SELECTION FOR RADIATION RESISTANCE IN MICE[1]

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IT is known that there are differences in susceptibility to the effects of radiation both between species of animals and between species of plants. It is also known from studies involving several inbred strains of mice that there are differences within species in various aspects of response to radiation (GRAHN 1954, 1958a, 1958b, 1960; GRAHN and HAMILTON 1957; REINHARD, MORAND, GOLTZ and HOFFMAN 1954; KOHN and KALLMAN 1956, 1957; STADLER and GOWEN 1957; LUCHNIK 1959; EHLING 1960; FRÖLÉN, LÜNING and RÖNNBÄCK 1961). The change in any character resulting from a breeding program utilizing selection of individual animals depends in theory on the variance of the character selected and the proportion of that variance which is genetically additive. Because differences between strains in response to radiation are at least partly genetic, we may expect selective breeding for radiation response of individuals of a genetically heterogeneous population to be successful. Selection experiments for high and low resistance to irradiation will be of considerable importance in estimating the extent of genetic adaptation possible in populations exposed to increased background radiation. A study of the differences between the selected lines in characteristics other than the selected variable (i.e., the correlated responses) will likely shed light on the physiology of the natural mechanisms which confer greater radiation resistance or susceptibility, particularly in mammals.

There is evidence that living material may be altered in radiation sensitivity by selection. DITTRICH, HÖHNE and SCHUBERT (1956) produced a radioresistant strain of Ehrlich carcinoma in mice by *in vivo* irradiation of the tumor. Recently studies by WHITFIELD and RIXON (1960) and by RHYNAS and NEWCOMBE (1960) have shown that it is possible to produce resistant strains of mouse fibroblast cultures by irradiating the cultures with X rays. After further doses of radiation, the resistant cultures showed better colony formation, better survival, less depression of initial growth, and quicker resumption of normal growth rate than did nonselected control cultures. In these studies the resistance to irradiation was probably brought about by the selection of preadapted radioresistant cells.

The purpose of the experiment reported in this paper was to determine if the radiation resistance of mice could be changed by selection, and to examine the

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correlated responses which might be found. Selection was successful with a marked correlated response of general fitness.

MATERIALS AND METHODS

The foundation population was obtained from a four-way cross of inbred mouse strains C57BL/6J, BALB/cJ, C3HeB/FeJ, and DBA/2J, followed by three generations of random mating. The random-mated population was sufficiently large that no common ancestors of the foundation population occurred after the matings of the original four strains. Therefore, the inbreeding coefficient of all mice of the foundation population was 0.25. (It did not exceed 0.59 after nine generations of selection under a double first cousin mating scheme.) Inbreeding coefficients were computed by the method of CRUDEN (1949). Two separate selection experiments from the foundation population were performed simultaneously. In one experiment the mice were subjected to daily doses of 100r and in the other to daily doses of 400r. To begin the selection, two large litters from the foundation population were chosen and the mice from one litter mated to those of the other. After offspring were produced and weaned, half of the mated pairs were exposed to daily doses of 100r and the other half to daily doses of 400r. The offspring of the two mated pairs which survived the longest under 100r/day were used for the breeding animals of the next generation in the 100r high line. The same general method was employed for the 100r low line, 400r high line, and 400r low line, with appropriate modifications for the dose rate and the direction of selection. After selection from the foundation population, the four lines (one high and one low under both dose schedules) were selected each in one direction under one dose schedule, and thus remained genetically separated. In each line the mice were mated to produce sufficient offspring for the succeeding generation. Then the sires and dams were irradiated until death, and the length of survival of each midparent for each mating was determined. The parents of the next generation were then selected from the offspring of two mated pairs of the irradiated animals. A double first-cousin mating system was used in each selected line. A diagram of this breeding system appeared elsewhere (RODERICK 1960).

