Evidence for an Inducible Repair-Recombination System in the Female Germ Line of *Drosophila melanogaster*. II. Differential Sensitivity to Gamma Rays

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ABSTRACT

In a previous paper, we reported that the reactivity level, which regulates the frequency of transposition of *I* factor, a LINE element-like retrotransposon, is enhanced by the same agents that induce the SOS response in *Escherichia coli*. In this report, we describe experimental evidence that, for identical genotypes, the reactivity levels correlate with the sensitivity of oogenesis to gamma rays, measured by the number of eggs laid and by frequency of dominant lethals. This strongly supports the hypothesis that the reactivity level is one manifestation of an inducible DNA repair system taking place in the female germ line of *Drosophila melanogaster*. The implications of this finding for the understanding of the regulation of *I* factor are discussed and some other possible biological roles of this system are outlined.

IN the I-R system of hybrid dysgenesis, transposition of the *I* retrotransposon may occur at high frequency in oogenesis of F_1 daughters from a dysgenic cross (denoted SF females). This transposition is regulated by a peculiar cellular state in the oocytes of the reactive females; this state exhibits very variable "strengths," called reactivity levels, which can be measured by the hatching percentage of eggs laid by the SF females. These levels follow complex rules of inheritance, involving both chromosomal control and a maternally transmitted component (BUCHETON and PICARD 1978). Moreover, they are liable to undergo heritable, cumulative and reversible changes through the effects of nongenetic factors on the maternally inherited component. Among these factors aging and breeding temperature are known to decrease the reactivity levels (BUCHETON 1978, 1979; reviewed in BREGLIANO and KIDWELL 1983).

It is interesting to note that a similar heritable aging effect was described a long time ago for the life span of rotifers (LANSING 1947). The older the parents, the shorter the life span of the offspring. Similar data were obtained on Drosophila by LINTS and HOSTE (1974 and 1976) with respect to longevity and also to other quantitative features such as daily fecundity and viability.

In a preceding paper, we proposed the hypothesis that the reactivity levels might be one manifestation of an inducible repair-recombination system, whose biological role might be comparable with that of the SOS response in bacteria. We reported experimental evidence that methotrexate and gamma rays, which are efficient inducers of the SOS network in *E. coli* (reviewed in WALKER 1985), enhance the reactivity (BREGLIANO *et al.* 1995). The main features concerning the present knowledge on the control of the reactivity levels are outlined in Figure 1.

To further investigate the analogy with the SOS response, we have to address the question whether different levels of reactivity are associated with different repair-recombination efficiencies. Until now, the only known phenotype associated with the reactivity level was the frequency of transposition of active *I* elements in the oocytes of female progeny from dysgenic crosses. In the present paper, we report evidence that, in identical genetic backgrounds, the level of reactivity correlates with the sensitivity of oogenesis to gamma rays. As the only known effect of this agent is to cause DNA damage, these differences in sensitivity reflect differences in repair efficiency.

MATERIALS AND METHODS

Fly stocks and culture conditions: The following *D. melanogaster* stocks were used: *ery*, a weakly reactive stock originating from crosses between an *ebony* stock and a *rosy* 506E stock; *se*F8, a strongly reactive strain bearing the *sepia* mutation, kept for a long time in our lab; *se*F8LG, a subline of *se*F8 bred with a long generation pattern (40-day-old mothers) for five generations (it is therefore completely isogenic with *se*F8 but has a medium level of reactivity instead of a strong one); *e*stM, a strongly reactive stock bearing the *ebony* mutation; and B2′ and Canton-S are standard inducer stocks. Mutations are as described in LINDSLEY and ZIMM (1992). To avoid any interference with the P-M system of hybrid dysgenesis, all the stocks used are devoid of *P* elements. Unless stated otherwise, all stocks were maintained with short generations (very young mothers). Flies were reared on the axenic food described by DAVID (1959) at 20 ± 0.5°C, with a normal light-dark cycle.

