MODIFICATION OF THE FREQUENCY OF CHROMOSOMAL REARRANGEMENTS INDUCED BY X-RAYS IN DROSOPHILA. IV. POSTTREATMENT WITH NEAR INFRARED RADIATION[1]

BERWIND P. KAUFMANN AND KATHERINE WILSON
Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, N. Y.

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PREVIOUS studies showed that exposure of spermatozoa of *Drosophila melanogaster* to near infrared radiation before treatment with X-rays effected a marked increase in the frequency of viable types of chromosomal rearrangement as compared with the frequency in controls receiving only the X-rays. On the other hand, exposure of males to near infrared radiation after treatment with X-rays did not significantly modify the frequency of induced rearrangements among the chromosomes of those spermatozoa that were utilized in insemination during the first few days following termination of the X-ray treatment. If, however, a period of ten days or longer intervened between the X-ray treatment and copulation, the spermatozoa derived from males receiving near infrared radiation during all or part of that period yielded a smaller proportion of viable rearrangements than the X-rayed controls; and this result was attributed to an accelerating effect of the near infrared radiation on processes that make available for transfer in copulation sperm that is not mature at the time of X-ray treatment (KAUFMANN and GAY 1945; KAUFMANN, HOLLAENDER, and GAY 1946). As was indicated in these reports, any effect of the treatment on the progress of spermatogenesis could be obviated, and more conclusive data concerning the effect of posttreatment on chromosome recombination could be obtained, if the near infrared radiation were administered after transfer of the X-rayed spermatozoa to the seminal receptacles of the female. In preliminary experiments of this type, oviposition proceeded with such celerity during the period of exposure to the near infrared radiation—24 to 48 hours—that at its termination the supply of treated sperm was largely exhausted, and few fertilized eggs were deposited subsequently. These experiments have now been extended by treating larger numbers of females, under conditions less conducive to oviposition. Among the progeny obtained from eggs deposited after such combination treatment, the frequency of chromosomal rearrangements was not significantly different from that in the X-ray controls. These results indicate, therefore, that posttreatment with near infrared radiation is not effective, as is pre-treatment, in modifying the frequency of chromosomal rearrangements induced by X-radiation of mature spermatozoa of *D. melanogaster*.

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EXPERIMENTAL PROCEDURE

Males of the Swedish-b[6] stock were selected, three to five days after their emergence, and exposed to about 5000 roentgens of X-rays, using a Coolidge tube operating at about 85 kilovolts and 5 milliamperes. At the termination of the treatment the males were mated with virgin females of the same stock; after 24 hours the males were discarded and the females divided into two groups of equal numbers. One of these, which served as a control, was stored at a temperature of 25°C. The other was exposed to the near infrared radiation for a period of 24 hours under conditions similar to those described previously (KAUFMANN et al. 1946). Oviposition was retarded by maintaining the flies—controls as well as infrared-treated—during the period of mating and the ensuing 24 hours on a diet that consisted exclusively of a five percent sucrose solution (KALMUS 1942). Frequency of rearrangements was determined by cytological analysis of acetic-orcein-stained preparations of salivary-gland chromosomes of the F_1 female larvae.

RESULTS

Quantitative aspects of the analysis are presented in the first two lines of table 1. No significant difference, with respect to frequency or complexity of

TABLE 1

Effect of posttreatment with near infrared radiation

TREATMENT (X-RAY IN r, NEAR INFRARED IN HOURS)	TOTAL SPERMS TESTED	NUMBER OF REARRANGEMENTS	% SPERMS SHOWING REARRANGEMENTS	NUMBER OF BREAKS	BREAKS PER 100 SPERMS
♂♂ ca. 5000 r	263	125	47.5±3.1	335	127.4
♂♂ ca. 5000 r+24 hrs. in ♀♀	315	158	50.2±2.8	427	135.5
		Diff./S.E.	2.7/4.2=0.64		
♂♂ 4000 r	203	63	31.0±3.2	178	87.7*
♂♂ 4000 r+72 or 144 hrs. in ♂♂	483	133	27.5±2.0	386	79.9
		Diff./S.E.	3.5/3.8=0.92		