The intervals of time between the generations of the two experiments were permitted to proceed at their respective paces. However, within the experiments, the high and low lines were synchronized in time of mating and in time of irradiation. The control for both experiments was an unsynchronized randomly mated population derived from the same foundation population. The length of survival of the control mice were taken about every other generation. All mice were irradiated between 150 and 250 days of age. Although males and females were irradiated at slightly different times in each generation, there was no bias incorporated in the comparisons of the lines, as all animals of the same sex from both lines were irradiated simultaneously.

The X rays were delivered from a therapy unit operated at 250 kvp, 20 ma with added filtration of 1/2 mm Cu and 1 mm Al. Target-specimen distance was

52.7 cm. Dosimetry was performed with a Victoreen ionization chamber within a masonite phantom with additional phantoms simulating the actual scattering conditions. The mice were confined individually in perforated Lusteroid centrifuge tubes and placed on a rotating table under the target. An average dose of 70r per minute was delivered to the animals under these conditions.

RESULTS

The 100r/day experiment: Figure 1 and Table 1 summarize the results of selection for survival under 100r/day. The high and low lines separated immediately and remained apart throughout the experiment. The differences between the lines in the later generations were roughly eight times the standard errors of the line means. The apparently immediate divergence of the lines with a suggestive plateau of the divergency may indicate that a few major genes are involved in variation of radiation resistance. The data on the control population are not adequate as yet to determine whether the response was asymmetrical. Realized heritability was + 0.26 calculated from the ratio of accumulated generation gains over accumulated within-generation selection differentials. It was + 0.22 when the gain was estimated from the regression of strain divergence on generation. GRAHN's (1958a) estimate of heritability (h^2) of radiation resistance in terms of LD_{50}, using another method, was + 0.58. The h^2 in the

TABLE 1

Results of selection for survival under daily doses of X-irradiation
Number of midparents (N), mean in days ($\bar{x}$), standard error of mean ($s_{\bar{x}}$)

Selected generation		100r/day Experiment				400r/day Experiment			
		N	$\bar{x}$	$s_{\bar{x}}$	High minus Low	N	$\bar{x}$	$s_{\bar{x}}$	High minus low
S_0		6	21.08	0.83		5	8.50	.39	
S_1	High	9	22.72	0.88	+ 1.22	12	9.33	.17	+ 0.78
	Low	9	21.50	1.38		11	8.55	.34	
S_2	High	8	31.75	0.95	+ 9.08	8	10.31	.34	+ 0.92
	Low	6	22.67	1.28		9	9.39	.16	
S_3	High	7	18.86	0.94	+ 4.29	7	7.43	.33	0.00
	Low	7	14.57	0.77		7	7.43	.38	
S_4	High	8	32.50	1.36	+ 9.56	9	6.78	.26	− 1.22
	Low	9	22.94	0.98		6	8.00	.34	
S_5	High	7	33.14	2.19	+11.56	6	9.33	.51	− 0.09
	Low	6	21.58	0.66		6	9.42	.51	
S_6	High	5	26.70	2.62	+ 9.00	9	10.00	.31	+ 1.07
	Low	5	17.70	1.01		7	8.93	.25	
S_7	High	5	30.00	1.59	+11.81	7	9.36	.40	+ 1.36
	Low	8	18.19	0.79		7	8.00	.22	
S_8	High	11	27.27	0.94	+10.35	5	9.30	.44	+ 0.72
	Low	6	16.92	1.18		6	8.58	.33	
S_9	High	.	....	...	....	8	9.19	.28	+ 1.44
	Low	.	....	...	....	4	7.75	.78	

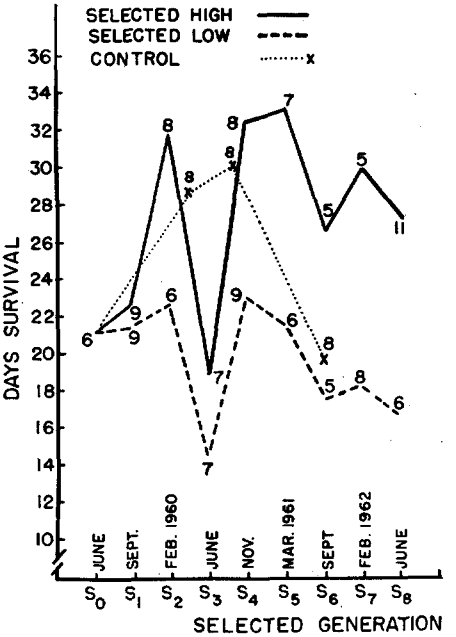

FIGURE 1.—Results of two-way selection for survival under 100r/day.