Experimental procedures: We followed the procedures described previously (BREGLIANO *et al.* 1995) for measuring fe-

We dedicate this work to the memory of PHILLIPE L'HERITIER, who died January 22, 1994.

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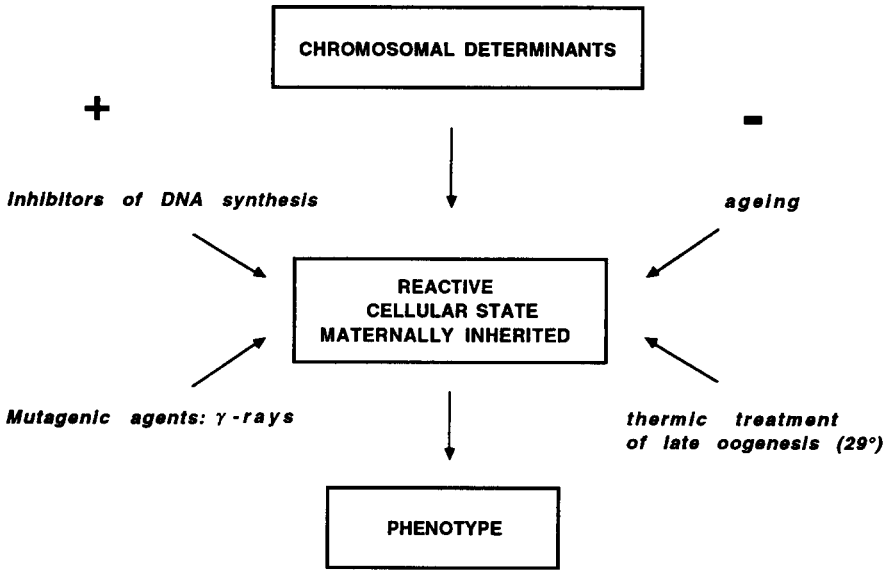

FIGURE 1.—Schematic presentation of the genetic behavior of the reactivity level. Until now the phenotype was only the frequency of transposition of *I* factor.

cundity (number of eggs laid), fertility (percentage of hatched eggs), and levels of reactivity, as well as irradiation with gamma rays.

Statistical procedures: Confidence limits and ANOVA statistical test on percentages were calculated after angular transformation.

RESULTS

The main experiment presented in this paper (referred to as experiment 1) was performed to compare the sensitivity (to gamma rays) of oogenesis in flies with identical nuclear genotypes but different levels of reactivity. For this purpose, we used hybrids from the following three crosses: *se*F8 females × *ery* males (A hybrids), *se*F8LG females × *ery* males (B hybrids) and *ery* females × *se*F8 males (C hybrids). For treated series as well as for control ones, four or five sets of six hybrid females each, were crossed with reactive males (*ery*) to check for fecundity, fertility and larval-to-adult viability. To allow measurement of reactivity levels, three or four sets of six hybrid females were mated with inducer males (Canton-S), and the hatching percentage of the eggs laid by their SF daughters was scored. The experimental scheme is described in Figure 2, the irradiation dose was 40 Gy. All parts of the experiment were performed together, at the same time, and therefore under exactly the same conditions.

Changes in reactivity levels after irradiation: For the three categories of hybrids, the reactivity levels of the control females are very similar to the levels of their respective mother strains. The A series is strong, B is medium and C is weak. The irradiated C flies (Cγ) exhibit only a slight, although significant, increase after treatment (Figure 3C), which corroborates the data reported previously with other weak strains (BREGLIANO *et al.* 1995). The irradiated B flies (Bγ) exhibit strong enhancement after irradiation; this lasts until day 21 (Figure 3B).

