERSKOWITZ 1954; ABRAHAMSON 1956), one would expect not much more than half (.58) the frequency obtained with 4250r to be produced per y^+ -bearing strand in the present experiments. Because, in the present experiments, only two of the four strands in the X chromosome tetrad carry y^+ , the frequency might be reduced again by one half, making the expected frequency of such half-translocations approximately 0.18 percent. It would seem on this basis that in the present experiments, where the induced rate of exchange is about 2.5 percent, only a relatively small part would be expected to come from half-translocation. This reckoning assumes that when a tetrad contains only two such y^+ -bearing strands, having no homologous region in the other two strands readily available to pair with, there is no greatly increased chance for half-translocation per y^+ -bearing strand as compared with that in a tetrad whose strands all bear the y^+ -containing right arm.

To obtain a more direct estimate of the contribution of half-translocation to the total induced frequency of seeming crossovers of early-laid eggs, the presence of half-translocations was tested for in the following way. Some y^+ -containing exchange males were crossed individually to virgin $y f$: = females. If the y^+ -containing piece was a half-translocation the cross should produce some gray-bodied forked-bristled daughters. Such a cross of exceptions from eggs laid the first four days showed 2 of 14 tested individuals from an intense irradiation and none of 22 tested from the controls to be half-translocations (table 3). This means, assuming car^+ -containing exchanges are half-translocations as frequently as are y^+ -containing ones, that about one seventh of the overall exchange rate in the intensely irradiated series for eggs laid early (about six percent) were half-translocations, or about 0.9 percent. Since the induced rate of exchange in late oocytes is about 2.5 percent, this more direct method of estimation indicates about 36 percent of this 2.5 percent is likely to be due to half-translocations the rest due to pseudo crossing over, crossing over and a few deletions of y^+ . It may be noted that one case of pseudo crossing over which had arisen in an egg deposited within four days of irradiation has already been genetically proven by MULLER (1954), and others are to be reported (MULLER and HERSKOWITZ, in manuscript).

Because the number of y^+ exchanges tested was limited it would be premature to conclude that the y^+ -containing strand is more likely to half-translocate when heterozygous than when homozygous. It should be noted that the testing of y^+ -containing exchanges would be biased against detecting half-translocations were these considerably less viable than the reciprocal class of exchange. That this is not the case is clear from the fact that in the first four days of egg-laying approximately

the same ratio of car^+ to y^+ exchanges was obtained amongst females in the intensely irradiated series (118/121, or 0.98:1) as was obtained in the controls (125/124, or 1:1). These data are consistent, therefore, with the conclusion that in late oocytes, as represented by eggs laid the first four days following irradiation, the greater part of the induced crossover-like exchanges are pseudocrossovers and/or crossovers.

The relatively high frequency of pseudocrossovers plus crossovers, as compared with gross structural changes involving the same region, attests to the importance of the initial proximity of the "broken" strands in determining which ones shall undergo recombination rather than restitution of "broken" ends.

The data prove the induced exchanges between car^+ and y^+ are intensity dependent, as would be expected both for half-translocations and pseudocrossovers since they result from independently produced multiple chromosomal breakages.

No clear effect was observed on pseudocrossover plus crossover frequency in the $v-f$ or $f-car$ regions tested. This is not surprising, so far as $v-f$ is concerned, once it is considered that the induced exchanges occurred in strands which previously had an opportunity to undergo a high frequency of spontaneous crossing over. Moreover, the smaller the crossover region and the greater its relative "breakability" when X-rays are applied, the larger the induced exchange rate would be. Thus, "breakage" followed by structural change is relatively very frequent between car and the centromere (only 3.5 units apart), much less frequent in the $f-car$ region (5.8 units long), and while frequent in the $v-f$ region taken as a whole, it is masked by being added to the normal crossing over rate of 23.7 percent. It is not entirely added, however, for in this region 23.7 percent of the induced exchanges would be undetected because they made what appear to be nonrecombinant strands out of strands which had previously undergone spontaneous crossing over.