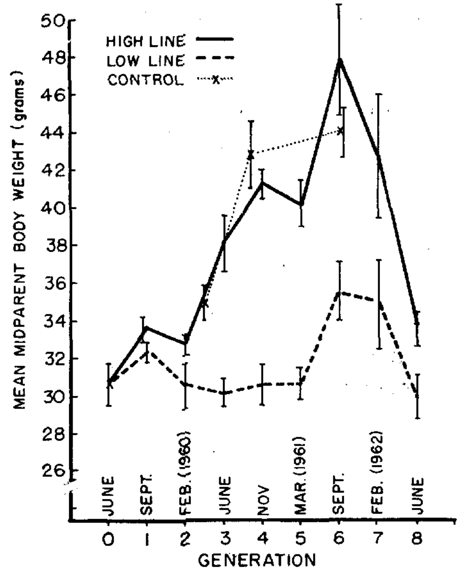

FIGURE 2.—The change in body weight which resulted from selection for survival under 100r/day.

present study (although it would not necessarily be comparable to GRAHN's if the genetics of the two traits are very different) may be underestimated if indeed a plateau had been approached in the early generations. Selection differentials were consistently higher in the high line (2.8 days average in the high line and 2.2 days average in the low line). Both lines showed a pronounced seasonal shift, which was characterized by reduced survival in the warmer months.

In the 122 pairs of animals of the selected lines in the entire experiment, there was no significant sex difference observed. Although a sex difference *was* found in survival when the animals selected for 400r/day were put on a 100r/day schedule (see 400r/day experiment in this paper), the sex difference is likely obscured here for the following reason. When the mated pairs had produced enough offspring for the next generation, the sires were removed while the dams remained in the cages to nurse the litters and to remain at least one week beyond the weaning of the last litter. When the males as a group were at least 150 days old, they began the irradiation regimen together immediately after removal of the last sire from the mating pens. Thus, the females in all generations except the foundation population (S_0) were irradiated at a three- or four-week period after the time of irradiation of the males. Environmental effects between the times of irradiation of sexes may have been great enough to obscure the sex differences.

The sexes of the control and S_0 populations were irradiated simultaneously. If the sexes of the three control populations were randomly paired within generations and sire-dam differences considered for the 30 pairs which include those of S_0, the males exhibited a survival 2.8 days longer than the females ($P < .01$, two-tail *t*-test).

In the 20 groups in which males and females were irradiated (eight generations in the high line, eight in the low, three control, and the S_0), the males had a greater variance of survival in 17 ($P = .004$, two-tail sign test). The individual variances of the 20 groups for each sex were significantly heterogeneous. However, pooling the variances indicated an approximate variance of 22 for the females and 29 for the males.

No significant correlation within mating pairs was found; thus, there is no evidence for a cage effect on radiation resistance resulting from cohabitation during the mating period.

Preliminary results indicated that the $LD_{50/30}$ of the high line is considerably greater than that of the low. Other experiments on these lines (VOGEL, JORDAN, and RODERICK 1962) showed a statistically significant difference between the lines in survival under chronic irradiation with fission neutrons. The high resistant line averaged 26.8 days survival and the low line averaged 21.8 days survival under approximately 40 rads per day with exposure times less than one hour.

