

LONG-TERM EFFECTS OF ^{239}Pu INJECTION IN ADULT, WEANLING,
NEWBORN AND FETAL RATS

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We have completed biological evaluations comparing long-term effects in rats exposed to ^{239}Pu citrate as adults, weanlings, newborns, or late fetuses, and statistical analyses have been initiated. In rats exposed postnatally, statistically significant alterations in terminal body weight and in weights of several organs were found at higher doses. Survivorship decreased with increasing dose in the postnatal groups, but not in rats exposed prenatally.

We previously described (Annual Report, 1972) the protocol of a study comparing long-term effects in rats injected with ^{239}Pu citrate as adults, weanlings, neonates, or prenatally via maternal injection. Preliminary assessments of some of the resulting data were presented earlier (Annual Reports, 1973, 1974, 1977). All evaluations, including histopathology, have now been completed and are presently being subjected to detailed statistical analysis. Two factors complicate the statistical analysis: 1) the design of the study led to nonequivalent radiation doses in the different age groups, so that direct comparisons, ignoring differences in dose, are difficult to interpret; 2) survivorship differed among the various exposure groups. In addition to increasing the variability of radiation dose within exposure groups, these survivorship differences suggested the need for adjustments in analyses of organ weight and in lesion comparisons. Since other recently completed ongoing studies have similar problems, a concerted effort is being made to establish appropriate statistical procedures for analysis of this type of data.

Table 3.32 summarizes the survival comparisons. The survival curves are compared, using the chi-square procedure described by Lee and Desu (1972). When a statistically significant difference was found among the four dose levels of a given age group, individual comparisons were made. Within each of the postnatal age groups, survivorship decreased with increasing dose level,

TABLE 3.32. Correlations Between Sex, Dose and Age at Exposure to ^{239}Pu on Longevity.

Variable	Age ^(a)	Sex ^(b)	Survival Rank Order ^(c)			
Dose	A	F	H	M	L	C
		M	H	M	L	C
Dose	W	F	H	M	<u>C</u>	<u>L</u>
		M	H	<u>M</u>	<u>L</u>	<u>C</u>
Dose	B	F	H	M	<u>L</u>	<u>C</u>
		M	H	M	<u>L</u>	<u>C</u>
Dose	P	F	<u>H</u>	<u>C</u>	<u>M</u>	<u>L</u>
		M	<u>H</u>	<u>L</u>	<u>C</u>	<u>M</u>
Age	All Hi Dose Groups	F	<u>A</u>	<u>B</u>	<u>W</u>	<u>P</u>
		M	B	A	W	P

(a) A = adult, W = weanling, B = newborn, P = prenatal (19 dg)

(b) F = female, M = males

(c) Increasing survival, left to right. Similar groups ($P > 0.05$) share common underlining, C = control, L = lowest, M = intermediate, H = highest dose.

although the differences between adjacent groups were not always significant. There was no clear progression with dose in the prenatal group, and most of the differences between groups were not statistically significant. While the radiation doses were not equivalent, a comparison of survivorship for the four age groups at high doses suggests a high incidence of early mortality in the newborn males, as indicated in earlier reports.

As suggested above, analyses of relatively simple measures, such as body weight and organ weight, pose problems when comparisons are made across age and dose groups. In the adult groups, terminal body weight (Figure 3.32) progressively decreased with dose in rats of both sexes, although differences were statistically significant only for the highest dose level. The highest dose level in the neonatal group also significantly depressed final body weight; however, this may be attributable to the shortened life span of this group. Attempts to normalize organ weight on the basis of body weight at death are questionable, since many animals were obese and others were emaciated prior to death. Normalization of organ weights by femur

weight (Figure 3.33) at death is also questionable since femur weight was affected by dose level. Thus, initial comparisons were based on non-normalized values. Because of nonequivalence of radiation doses between age groups, comparisons were restricted to doses administered within age groups. There appear to be clear differences in organ weights; for example, femur weight significantly decreased with dose in the adult groups. Femur weight in female weanling and prenatal groups also was significantly lower at the high dose level. In both males and females exposed at birth, there was a progressive decrease in femur weight with dose, with most treated groups differing significantly from controls. Liver and kidney weights (Figures 3.34 and 3.35), on the other hand, were markedly affected only in the male adult and newborn groups, the other groups being essentially unaffected.

We are investigating the use of other, related statistical procedures, including multivariate analysis and survival analysis with time-dependent covariates. Survival adjustments will form a basis for analysis of the incidences of gross and histopathologic lesions detected in this study.