For the Aγ flies, the reactivity level is identical to that of the control until day 20, when it becomes significantly lower (Figure 3A). To try to understand this effect, experiment 2 was performed with another strongly reactive stock (*es*tM). Pupae 48 hr old were irradiated with 30 Gy, (below the induction threshold of nearly 36 Gy) (see BREGLIANO *et al.* 1995), then crossed with reactive males. The daughters were mated with standard inducer males (B2′) and their reactivity levels were measured during the first 3 weeks of their life. The same protocol was applied to nonirradiated *es*tM flies. Until day 12, the reactivity level of the irradiated series appears significantly lower than the level of control flies; then when the reactivity of the control drops, the levels of the two series become identical (Table 1). These data may be connected with the fact that the Aγ flies yield a high frequency of dominant lethals (see below). Altogether, these results suggest that, above a certain level of reactivity, a treatment with gamma rays

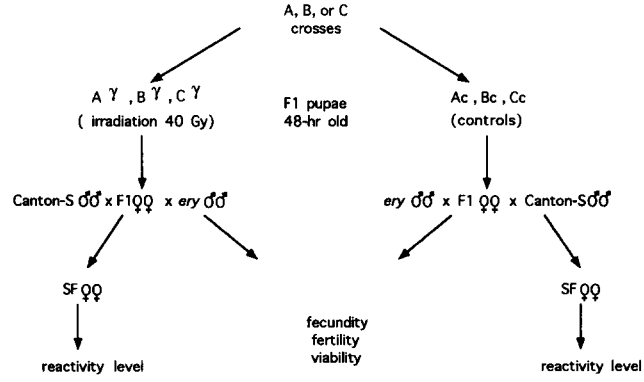

FIGURE 2.—Experimental scheme used to compare sensitivity to gamma rays of flies bearing the same genetic background but with different reactivity levels. A cross is: *se*F8 females × *ery* males; B cross is: *se*F8LG females × *ery* males; C cross is: *ery* females × *se*F8 males.

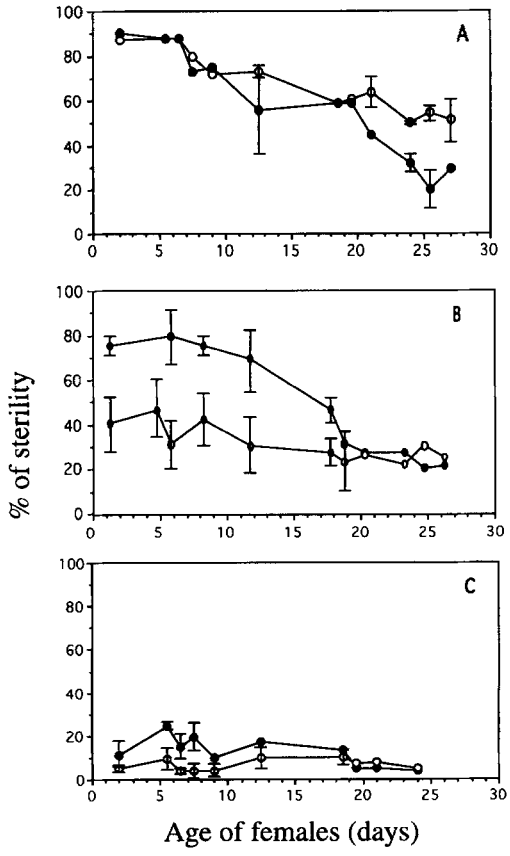

FIGURE 3.—Changes in reactivity induced by 40-Gy irradiation of females sharing the same nuclear genotype but with different reactivity levels; irradiation was applied at pupal stage. Control series (○), irradiated series (●) (A) Strongly reactive flies. (B) Flies with medium reactive level. (C) Weakly reactive flies.