Figure 2 shows the concomitant change in body weight resulting from selection for radiation resistance. The within-generation, midparent correlation between radiation resistance and body weight was +.26 for the high line and +.30 for the low line. These correlations were not significantly different from each other. The overall within-generation correlation of +.28 was significant ($.05 > P > .02$, two-tail test). This correlation must be genetic to some extent in order to account for the consistent and large changes in body weight in the selected lines. FALCONER (1960a, p. 315) gave an expression for the phenotypic correlation in terms of the genetic and environmental correlations as follows: $r_P = h_X h_Y r_A + e_X e_Y r_E$, where r_P is the phenotypic correlation, r_A is the genetic correlation, r_E is the environmental correlation, h_X and h_Y are the square roots of the heritabilities of the two variables, and e_X and e_Y are the square roots of the proportions of nonheritable variation of the two variables. In this case X is radiation resistance in terms of days survival and Y is body weight. From a study of 27 inbred strains, no general within-strain correlation was found; thus r_E can be estimated as zero (RODERICK, in preparation). The heritability of six-week body weight in mice was estimated by FALCONER (1953) as +.35, which is in close agreement with heritabilities of body weight found in several other mammalian species. The heritability for radiation resistance as estimated above was +.26, and r_P was +.28. Substituting these estimates into the equation above, r_A is estimated roughly as +.93. Another estimate of r_A can be made from the knowledge of the correlated response of body weight. The genetic regression is $b_{(A)Y.X} = \frac{\Delta_Y}{\Delta_X} = r_A \frac{\sigma_{(A)Y}}{\sigma_{(A)X}} = r_A \frac{h_Y \sigma_{(P)Y}}{h_Y \sigma_{(P)X}}$. In this experiment $\frac{\Delta_Y}{\Delta_X} = \frac{.64}{1.12} = .57$ as estimated from the ratio of the regression of body weight on generation to the regression of radiation resistance on generation. Substituting in the above equation the within-generation standard deviation of the body weight of midparents ($\sigma_{(P)Y} = 3.38$ g.), the within-generation standard deviation of the survival of midparents ($\sigma_{(P)X} = 3.01$ days), and h_Y and h_X as before, r_A becomes $+.44$. Neither estimate of r_A is very reliable, but together they suggest a high genetic correlation between the two variables.

The high line and controls appear to have increased in body weight over the duration of the experiment, whereas the low line appears to have remained approximately the same (Figure 2). The increase in body weight of the controls and high line may have been brought about by a change to a new food with a higher fat content. The change was made between generation S_0 and generation S_1. If the weights of the selected lines are compared with the controls, it is apparent that the low line has declined generally. Preliminary investigations by MISS JANET CRUDEN in our laboratory indicate that the high body weight of the control and high lines is primarily due to excessive fat deposits. Sterility up to 30 percent in a generation has been encountered in the control and high lines; in all cases of sterility observed, the body weight of either the female or male or both was higher than the mean body weight for that generation. Thus it is probable that this sterility was due to, or related to excessive fat.

The upper half of Figure 3 shows the mean litter sizes for each generation of the lines selected for survival under 100r/day. The high line was consistently greater in both first and second litters for the greater part of the experiment. The separation becomes distinct after the third generation of selection. For the entire experiment the matings of the high line averaged 0.5 mice more than first litter than the matings of the low line ($P = .10$, two-tail *t*-test). For second litters the high line averaged 1.1 mice more ($P < .05$, two-tail *t*-test).

The 400r/day experiment: Figure 4 and Table 1 summarize the results of selection for survival under 400r/day. To determine whether selection has been successful in separating the lines, a test of the following nature was made: For each selected generation (S_1 through S_9) a mean was calculated from all the midparent values of both lines. The midparent values which deviated from the mean in the direction of selection (i.e., those which were below the mean in the low selected line and those which were above the mean in the high selected line) were scored plus, and those which deviated in the opposite direction from selection were scored minus. Eighty midparents were plus and 54 were minus, with $.05 > P > .02$. Thus selection was successful in this experiment, although the gain was apparently made in the first two or three generations, after which a plateau was reached. There was a possibility of a line-season interaction as the high line fell below the low line during the very warm summer of 1960. It is apparent that the heritability is very low and significantly less than that for survival under 100r/day.