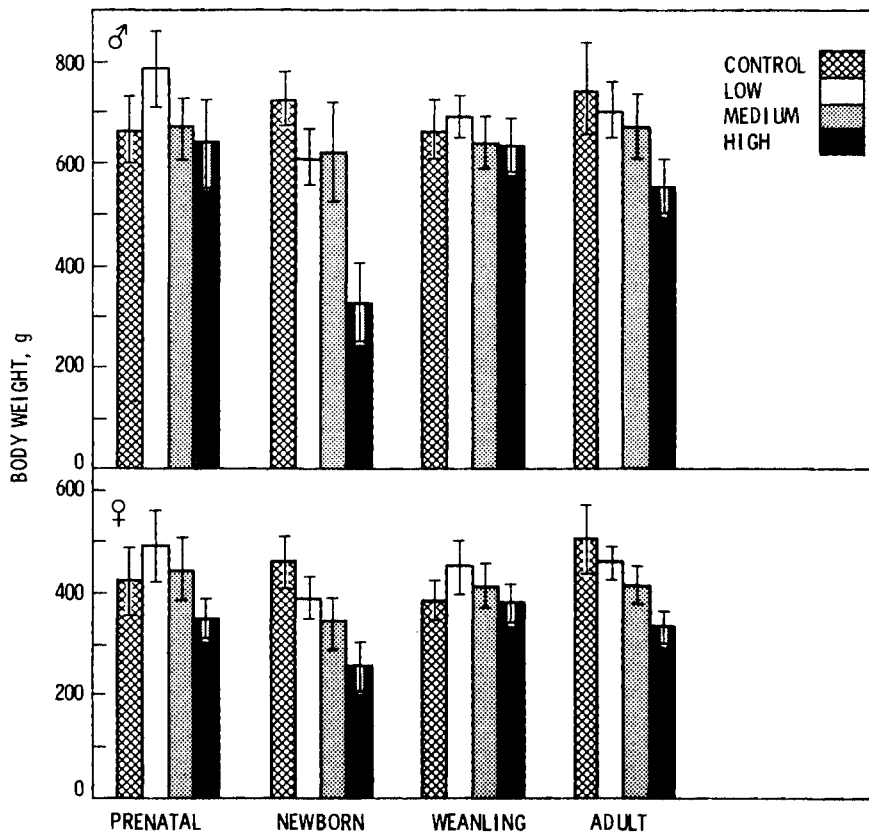


FIGURE 3.32. Effect on Terminal Body Weight of Intravenous Injection of ^{239}Pu of Rats of Various Ages (95% confidence interval shown).

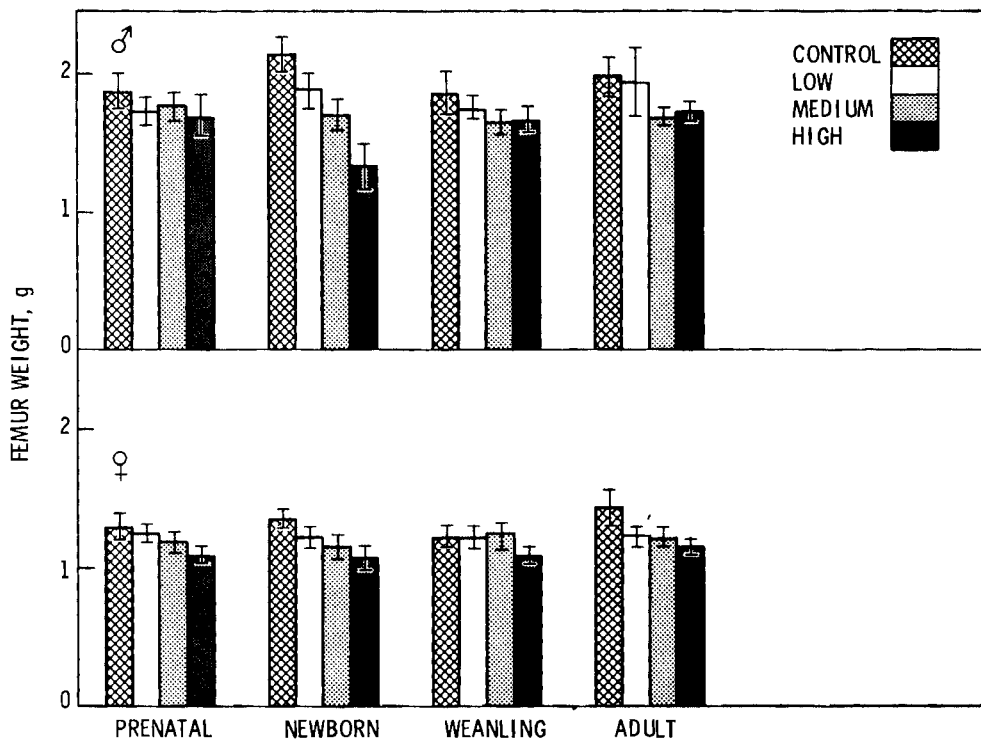


FIGURE 3.33. Effect on Terminal Femur Weight of Intravenous Injection of ^{239}Pu to Rats of Various Ages (95% confidence interval shown).