* This includes the 34-break rearrangement described by KAUFMANN (1943).

rearrangements, was detected between the progeny obtained from eggs fertilized by spermatozoa that had been exposed to X-rays and near infrared rays, and those fertilized by spermatozoa that had been treated with only the X-rays. These results parallel those obtained in the earlier experiments, in which spermatozoa that had been treated by exposure of males to X-rays, or

to X-rays plus near infrared rays, were transferred in copulation within the first nine or ten days following termination of the X-ray treatment. Summarized data for these experiments are presented in the lower half of table 1; a detailed analysis is to be found in an earlier publication (KAUFMANN et al. 1946).

DISCUSSION

Qualitative differences among breaks induced by irradiation of spermatozoa: The data here presented, together with those obtained previously, indicate that the frequency of chromosomal rearrangements induced by X-ray treatment of the mature spermatozoon of Drosophila can be modified by near infrared radiation when it is used before the X-rays, but not when the sequence is reversed. (A similar difference between the effects of pretreatment and posttreatment was detected in experiments in which breakage was induced by the nitrogen mustard, methyl-*bis*(betachloroethyl)amine hydrochloride; KAUFMANN and GAY 1948.) This difference seems to warrant further consideration of the sequence of events that transpires between induction of breaks and utilization of the breakage ends in structural alteration.

Previous studies also showed that near infrared radiation in itself is ineffective in inducing gene mutations or chromosome breaks, and that its use in combination with X-rays does not produce any significant increase in the overall frequency of induced recessive and dominant lethals (KAUFMANN et al. 1946; KAUFMANN and GAY 1947). Cytogenetic analysis has shown that in some cases the recessive lethals are associated with rearrangements, and that in other cases they are independent of detectable aberrations. Although the frequency of rearrangements is modified by pretreatment with near infrared radiation, no parallel increase was detected among the associated recessive lethals; and this finding indicates that lethals are not dependent for their expression on the formation of rearrangements. Dominant lethals are nonviable alterations, most of which presumably result from single breaks as a consequence of end-to-end union of sister chromatids (MULLER 1940, 1941; PONTECORVO 1941, 1942; DEMEREC and FANO 1944; CATCHESIDE and LEA 1945a, 1945b). A small proportion of the dominant lethals may represent unbalanced, multiple-break rearrangements, and it has been suggested that the frequency of this class, like that of the homologous class of viable rearrangements, may be increased by pretreatment with near infrared radiation (KAUFMANN et al. 1946).

Thus the action of near infrared radiation in "sensitizing" the chromosomes of Drosophila appears to be restricted to the control of processes involved in the formation of chromosomal rearrangements. That the higher frequency of these rearrangements resulting from pretreatment is not referable to an overall or general increase in number of all types of induced breaks is indicated by the fact that no increase was observed in frequency of the single-break type of dominant lethal. This finding, considered together with the observation that near infrared radiation in itself is not a mutagenic agent, has led to formulation of the interpretation that the sensitizing action of the portion of the spectrum

centering around wave length 10,000 Å is attributable to facilitation of recombination among the breaks provided by the ionizing radiations (KAUFMANN et al. 1946; KAUFMANN and GAY 1947). It is also apparent from these observations that breaks fall into qualitatively different classes, since the subsequent behavior of some breakage ends was modified by conditions created as a consequence of pretreatment with near infrared radiation, whereas that of others was not. The question accordingly arises whether such qualitative differences in Drosophila may be ascribed to variations in the time at which the different types of aberration are produced. Although the experiments utilizing near infrared radiation do not in themselves permit a final answer to this question, they provide clues that can be evaluated in terms of the total evidence now available.