A sex difference was also found in survival under 400r/day; females survived 0.81 days longer than their mates ($P < .001$). No differences in the degree of sex difference were observed between the high and low lines. No general correlation between mated pairs, and no differences in survival variance between females and males were found.

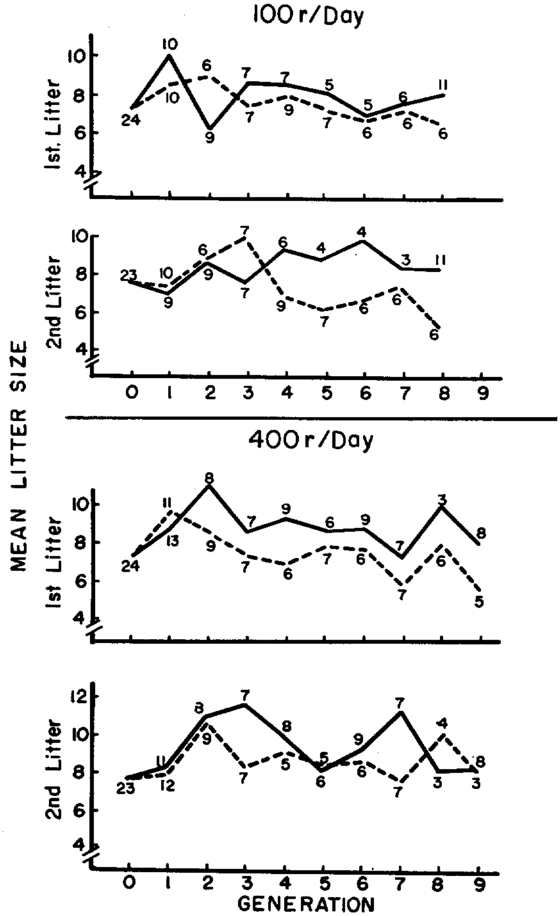

Figure 3.—The change in litter size which resulted from selection for survival under 100r/day and 400r/day.

From the sixth selected generation, 222 extra animals were studied for their survival under 100r/day. Because selection had produced a genetic difference in survival under 400r/day, then depending on the genetic correlation of the resistances under the two dose schedules, a greater difference between the lines might be observed under the lower dose (which exhibited a higher heritability). These animals were drawn from 30 litters (59 females and 85 males from the selected high line, 36 females and 42 males from the low selected line) and began the irradiation schedule at 150 days of age. No differences were found in means or variances between these lines for survival under 100r/day. With the number of mice used and the variation observed, a difference of approximately 2.9 days in the means would be necessary to be significant at the five percent level, one-tail test; the test for a difference is therefore not very sensitive. The low sensitivity of this test is perhaps explained by the high seasonal and weekly variation in survival under irradiation under our conditions; the age variable of the 222

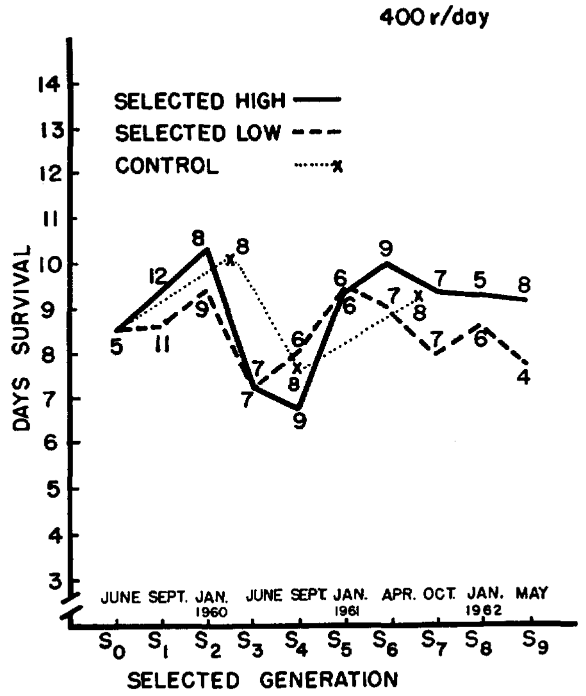

FIGURE 4.—Results of two-way selection for survival under 400r/day.

animals was controlled, and thus very few began the irradiation schedule at the same time.