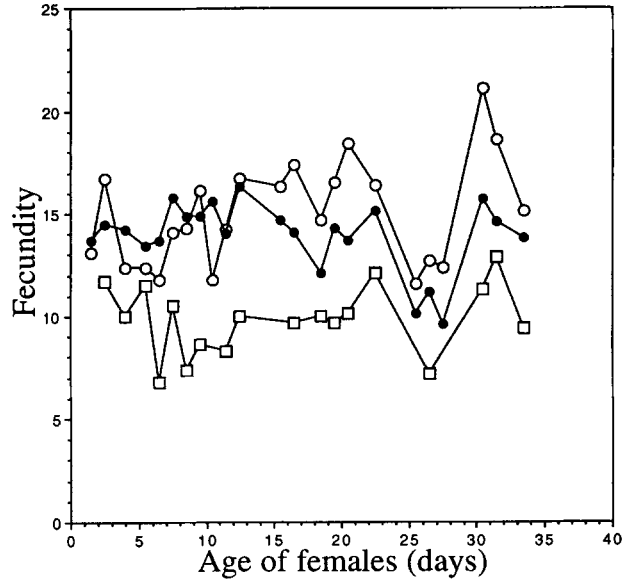

FIGURE 4.—Fecundity of irradiated flies of the A series (○), the B series (●) and the C series (□). Statistical analysis of these data is presented in Table 2. Fecundity is expressed in mean number of eggs laid by female by 24 hours.

may have a tendency to be more deleterious and to eliminate embryos derived from the most reactive oocytes (see DISCUSSION).

Effect of irradiation on fecundity is inversely correlated with the reactivity level: Figure 4 shows the fecundities of the three series of treated females of experiment 1; the statistical analysis of these data is presented in Table 2. Fecundities of the three control series are not shown; they are very similar to those of the Aγ flies. The fecundities of the Aγ and Bγ flies show only random differences until day 15, then the Aγ series is always higher than the Bγ; this difference is significant at the 5% level with the ANOVA statistical test (Table 2). One may note that the reactivity levels of Aγ and Bγ flies are also identical until day 15, then the level of Bγ seems to be lower than that of Aγ (Figure 3, A and B).

The Cγ series exhibits stronger differences with the others: fecundity is always highly significantly lower than with the Aγ and Bγ series (Figure 4 and Table 2), as is reactivity (Figure 3).

The most strongly reactive flies are rather sensitive to irradiation with regard to fertility and larval-to-adult viability: Nonhatched eggs allow detection of what are usually called dominant lethals. This term covers all anomalies that prevent embryonic development, whether nonfertilization or genomic abnormalities. There is no reason for the proportion of unfertilized eggs to be different in control and in irradiated series; therefore the differences in nonhatched eggs reflect the genetic impairments of the oocyte genome caused by gamma rays. Figure 5 shows the changes in the per-

TABLE 1

Effect of a 30-Gy irradiation on the reactivity level of a strongly reactive line

	Age of adult females (days)				
*e*stM flies	0–3	4–7	9–12	15–17	18–20
Control	92.2 ± 2.2	91.0 ± 1.2	77.1 ± 1.4	63.4 ± 2.5	62.4 ± 2.6
Irradiated	86.3 ± 1.5*	81.3 ± 1.7*	67.2 ± 3.7*	67.2 ± 4.3	56.8 ± 5.4

Reactive females of the *e*stM stock were irradiated at pupal stage, adults were mated with reactive males and the F_1 daughters mated with standard inducer males to measure their reactivity level. Reactivity is given as the mean percentage of nonhatching eggs ± SE, laid by SF progeny. Asterisks indicate a significant difference (5% level) between the irradiated and the corresponding control sets (Student *t*-test).