Origin of the single-break dominant-lethal aberrations: Evidence previously available indicated that breakage ends induced by X-ray treatment of chromosomes of mature spermatozoa do not participate in the formation of viable types of rearrangements until after the sperm has penetrated the egg in fertilization. This evidence was provided by MULLER (1940), who observed by genetic analysis approximately the same frequency of translocations between the second and third chromosomes whether equivalent doses of X-rays were administered continuously or in a series of widely spaced fractions; and the same result was reached by KAUFMANN (1941a), who found by salivary-gland chromosome analysis that continuous and fractionated treatments yielded comparable frequencies of breaks and proportions of different types of rearrangements. This evidence led to the conclusion that exposure to ionizing radiations produces in the chromosomes of the spermatozoon a series of breaks or potential breaks whose ability to participate in structural rearrangement depends on the availability of other similar breaks. It was assumed, moreover, that breakage ends that fail to establish contacts with other similar ends—when chromosome movement is initiated after the spermatozoon has entered the egg—may subsequently undergo restitution, to establish the original sequence of parts. By analogy the further assumption was made that breaks not recombined or restituted may remain "open" until longitudinal division of the chromosome occurs in the male pronucleus, whereupon an opportunity is provided for end-to-end union of sister chromatids to establish a dicentric chromosome with dominant lethal potentialities (MULLER 1940). The latter assumption, however, is not an essential concomitant of the experimental findings, which concern only that fraction of the total number of breaks that is involved in the production of detectable rearrangements. The additional experimental evidence now available shows that this class of breaks is subject to modification by pretreatment with near infrared radiation, whereas the group utilized in the formation of the bulk of dominant lethals is not. As an explanation of the difference, the possibility may be considered that eventuation of the single-break dominant-lethal aberrations occurs before and not after the sperm has entered the egg in fertilization.

If production of a nonviable arrangement from a single break merely rep-

resented an alternative pattern of reunion to that provided by restitution, it might be expected that the frequency of dominant lethals would be reduced as a consequence of pretreatment, because some of the breaks would be converted to the type capable of recombining, and fewer would be available for either restitution or production of arrangements with dominant lethal potentialities. No such reduction was obtained; but it must be kept in mind that the argument involves two assumptions: first, that pretreatment does not increase the store of breaks primarily induced by the X-rays, and second, that the proportion of breaks normally available for restitution is not exceedingly large as compared with the proportion recombining (calculations by CATCHESIDE and LEA 1945b, and LEA and CATCHESIDE 1945, indicate that it is not). Another line of evidence is provided by combination treatments in which ultraviolet rays were used after X-rays. It was found that posttreatment with radiation of wave length 2537 Å effected a marked decrease in the frequency of chromosome rearrangements, but no commensurate modification in the frequency of dominant lethals (KAUFMANN and HOLLAENDER 1942, 1946). Such a result might be expected if breaks utilized in the production of dominant lethals were no longer subject to modification at the time the ultraviolet treatment was administered. The conditions requisite for formation of aberrations during this period would be realized if the chromosome of the mature spermatozoon contained at least two chromonemata, and if creation of a thoroughgoing lesion was followed promptly by the union of sister chromatids end-to-end to produce dicentric bodies and acentric fragments (following the pattern described by MCCLINTOCK 1938a, 1938b for maize).

Parallel lines of evidence also leading to the conclusion that different types of rearrangements may be realized at different stages in the breakage-recombination cycle have been furnished by studies on Tradescantia. Microspores of these plants irradiated during early prophase yield a type of break that traverses simultaneously sister chromatids lying close together. If end-to-end union of strands occurs later at the sites of these isochromatid breaks, there results a type of aberration (a dicentric body with an associated acentric fragment) that is homologous with the type considered to be responsible for the major portion of the dominant lethals in Drosophila. Treatment of pollen-tube chromosomes of Tradescantia with ultraviolet rays (λ2537 Å) after X-rays inhibits production of chromatid breaks and translocations, but not of isochromatid breaks (SWANSON 1944). Similarly, posttreatment with near infrared radiation increases the frequency of chromatid breaks and exchanges, but not of isochromatid breaks (SWANSON and HOLLAENDER 1946). SWANSON has concluded from these observations that aberrations resulting from isochromatid breaks are realized immediately on X-radiation, and hence are not subject to modification by posttreatment. Results obtained from pretreatment experiments do not correspond so closely to those obtained with Drosophila, since ultraviolet radiation effects some inhibition, and near infrared radiation some augmentation of the frequency of isochromatid-break aberrations as compared with X-ray controls; but such differences between Tradescantia and

Drosophila may be referable to differences in organization of materials in the prophase chromosomes of the treated microspores and in the condensed chromosomes of the mature spermatozoa.