No association between midparent body weight and midparent survival was found either between or within the selected lines under 400r/day.

The high selected line had a higher mean first litter size in S_2 and continued to exhibit larger litters through S_9, although the difference remained much the same in each generation (Figure 3). The distributions of sizes of litters were nearly normal for both lines. The mean of all first litters over all generations was 8.91 for the selected high line and 7.75 for the selected low, a difference significant at the 0.01 level, two-tail *t*-test. In only two of the nine generations did the low line show a higher mean of second litters than the high line.

DISCUSSION

It was clear from these experiments that a great amount of the environmental variation in survival under chronic irradiation was due to day-to-day effects and particularly seasonal effects. Probably most of this temporal variation is due to the variation of response of the mouse under different conditions of temperature and humidity, and not to variation in experimental techniques. Thus, if sensitive comparisons are to be made between groups of animals, under these conditions, the groups must be irradiated simultaneously, or if that is not possible, it is important to have a block design, with each block comprising comparable numbers of each group. It was impossible to determine whether selection success was asymmetrical in the two experiments, mainly because the control groups were not irradiated simultaneously with the selected lines.

Although selection for survival under 400r/day was barely successful, a significantly higher litter size was found in the selected high line. This difference may have resulted from a chance segregation for litter size genes during the first generation. However, the difference of 1.2 animals per litter seems to be too large to be dependent on chance segregation of genes, particularly since there is evidence that litter size is a multifactorial trait in mice (FALCONER 1960b). The change in litter size in this case is probably a correlated response, as it was also found in selection for survival under 100r/day. It is interesting to note that even though the success of selection might not be statistically ascertained from the difference between the lines for the *selected variable itself*, success of selection might be inferred from a significant difference between the lines in a character which is highly correlated genetically with the selected trait and which has a higher heritability than the selected trait.

The realized heritability is considerably larger for survival under 100r/day than for survival under 400r/day. These results suggest that heritability may be inversely proportional to the degree of chronic stress for irradiation—that is, the greater the stress, the greater is the proportion of environmental variance of the response. The inverse association between heritability (h^2) and degree of stress may be a general phenomenon for selection criteria in which the stress can vary quantitatively. The verification of such a generalization would be important to selection theory, even though it is likely that different organic target systems are involved when different intensities of the stress are employed.

Sex differences in response to irradiation have been reported by many authors for various species. The evidence from this study suggests that there is a sex reversal in resistance from low to high chronic irradiation, with the females being more resistant under 400r/day and the males more resistant under 100r/day. These findings are in close agreement with the findings of SACHER (1960) for similar survival times.

Studies of correlated response: For an understanding of the physiological basis of the differences brought about by selection for a trait, the correlated responses can be very useful. An obvious difference brought about in a quite different organ system as a result of selection for another trait may indicate an important physiological relationship between the organ system and the selected trait—perhaps even a direct effect relationship. Or it could mean a genetic correlation alone, and no direct causative relationship between the organic system and the selected trait.

Body weight was shown in this study to be a high correlated response to selection for survival under irradiation. Several studies on various organisms have shown that heavier animals tend to be more radioresistant (see GRAHN 1954, for review of literature). One suggestion has been made that more weight means more tissue reserve for the organism, permitting longer survival under irradiation when anabolism is practically nonexistent. Figure 5 shows two hypotheses which