TABLE 2

Effect of 40-Gy irradiation at pupal stage on oogenesis of isogenic flies with different reactivity levels

		Age of adult females			
		Days 1–12		Days 15–35	
	Compared series	d.f.	*P*	d.f.	*P*
Fecundity	Aγ and Bγ	96	0.229	115	0.015
	Aγ and Cγ	85	<0.001	102	<0.001
	Bγ and Cγ	97	<0.001	115	<0.001
Fertility	Aγ and Bγ	78	0.0014	115	<0.001
	Aγ and Cγ	69	0.184	102	0.019
	Bγ and Cγ	79	<0.001	115	<0.001

ANOVA statistical analysis of data plotted on Figures 4 and 5. d.f., degree of freedom; *P*, probability that the difference between the compared series is due to chance. Aγ flies are strongly reactive, Bγ flies have a medium reactivity level, Cγ are weakly reactive; all have the same nuclear genotype (see text).

centage of hatched eggs with age of the reactive females, statistical analysis is presented on Table 2. The data of the control series, which are not presented in the graph, are all in the range from 90% to 99% throughout the experiment. The three treated series begin near 75% and exhibit a regular decrease from the 15th day on. Again, the Cγ series yields the lowest values, which confirms its greater sensitivity to γ rays. From the 6th day on, the Bγ series exhibits a much lower proportion of dominant lethals than the Aγ series and the difference increases as the females get older.

The larval-to-adult viabilities of the treated and control series are presented in Table 3; the number of larvae in each vial being lower than 100, the measure of viability is not impaired by crowding. Data show that within the first 14 days, the Cγ series has the best viability among the irradiated flies and the Aγ series has the worst viability (respectively, 85.6 ± 2.3% and 73.3 ± 2.6%; Table 3). After the 14th day, the difference is slighter and not significant but the Aγ series shows consistently lower values than the others.

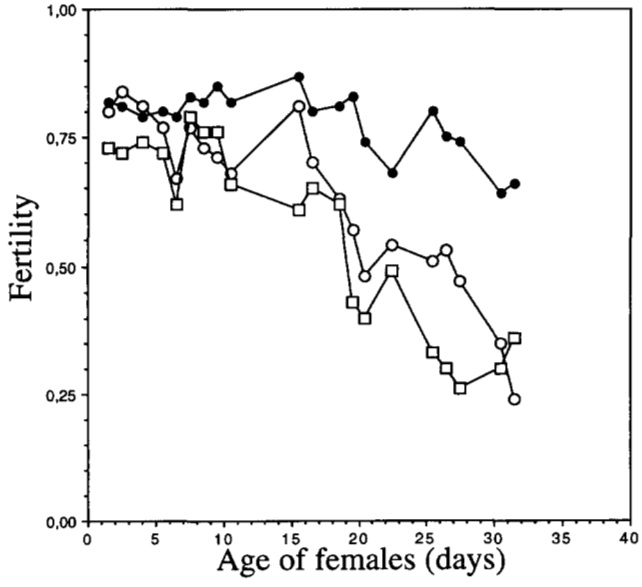

FIGURE 5.—Fertility of irradiated flies of the A series (○), the B series (●) and the C series (□). Statistical analysis of these data are presented in Table 2.

The higher sensitivity of oogenesis of the C flies is very likely due to their low reactivity level: The C hybrids originate from the reciprocal cross compared with the A and B hybrids (Figure 2). Therefore it might be argued that the greater sensitivity to irradiation of their oogenesis could be due to some maternally inherited factor independent of reactivity. Results of a third experiment are not consistent with this interpretation.

In the third experiment, we used two sublines of the *e*stM stock, one subline was bred as usual with short generations (*e*stM), the other subline had undergone 13 successive long generations (*e*stMLG). For another purpose, females of each subline had been crossed with males of another reactive stock. Samples of 48-hr-old F_1 pupae issued from the two crosses were irradiated with 40 Gy. The reactivity level of the adult females was

TABLE 3

Effect of 40-Gy irradiation of females with different reactivity levels on the larval-to-adult viability of their progeny

	Age of females		
Series	First week	Second week	Third week
Irradiated			
Aγ	73.3 ± 2.6		74.8 ± 2.4
Bγ	83.8 ± 0.86	72.2 ± 2.2	83.8 ± 6.1
Cγ	85.6 ± 2.3		80.1 ± 2.2
Controls			
Ac	86.2 ± 2.9	80.5 ± 4.7	87.0 ± 0.9
Bc	85.7 ± 1.3	86.7 ± 1.3	91.8 ± 1.8
Cc	—	85.1 ± 2.6	—

Females were irradiated at pupal stage (48 hr old). A flies are strongly reactive, B flies have a medium reactivity level and C flies are weakly reactive. They share the same nuclear genotype. Data are given as mean percentage of adult progeny with regard to larvae ± SE.