The interpretation that dominant-lethal aberrations of the single-break type are produced immediately after induction of thoroughgoing breaks by the ionizing radiation implies that each chromosome of the mature spermatozoon contains at least two independent chromonemata. This type of structural organization had previously been suggested by the occurrence of gene mosaics (PATTERSON 1933; MOORE 1934), and chromosome duplications (KAUFMANN 1941b). Breaks utilized in the production of the duplications sometimes occur at identical loci in the two chromatids of the irradiated chromosome, sometimes independently in each strand. These chromatid breaks in themselves do not provide unequivocal evidence that the chromosome is longitudinally double at the time of irradiation. Since the number of strands in the mature spermatozoon cannot be determined cytologically, the alternative possibility must be considered that the chromosome is single at the time of treatment, and that differences between the locations of breaks in sister chromatids are referable to differential patterns of recombination and restitution in the two strands after their separation. There is, however, abundant cytological evidence that chromosomes of some spermatozoa are multiple stranded (review in KAUFMANN 1948), and this factor together with the evidence provided by the combination-treatment experiments, and the experimental verification of the occurrence of isochromatic breaks in Tradescantia, substantiates the interpretation that isochromatid breaks may also occur in Drosophila.

Some of the duplications have shown that broken ends may establish independent patterns of reunion distal and proximal to a break (KAUFMANN 1941b). Comparable differences in the behavior of ends of an isochromatid break have been observed in Tradescantia (CATCHESIDE, LEA, and THODAY 1946a; LEA 1947; KOTVAL and GRAY 1947). Quantitative analyses have indicated, however, that such behavior is exceptional, and that in a high percentage of cases the ends proximal and distal to the break behave similarly (CATCHESIDE et al. 1946a). The low frequency of duplications of the reversed-repeat type encountered in analyses of salivary-gland chromosomes of F_1 larval progeny of treated males of Drosophila also indicates that the same pattern of reunion usually occurs proximal and distal to the break.

Union of chromatids end-to-end following the production of a thoroughgoing break in the chromosome of the spermatozoon would also explain the extreme rarity of terminal deficiencies among the quota of rearrangements that are available for salivary-gland chromosome analysis. Aberrations of this type are not necessarily lethal in Drosophila (DEMEREC and HOOVER 1936; SUTTON 1940; BISHOP 1941), and their failure to be detected cytologically is probably attributable to some pattern of behavior of the breakage ends. CATCHESIDE and LEA (1945b) irradiated ring-X chromosomes but did not detect among 749 tested the V-shaped chromosome that would arise from an intercalary break followed by healing of the broken ends. Failure of such chromosomes to appear was attributed to the low frequency with which healing of both broken ends

occurred simultaneously; but the interpretation here presented emphasizes the possibility that "healing" does not occur because the two chromatids of each chromosome unite end-to-end immediately following breakage to give rise to a dicentric double ring—an inviable, dominant-lethal type of aberration. This interpretation also obviates the necessity of postulating the existence in the chromosomes of Drosophila of a special particle, or telomere, whose presence is essential to the viability of the chromosomes (MULLER 1940).

Restitution and recombination of breakage ends: The pattern of analysis presented in the foregoing paragraphs suggests that thoroughgoing breaks provide a mechanism for the production in the mature spermatozoon of dominant-lethal aberrations, whereas other lesions of lesser magnitude persist until the sperm has entered the egg—when movement of chromosomes provides the opportunities for establishment of new associations. On this basis, breaks might be classified as "complete" or "potential." The analysis must now be extended to determine whether the total experimental data permit such simple classification. More specifically the question is whether all the breaks not utilized in the formation of dominant lethals persist until the time of fertilization. Combination-treatment experiments again serve to provide illuminating information.