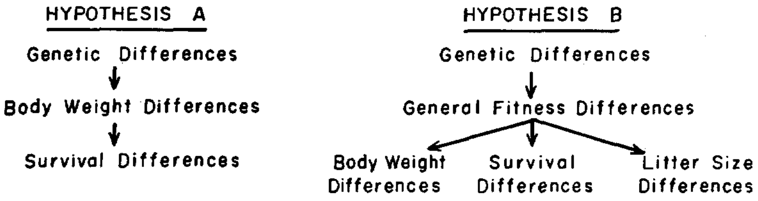

FIGURE 5.—Two hypotheses which might account for the correlated response of body weight to selection for survival under 100r/day.

might account for the association between these body weights and survival under irradiation. Hypothesis A suggests that tissue reserve (or whatever it is that might make heaviness valuable to survival under daily irradiation) has been the primary mechanism upon which the selection has acted to bring about differences in survival. However, the within-generation phenotypic correlation between body weight and survival of +.28 was too low to account for the high correlated response of body weight. The fact that no within strain association exists between the variables suggests that no environmental correlation exists, and thus no survival advantage is conferred on the animal by its being heavier if the genotypes are the same (RODERICK, in preparation). Therefore, to explain the association we prefer Hypothesis B, which is further corroborated by the fact that litter size, another characteristic of fitness, was also a correlated response to selection for survival under daily irradiation. Upon further study it might be shown that some correlated responses may have occurred in certain organs or systems which are not strictly a function of general fitness; such responses may have occurred which are not generally found in fitter organisms but which are peculiarly adaptive to the organism under daily irradiation.

An important question is whether radiation sensitivity is a general phenomenon for various dose schedules and various kinds of irradiation. It is possible that 100r/day brings about death from damage primarily to the hematopoetic system, and 400r/day from damage primarily to the gastro-intestinal tract. If the animals which are more resistant under 100r/day also are more resistant under 400r/day, the implication then is that there is a more general basis for radiation resistance in addition to the resistance of different target systems affected under different doses. From unpublished data there is strong evidence that the $LD_{50/30}$ is indeed higher for the 100r/day high line, and it has been definitely established elsewhere that the high line is also more resistant to repeated doses of fission neutrons (VOGEL, JORDAN, and RODERICK 1962). Therefore it is suggested that at least two basic genetic components to radiation resistance exist: (1) the genes responsible for the resistance of the particular target system involved at any specific dose schedule, and (2) the genes responsible for a general more basic (perhaps cellular) resistance to irradiation, a resistance which would be operative to some extent under all doses and types of irradiation. The more general type of resistance may be equivalent to the general fitness of the organism. In this experiment correlated responses of selection for resistance to 100r/day were body weight and litter size, both of which may be considered as characteristics of fitness within a limited range around their mean. Litter size has been shown in mice to be genetically correlated with life span, another characteristic of fitness (RODERICK and STORER 1961).

The fact that the high line appeared not to deviate in body weight from the controls indicates that selection in the low line was completely responsible for the correlated response in body weight. Such asymmetry of correlated response, or asymmetry in the selected variable itself, suggests that selection in the opposite directions may be acting on somewhat different physiological systems. In this case selection may be decreasing fitness in a population which was operating at a maximum fitness at the start of selection.

SUMMARY

From a four-way cross of inbred strains, two separate selection experiments were performed: (1) two-way selection for survival under 100r/day of X rays and (2) two-way selection for survival under 400r/day of X rays. Selection was successful in both experiments but was much more pronounced under 100r/day. A possible inverse relationship of intensity of stress and heritability is suggested.

Body weight had a low positive phenotypic correlation and a high genetic correlation with survival under 100r/day. Litter size was also a correlated response in both selection experiments. We conclude that body weight is not important *per se* in conferring greater resistance to irradiation but is rather a component of fitness in this genetically heterogeneous stock. Body weight is likely genetically correlated with radiation resistance because they are both components of fitness.

It was not possible to establish whether an asymmetrical response in the selected trait had occurred, but it was apparent that the correlated response in body weight was in the low direction only. Possibly two-way selection has brought about a difference between the lines mainly through selection for a general lowered fitness in the low line alone.

Females were found to be more resistant than males under 400r/day, but the reverse was true under 100r/day.

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