TABLE 4

Effect of gamma rays on the number of adult progeny of strongly and weakly reactive females with identical genotype and maternal lineage

Maternal line	Age of females (days)	No. of progeny[a]		(C − γ)[b]	Level of significance
		Control	Irradiated		
*e*stM[c]	2–4	101.0	130.7	−29.7 ± 64.6	NS
	4–7	213.0	179.5	33.5 ± 59.8	NS
	7–9	219.8	157.2	62.6 ± 79.2	NS
	9–14	—	—	—	
*e*stMLG[d]	3–5	191.6	104.6	87.0 ± 69.3	*
	5–7	197.4	88.4	109.0 ± 38.8	**
	7–9	172.6	96.2	76.4 ± 53.4	*
	9–11	198.0	84.0	114.0 ± 44.7	**
	11–14	250.0	90.0	160.0 ± 54.7	**

C, control; γ, irradiated. * $P < 0.05$; ** $P < 0.01$; NS, not significant.
[a] Mean number of adult progeny for a set of 6 females.
[b] Difference between control and irradiated series with its confidence limits for $P < 0.05$ (Student *t*-test).
[c] Line of the strong reactive *e*stM stock bred with short generations.
[d] Line of the *e*stM stock bred with long generations and therefore weakly reactive.

measured at the beginning of their life. It was 86.3 ± 1.3% for the daughters of the *e*stM females and 17 ± 2.5% for the daughters of the *e*stMLG females. The number of adult progeny of controls and irradiated F_1 females for each subline was counted during the first days. The data clearly show that the oogenesis of the weakly reactive flies is far more sensitive than the oogenesis of the strongly reactive ones (Table 4). Fecundity and fertility were not scored accurately in this case, but rapid observations indicated that they were both affected in the weakly reactive females.

In this experiment, both the nuclear genotype and the maternal lineage of the flies were identical. This strengthens the conclusion that the stronger sensitivity of the C hybrids is actually due to their low reactivity level.

DISCUSSION

Effect of gamma rays on different reactivity levels: The enhancement of reactivity level of the most weakly reactive flies is very low (Figure 3C). This is in agreement with the data reported previously (BREGLIANO *et al.* 1995). The lack of enhancement for the Aγ series (Figure 3A) might be interpreted as indicating that the A flies have reached their maximum possible level and cannot go any higher, but this cannot explain the significant decrease, below the control level, after day 20. All in all, data on Aγ flies and of experiment 2, suggest that the unchanged reactivity level of Aγ flies prior to day 20 may be the result of two counterbalanced effects: an enhancing effect, as observed for Bγ flies (Figure 3B), and selection against the strongest reactive oocytes; the latter effect becoming dominant (and detectable) only when the first is over. This is consistent with the fact that in Aγ flies the decrease of reactivity level below that of control flies begins at day 20, when the induction effect comes to end (as indicated by the B series). In experiment 2 with the *e*stM stock, the dose of gamma rays being under the induction threshold, only the selection effect is visible, as long as the reactivity is high. This explanation is plausible because in all reactive stocks, we observe a significant interindividual variability in reactivity levels.

