The Possible Influence of a Single Gene Locus on Life Span and Its Relationship to Radiation Resistance and Activity[1] (35434)

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Life expectancy among species varies widely and is obviously a genetically-controlled characteristic. The genetic control of life span among different strains of the same species also varies significantly (1) and is a subject of considerable scientific interest. An early radiation-effects study reported that genetically-controlled life span was shortened by radiation-induced mutations with slight dominant effects (2). The conclusions of this early report have been discredited by substantial conflicting experimental evidence (3, 4), and reduction in life expectancy has since been shown to be a poor indicator of radiation-induced genetic injury (4). The theory that radiation-induced multiple mutations with minor effects accumulate to cause significant decrements to such characteristics as life span, activity, and radiation resistance is consistent with present knowledge of the genetic control of these characteristics. However, if a significant effect on these characteristics can be attributed to a single gene locus, it becomes necessary to take another look at the reliability of these end points as measures of accumulated genetic injury suggested by the multiple minor mutation theory. The results of an investigation on the possible influence of a single gene locus on life span and its relationship to activity and radiation resistance are described below.

Experimental Methods. Two lines of strain RFM mice from the same parent pair were found to have different radiation resistance characteristics (5). Mice in the two lines were serotyped by the hemagglutination method of Gorer and Mikulska (6). Both H-2^k and H-2^f serotypes were segregating in each line, one line being predominantly H-2^k and the other predominantly H-2^f. Two sublines were developed within each of the two lines so that each line had an H-2^k and an H-2^f subline. Radiation resistance characteristics were shown to segregate with the H-2 serotype, with H-2^k mice showing more resistance to protracted gamma-ray exposure than the H-2^f mice (7). Radiation resistance in the two sublines was also consistent with a single gene locus hypothesis (8). These sublines originated from common parents with over 50 generations of inbreeding and were considered to be genetically homogeneous except for the tested difference at the H-2 gene locus. Mice used in this investigation were obtained from the two H-2 sublines of the nonirradiated control line.

Two hundred and fifty-three female mice from strain RFM, subline designated H-2^f, and 199 female mice from strain RFM, subline designated H-2^k, were set up for life-span studies at weaning age (20–22 days). All mice were housed approximately 5/cage in 5 × 8 × 12-in. stainless steel cages. They were provided with fresh bedding (wood shavings) and water weekly and fed Rockland-Teklad rodent food *ad libitum*. The mice were checked daily, and life span was recorded in days.

Results and Discussion. Mean life spans and analysis of life-span data are tabulated in Tables I and II, respectively. The mean life span for the H-2^f subline was 655 ± 8.2 days compared with 604 ± 10.0 days for H-2^k mice. The 51-day difference between the mean life spans of the two RFM sublines was significant at the 0.01 level. Figure 1 shows plots of cumulative deaths vs longevity in days for the two H-2 sublines. The two curves are very similar in shape and slope, indicating that the difference in life span of

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TABLE I. Mean Life Span of H-2^f and H-2^k Sublines from an Inbred Strain of RFM Mice.

Subline	No. of mice	Mean life span ± SE[a] (days)
H-2^f	253	655 ± 8.2
H-2^k	199	604 ± 10.0

[a] SE = standard error.

the two H-2 sublines is not due to an abnormally large cluster of early or late deaths in either group. Since the two sublines of mice are known to differ genetically only at the H-2 gene locus, it follows that a single gene locus may have a significant effect on longevity. Selection at this same H-2 locus was also shown to segregate a significant genetic effect on radiation resistance (7, 8) and voluntary activity (9). The subline segregated out as H-2^k is, by comparison with H-2^f subline mice, radioresistant (7), nonactive (9), and, as shown in this study, shorter lived. This within-strain inverse genetic relationship between survival under continuous exposure and life span does not support Grahn's thesis that mean survival time under continuous gamma-ray exposure varies directly with control survival (10).

These findings provoke some rather interesting questions about the above end points, previously thought to be useful measures of radiation-induced genetic decrement. At this date, none of these end points has been shown to be significantly affected by ancestral irradiation. However, had past experiments, or should future ones, indicate radiation-induced genetic effects on these or similar characteristics, it would not necessarily confirm the accumulated genetic decrement theory because, in view of the above findings, a single gene locus may be responsible. Further, perhaps a significant change in one characteristic should not be considered as a decrement without relating it to other characteristics. For example, if a genetically-induced reduction in radioresistance was considered to be a decrement in the RFM strain studied here, it might be necessary to consider increased activity and longevity as genetic decrements because they appear to be inversely related to radioresistance and, quite possibly, at the same gene locus.

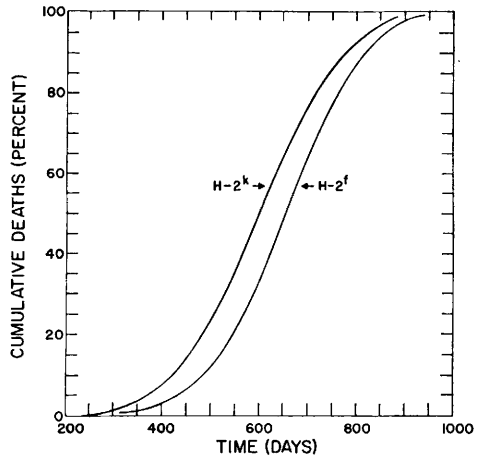

FIG. 1. Cumulative deaths (%) plotted against life span (days) for two H-2 gene locus sublines of strain RFM mice.

The results of this investigation also raise one other point of interest. Storer, in his investigation of longevity and gross pathology in 22 strains of mice, reported 43% leukemia at death in virgin female RF/J mice (1). When serotyped, the RF/J mice tested H-2^k. The H-2^k serotyped mice in the present study were shorter lived than the H-2^f serotyped subline. If the life-span difference could be attributed to a difference in inci-

TABLE II. Variance of Life-Span Data on Two H-2 Sublines from an Inbred Strain of RFM Mice.

Source of variation	Degrees of freedom	Sum of squares	Mean square	*F* ratio
Group	1	287,946.00	287,946.00	15.71712[a]
Individual	450	8,247,013.90	18,326.70	
Total	451	8,534,959.90		

[a] Significant at the 0.01 level.

dence of leukemia, a single gene locus (namely, the H-2 locus) might be responsible for this sensitivity or resistance to leukemia. If this relationship were found to be true, it would suggest an inverse relationship between sensitivity to leukemia and radioresistance (H-2^k being sensitive to leukemia and resistant to radiation), which is contrary to what one might expect. The above conjectures can be tested with additional radiation and life-span studies on the two RFM strain sublines used in the present investigation.

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