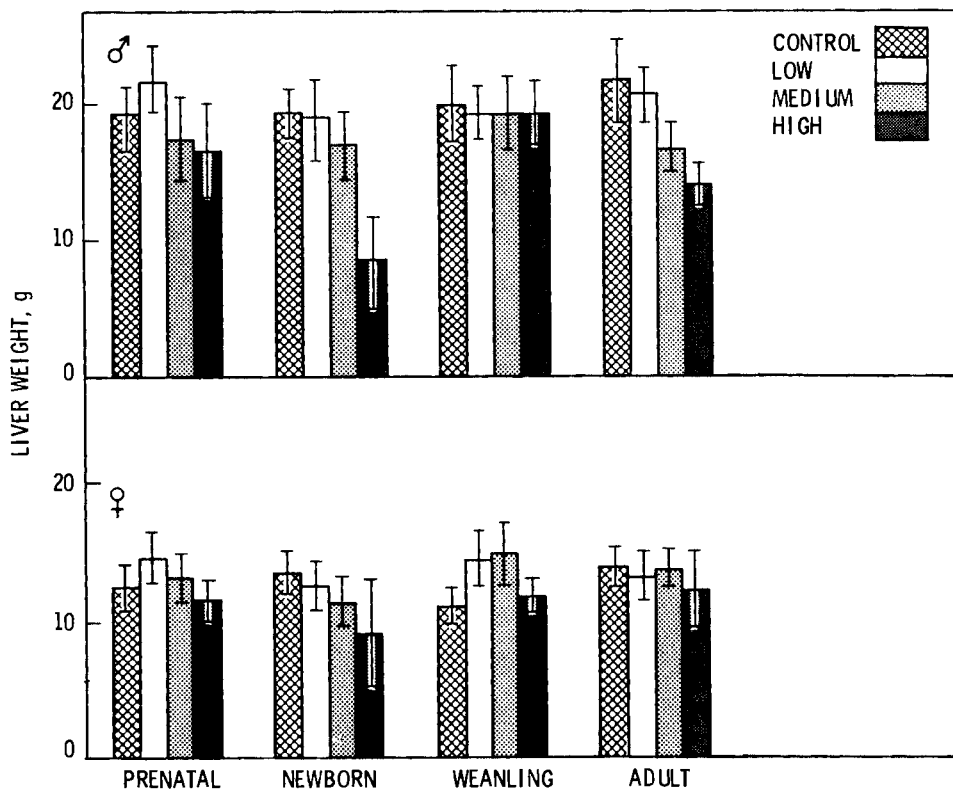


FIGURE 3.34. Effect on Terminal Liver Weight of Intravenous Injection of ^{239}Pu to Rats of Various Ages (95% confidence interval shown).

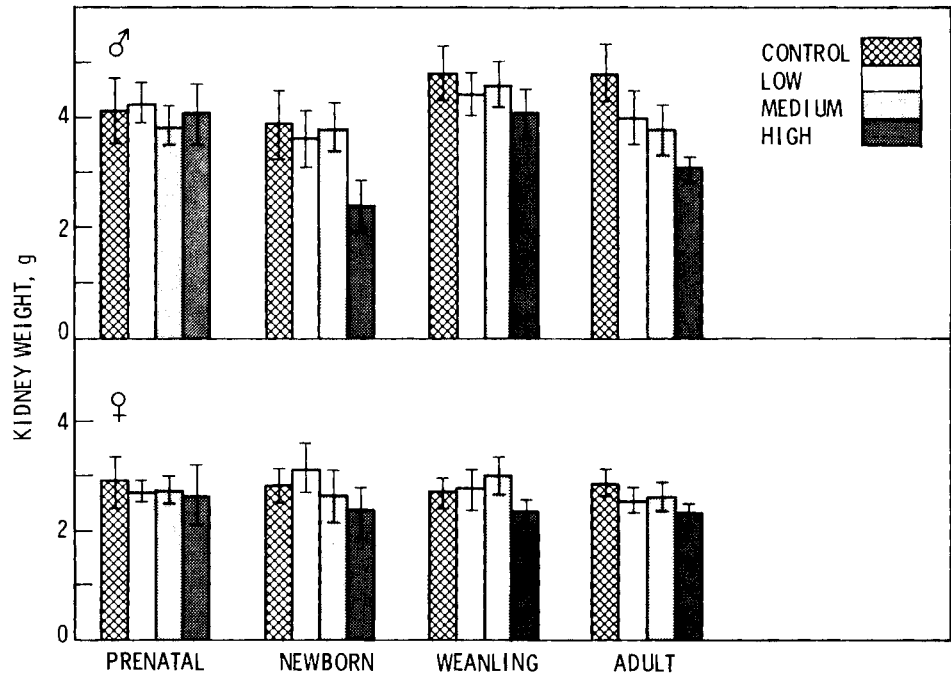


FIGURE 3.35. Effect on Terminal Kidney Weight of Intravenous Injection of ²³⁹Pu to Rats of Various Ages (95% confidence interval shown).