Consider next the contribution of half-translocations, pseudo crossing over, and crossing over to the induced "exchange" rate in early oocytes and oogonia. The contribution of half-translocations is probably negligible because the rate of this event is known to decline in eggs laid after the first few days. Moreover, none of 68 exchanges of the y^+ -containing type from eggs laid five or more days after the intense treatment could be demonstrated to be half-translocations (table 3) when tested in the manner already described. Pseudocrossovers also probably contribute little since, as already mentioned, the recessive lethal rate and the structural change rate in general (see MULLER, VALENCIA and VALENCIA 1949) decrease sharply in later laid eggs. It is concluded then, that the induced exchanges in early oocytes and in oogonia are almost entirely crossovers.

The data from later broods confirm the fact that X-ray treatments given both intensely and dilutely produce a definite increase in crossing over, which is, as is well known, greater the closer the region is to the centromere. The fact that crossing over is increased more by an intense than a protracted dose proves, further, that X-ray-induced crossing over is a multihit event. Since there is an intensity effect the more immediate X-ray effect is a temporary one. This gives evidence that the induced crossing over probably takes place in effect (i.e. is determined) very soon after the irradiation is administered. However, since the X-ray effect persists in eggs laid over a period of a week and more, the "decision" or the inclination to crossover can be brought about in cell stages earlier than the one to which spontaneous meiotic crossing

over is usually limited. Moreover, the effect is precise in producing exchange between two strands at what is apparently exactly the same place in both although the "hits" could not have been localized in this way. Of course, the points of exchange in X-ray-induced crossing over could be inexact insofar as any nongenetic material is concerned—but the evidence is that it must be exact from the standpoint of producing no deficiencies of genes or gene parts whose absence would have lethal or visible effects. The X-ray effect is very likely, therefore, not directly on the genes which undergo the exchange, but is more indirect. Experiments to test the effect of oögonial dehydration on X-ray-induced crossing over have been performed (HERSKOWITZ 1956) and showed a definite enhancing effect, also suggesting that X-rays act indirectly on the chromosome in increasing crossing over.

SUMMARY

Females heterozygous for X chromosomes, one of which was normal in length and carried $y^2 v f car$ while the other carried y and car^+ in the long left arm and y^+ attached to the right arm as part of $Dp\ sc^{v1}$, were irradiated intensely or protractedly or not irradiated, crossed to males bearing the recessive alleles of the marker genes, and the frequency of exchange between the markers determined in F_1 from successive groups of eggs laid. The greatest increase in exchange frequency was for the car^+-y^+ region containing the centromere.

The frequencies of exchange in this region were, in all broods of eggs, highest after the intense irradiation, lower after the protracted one, and lowest for the control. For example, in eggs laid 1–2 days after treatment the rates were, respectively, 5.2 percent, 4.5 percent and 3.6 percent, while for days 12–14 the rates were, respectively, 9.2 percent, 6.0 percent and 1.4 percent. This proves that the events responsible for intensity-dependent exchange depend upon more than one hit and that the process whereby the effects of these hits cooperate to induce the occurrence of the exchange is localized in time.

Amongst eggs laid the first four days after treatment the induced exchanges are attributed partly to half-translocations, but mostly to crossovers or pseudocrossovers (exchanges between different strands of a tetrad involving breakages at loci which are nearby but not necessarily homologous). In eggs laid later the induced exchanges are probably almost entirely crossovers (exchanges between exactly homologous loci). It is inferred that the effect of X-rays in increasing crossing over is not directly on the chromosome loci at which exchange occurs.

The relatively high frequency of pseudocrossovers plus crossovers, as compared with gross structural changes involving the same region in late oocytes, attests to the importance of proximity of the strands undergoing exchange in determining which ones shall undergo recombination rather than restitution.

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