The medium reactive flies show very strong enhancement (Figure 3B). This strong effect may surprise, especially if one considers that the dose used (40 Gy) is not far above the threshold dose observed in the previous work (36 Gy). One explanation might be that, in the present work, we treated young pupae instead of adults. This is probably not the right explanation because in experiments with another medium reactive stock, we also treated young pupae and we did not get a much stronger effect than after treatment of adult flies (J.-C. BREGLIANO, unpublished results). It is more likely that this strong enhancement is due to the fact that, in the present case, we irradiated a subline bred with long generations, it has therefore a tendency to return to its high original constitutive level. This probably amplifies the enhancing effect of gamma rays.

It may be worth noting that the results obtained with B hybrids provide further evidence that reactivity enhancement is actually the result of an induction process and not the result of a selection of more reactive progeny. If the latter hypothesis were true, we would expect the difference in reactivity levels between Bγ and Bc to parallel the differences in fecundity, fertility, and viability. This is not the case, the greatest difference in reactivity between Bγ and Bc flies is within the first week (Figure 3B) when there are only slight differences in fecundity and fertility between the two groups (Figures 4 and 5), and no significant differences in larval-

to-adult viability (83.8 ± 0.86% for Bγ and 85.7 ± 1.27% for Bc; Table 3).

The sensitivity of oogenesis to gamma rays depends on the reactivity level: After irradiation, the medium reactive flies (Bγ) exhibit good fecundity and the lowest frequency of dominant lethals (Figure 4 and 5). This strongly suggests that they have the most efficient error-free repair, with both few losses of genetic material and few rearrangements. They in fact yield the greatest number of adult progeny (data not shown).

The most weakly reactive flies (Cγ), exhibit the lowest fecundity and fertility (Figures 4 and 5). This result clearly indicates a great sensitivity to DNA damage, leading to loss of functions necessary for oogenesis or for embryogenesis; it strongly suggests that most defects are unrepaired breakages, leading to arrest of DNA replication and (or to deletion of genetic material. Data from the third experiment, with flies sharing the same nuclear genotype and the same maternal lineage, provide further evidence that this sensitivity to DNA damages is actually related to the low level of reactivity rather than to another maternally inherited factor.

The data provided by the strongly reactive flies (Aγ) are the most interesting. Their fecundity appears to be rather insensitive to irradiation (Figure 4), indicating that oogenesis is able to process normally. Therefore there are neither arrest of DNA replication nor production of chromosomal deletions, which means that these flies have a high capacity to rejoin breaks. However the high level of dominant lethals (Figure 5) indicates that these meiosis yield gametes with genetic abnormalities which prevent embryogenesis; the development of larvae and pupae is also affected as shown in Table 3 (remember that in Drosophila meiosis is arrested in prophase I throughout oogenesis and is completed only after fertilization). Therefore we are led to assume that in Aγ flies many break repairs are illegitimate and produce chromosomal rearrangements. As is well known, most rearrangements are readily transmitted through mitosis but yield abnormal chromosomal complements in meiosis. These interpretations of Cγ and Aγ flies data are consistent with preliminary results obtained in our laboratory on *X* chromosome losses and recessive lethals produced by irradiation: weakly reactive flies exhibit a higher frequency of losses and a lower frequency of lethals than isogenic strongly reactive flies (A. Laurençon and J.-C. Bregliano, unpublished data). This probably means that high levels of reactivity are associated with some kind of error-prone repair of DNA strand breaks.

Interestingly, this is reminiscent of SOS mutagenesis in *E. coli* which takes place when the SOS network is strongly induced (Walker 1985; Devoret 1993). But this similarity does not means a similar molecular mechanism.

The results described in the present report clearly indicate that, for identical genetic backgrounds, different reactivity levels are related to different degrees of repair efficiency. These data, together with those presented in the previous paper, strongly support our working hypothesis that the so-called reactivity levels are one manifestation of a modulable repair system. Other work currently in progress in our laboratory also provides evidence for a strong correlation between reactivity levels and recombination fraction, at least in some chromosomal regions (A. Laurençon and J.-C. Bregliano, unpublished data). Therefore it may be of interest here to make a first rapid survey of some implications of this system. A more thorough discussion on its possible biological roles will be developed elsewhere.