It was indicated previously that ultraviolet radiation (λ2537 Å) when used after X-rays will lower the frequency of chromosomal rearrangements. This means that fewer breaks recombine after the sperm has entered the egg. If the energy supplied by the ultraviolet radiation were effective in transforming potential into thoroughgoing breaks such conversion should be reflected in a rise in the frequency of dominant lethals. Since no such rise was detected, the conclusion was reached that the effect of posttreatment with λ2537 Å is attributable to increased restitution rather than to an increase in frequency of the single-break type of derangement (KAUFMANN and HOLLAENDER 1946). A similar conclusion was reached by SWANSON (1944) from parallel studies on Tradescantia. These experiments agree in indicating that modification of the potential breaks induced by ionizing radiations may be effected by supplementary treatment in the interval between induction of breaks and formation of rearrangements.

Treatment with near infrared radiation during this period was not effective, however, in modifying the frequency of rearrangements in Drosophila. The amount of energy provided by absorption of a radiation quantum of λ10,000 Å is considerably less than with ultraviolet radiation, and this factor may account for the difference in efficiency of the two regions of the spectrum; but it must be kept in mind that near infrared was effective, when used before the X-rays, in altering the frequency of rearrangements. If all the breaks induced by X-rays maintained until the time of fertilization the capacity to participate in restitution or recombination, some modifying action of posttreatment with near infrared radiation might be anticipated. This anticipation is realized in Tradescantia, as the experiments of SWANSON referred to previously have shown. Since in Tradescantia breakage and recombination proceed concurrently, it is possible that movement of chromosomes, which is lacking in Dro-

sophila, may be the essential factor facilitating recombination in one species and not in the other. It is also possible that the potential breaks available at this period are not modifiable by the limited amount of energy provided by near infrared radiation because the more labile breaks have previously been eliminated by restitution. Some experimental data are available that bear on this problem.

In the first place it has been reported by KANELLIS (1946) that if irradiation of the mature spermatozoon is carried on at a very low temperature (ca. 2°C) a higher frequency of rearrangements is obtained than with irradiation at a high temperature. This result is in harmony with earlier ones of PAPALASHWILI (1935) and MICKEY (1939), although other experiments in which irradiation was undertaken at different temperatures within the range between 5° and 37°C showed no significant difference in frequency of rearrangements (MULLER 1940; KAUFMANN unpublished data). KANELLIS suggests that less restitution takes place at low than at high temperature, so that more breaks are available for recombination, and this in turn implies that restitution may be occurring even during the period of X-ray treatment.

A comparable increase in frequency of chromatid breaks and chromosome aberrations has been obtained in Tradescantia by irradiating microspores at low temperature. This result has likewise been attributed to delay of restitution (SAX and ENZMANN 1939). More recent evidence indicates that the temperature factor operates primarily or exclusively during irradiation, even when it is restricted to a period of 80 seconds (FABERGÉ 1948; cf. also SAX 1947; CATCHESIDE, LEA, and THODAY 1946b). If the increase in frequency of rearrangements is attributable to inhibition of restitution, such restitution must normally occur immediately after the breaks are induced, because the temperature-treatment period is relatively short as compared with the time the breaks remain "open" (average ca. 4 minutes according to calculations of LEA and CATCHESIDE 1942, although recent data by SWANSON, 1947 indicate that some restitution may be delayed as long as 4 hours after irradiation).

These studies on Drosophila and Tradescantia thus suggest that restitution may take place in some of the potential breaks before the time of recombination. Inhibition of restitution during this period should increase the store of potential breaks available for subsequent recombination; and perhaps the "sensitizing" action of pretreatment of chromosomes with near infrared radiation is attributable to changes in the quality of potential breaks that prevent such post-irradiation restitution (cf. also the recent report of FABERGÉ (1948) that change of temperature in either direction immediately preceding irradiation increases the number of aberrations in Tradescantia).

A considerable portion of the potential breaks must nevertheless persist until movement of chromosomes provides opportunities for recombination. The opportunities may be increased by supplementary treatment; for example, it has been found in Drosophila that treatment with near infrared radiation at the time of syngamy is effective in increasing the frequency of rearrangements (KAUFMANN 1946). Potential breaks that fail to establish new contacts during

the period of recombination presumably undergo restitution soon thereafter, although some experimental evidence suggests that recombination may be delayed under certain conditions until after the first cleavage mitosis (HELFER 1940).