Interaction with *I* factor: Previous work has shown that transposition of active *I* elements is regulated in three ways: regulation prevents transposition in the inducer strains, it is disrupted in the progeny of the dysgenic cross; in these progeny, a tissue-specific control restricts transposition to oogenesis; and the level of reactivity regulates the frequency of transposition. The first regulation may be interpreted, as in the P-M system of hybrid dysgenesis, as due to a repressor encoded by the transposable element itself (Rio 1990; Lemaitre *et al.* 1993). The existence of such a repressor in the I-R system is strongly suggested by several data (Pelisson and Bregliano 1987; McLean *et al.* 1993). With regard to the two other regulations, previous studies have demonstrated that in reactive females, *I-lacZ* and *I-CAT* constructs are expressed only in ovaries and that the level of *I-lacZ* expression correlates with the reactivity level (Lachaume and Pinon 1993; McLean *et al.* 1993). Recently Tatout *et al.* (1994) more closely defined the timing of expression of the *I-lacZ* constructs, which coincides with the presence of the synaptonemal complex, and therefore with the recombination process. In the light of our results, these data may be easily explained by assuming that efficient transcription of *I* factor depends on some host factor(s) involved in the meiotic recombination process. This (or these) factor(s) may be responsible for both tissue specificity and frequency of transposition. Interestingly, recent data on the LINE-1 family in mice, show expression of L1 RNA and L1-encoded protein in the meiotic prophase of the testis (Branciforte and Martin 1994). This raises the interesting question of whether all LINE retrotransposons are regulated by recombination functions.

In the past, the term reactivity was defined as "the permissive condition for *I* factor transposition at high frequencies" (Pelisson and Bregliano 1987); thus, the repression of *I* mobility in inducer strains and the levels of reactivity were implicitly believed to depend on one and the same regulatory mechanism. Our results show that reactivity levels depend on a host function, therefore it must be dissociated from the regulation by *I*-encoded repressor in inducer strains. This statement also leads us to assume that this function exists in inducer strains, but in this case the autoregula-

tion of the *I* factor prevents transposition and our method for measuring reactivity levels is worthless. This will be possible only when we have molecular markers for this repair-recombination system. The search for such markers is underway in our laboratory.

Outlines of some possible biological roles of the system: This inducible response of Drosophila, with its peculiar rules of inheritance, is probably a very appropriate adaptative mechanism. We may imagine that when a female is suffering from DNA damaging agents, its germ line is able to detect damage and to enhance repair efficiency. Therefore the germ cells of its daughters are better protected against the damaging effects. Moreover, preliminary evidence seems to indicate that part of this system might also be expressed in the somatic tissues, hence it is possible that all the development, and therefore the fitness, of the progeny can be improved by the enhancement of repair efficiency in the oogenesis of the mother. The large phenotypic variability of the reactivity level between individual flies adds to the flexibility of this adaptative system at the population level. Certainly, a population-level investigation of reactivity would be very interesting but it is not possible yet, because all natural populations are of the inducer type; therefore, as was pointed out above, their reactivity level cannot be measured by our current technique.

Another possible role of this mechanism may be suggested. In the introduction, we mentioned that the life span in rotifers (LANSING 1947) and in *D. melanogaster* (LINTS and HOSTE 1974, 1976) undergoes the same heritable and cumulative effect of aging as reactivity level. This has been denoted the "LANSING effect" (reviewed in LINTS 1988; FINCH 1990). To date, this puzzling phenomenon has not received satisfactory explanation and is considered a biological oddity. Increasing experimental data support the hypothesis that accumulation of unrepaired DNA damage plays an important role in the aging process (reviewed in BERNSTEIN and BERNSTEIN 1991). Therefore, it is very likely that the heritable aging effects on both reactivity level and life span are two consequences of one and the same biological function. This hypothesis is currently under investigation.

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