Recapitulation: An analysis of frequencies and types of rearrangements provided by experiments in which supplementary agents were used in combination with ionizing radiations in treatment of the mature spermatozoon of Drosophila indicates that breaks fall into qualitatively different groups that may be classified tentatively as "complete" and "potential." These differences are reflected in the subsequent behavior of the breakage ends.

It is suggested that the complete, or thoroughgoing, breaks provide the opportunity for formation within the chromosomes of the mature spermatozoon of aberrations involving end-to-end union of sister chromatids, and that these eventuate as dominant lethals. The further suggestion is made that some of the potential breaks are restituted during the period of irradiation or shortly thereafter, whereas others persist until opportunities are offered for recombination after the spermatozoon has entered the egg in fertilization. Although based on an appraisal of available data, these suggestions concerning the time of realization of different types of aberrations must be regarded as tentative, pending the accumulation of additional experimental evidence that will help resolve some of the existing perplexities. Why, for example, if the chromosome of the mature spermatozoon is longitudinally double, do both chromatids together usually behave as a unit in establishing new connections at the time of restitution? In the absence of the definitive evidence necessary to answer such questions, a reevaluation of the data now available has served to focus the problem of structural rearrangement on the analysis of the behavior of individual breakage ends. As MCCLINTOCK (1941) concluded from studies on maize, the factors responsible for fusion or restitution are probably related not only to the method of origin of the breaks but to the physiological conditions surrounding the broken ends.

Of the various types of supplementary treatment utilized, the near infrared portion of the spectrum has proved most serviceable in analysis of the cycle of breakage and recombination in Drosophila. Studies on Drosophila indicate that near infrared radiation can modify the processes that lead to structural rearrangement of chromosomes, but not those responsible for gene mutation. Accordingly, this type of radiation may serve as a useful diagnostic tool, if applied to organisms in which cytological analysis is not feasible, in distinguishing between genetic changes that are attributable to chromosomal alterations and those that are not. It was reported following the earlier studies on Drosophila that the "sensitizing" action of near infrared radiation is not attributable primarily to an over-all or general temperature effect, but to a more specific influence of the radiation on certain materials of the chromosome; and this point of view has been substantiated by SWANSON'S experiments on Tradescantia. The potentialities of this portion of the spectrum for further experimental work lie, therefore, in the prospect of securing intense mono-

chromatic radiation of known physical properties. Experiments directed to this end are now in progress.

SUMMARY

Exposure of mature spermatozoa of *Drosophila melanogaster* to near infrared radiation after treatment with X-rays did not effect an increase in the frequency of rearrangements similar to that obtained when the near infrared preceded the X-rays. A comparison of these results and those obtained in previous experiments suggests that breaks induced by ionizing radiations may be qualitatively different—with respect to their potentialities for subsequent behavior—from the time of their inception. It is suggested that some breaks are thoroughgoing and therefore provide immediate opportunities for union of sister chromatids end-to-end to produce dicentric bodies and acentric fragments which result in dominant lethals. It seems probable that the close proximity of chromatids in the compact sperm head facilitates sister union and inhibits thereby the formation of a class of dominant lethals characterized by "healing" of breakage ends and the production of terminal deficiencies. Less damage to the chromosome presumably occurs at other breaks, at which restitution may be effected either during the time of X-ray treatment or shortly thereafter; or the breaks may remain "open" until opportunities for recombination are provided after the spermatozoon has penetrated the egg in fertilization.

The analysis also indicates that the sequence of events which transpires between irradiation and the production of aberrations may not differ so greatly in Drosophila and Tradescantia as has previously been assumed. If some restitution occurs prior to the time of recombination—and not merely as a consequence of failure of recombination, as has generally been assumed—the essential difference in the breakage-recombination cycle in Tradescantia and Drosophila lies in the fact that movement of chromosomes to facilitate recombination may occur in the cells of Tradescantia during or shortly after exposure to the ionizing radiation, whereas such movement is not possible in Drosophila until the attenuated sperm head is transformed into the spherical male pronucleus at the time of fertilization.

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