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THE COMPARATIVE RESPONSE OF DOGS AND MONKEYS TO SUBLETHAL
ACUTE AND CONTINUOUS LOW DOSE-RATE GAMMA-RAY EXPOSURE

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ABSTRACT

Monkeys (*Macaca mulatta*) and dogs (beagle) were given thirteen 100-rad gamma-ray doses at 28-day intervals. The comparative response (injury and recovery) of the hematopoietic system of the two species was observed at 7-day intervals during the exposure regime. At 84 days after the thirteenth gamma-ray dose, the 1300-rad conditioned and control dogs and monkeys were challenged continuously with 35 R/day until death to determine the amount of radiation-induced injury remaining in conditioned animals as a reduction in mean survival time. Dogs (50%) and monkeys (8%) died from injury incurred during the conditioning exposures. Thus, the comparative response of dogs and monkeys to dose protraction by acute dose fractionation was similar to what might be expected from a single acute dose. Mean survival times for nonconditioned dogs and monkeys during continuous exposure at 35 R/day were the same (approximately 1400 h). Thus, hematopoietic response of the two species by this method of dose protraction was not significantly different. Mean survival times of conditioned dogs and monkeys during the continuous 35 R/day gamma-ray challenge exposure were greater than for their control counterparts. Thus, the long-term radiation-induced injury was not measurable by this method. Conditioning doses of more than four times the acute LD₅₀₋₃₀ in dogs and approximately two times that of monkeys served only to increase both mean survival time and variance in a gamma-ray stress environment with a dose rate of 35 R/day.

I. INTRODUCTION

Predictions of biological response of humans exposed to ionizing radiations at various doses and dose rates are based primarily on accident report data in which the exposure factors are not well known, and from experimental data obtained from other animal species. The physiological response to radiation exposure differs widely among mammalian species, and these differences are not necessarily consistent within a wide range of dose rates.¹

The lethal dose (LD₅₀₋₃₀) from acute (high dose-rate) whole-body exposure to x or gamma rays in man is estimated to be 400 to 500 rad. This is intermediate to the acute LD₅₀₋₃₀ of the monkey (*Macaca mulatta*) of approximately 600 rad²⁻⁵ and the dog (beagle) of approximately 300 rad.⁶⁻⁸ The ameliorating effects of dose protraction by either the fractionation or continuous low dose-rate

exposure method have been documented for the dog⁹⁻¹² but are not as well known for subhuman primates.¹⁰⁻¹⁴

It is felt that if man's biological response to acute exposure is intermediate to that of the dog and monkey, it is probably intermediate to, or at least within, the response range of these two species over a wide spectrum of dose rates. Thus, comparative studies with dogs and monkeys on exposure effects at sublethal dose rates are needed. This investigation was performed to obtain data essential for reasonable predictions concerning dose-rate effects in man.

II. METHODS

This investigation was performed to obtain data on comparative effects between and within two species, the monkey and the dog. Data were compiled on prompt and long-term injury induced by

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radiation dose protraction, by acute fractionation, and by continuous low dose-rate exposure methods.

Twenty-four animals, 12 male dogs and 12 male monkeys, were given thirteen separate 100-rad gamma-ray exposures spaced at 28-day intervals. Periods of 28 days between exposures were used because this time span is a reasonable estimate of recovery half time for x-ray or gamma-ray radiation injury in dogs, monkeys, and man. These acute conditioning doses were given at a dose rate of approximately 16 R/h. Eighty-four days after the thirteenth 100-rad exposure, these conditioned animals and 12 nonconditioned animals of each species (8 male and 4 female dogs and 12 male monkeys) were placed in a continuous gamma-ray environment at a dose rate of 35 R/day for terminal challenge exposures. The continuous challenge exposures were used to compare the responses of dogs and monkeys to dose protraction and to determine residual injury in conditioned animals expressed as a reduction in mean survival time.

The dose rate for challenge exposures (at 35 R/day) was selected so that the response of non-conditioned dogs could be compared with dog studies being done at the Argonne National Laboratory at the same dose rate⁹ and also with our own conditioned dogs and monkeys and nonconditioned monkeys. Aluminum alloy squeeze-type cages 813 mm in width, 813 mm in depth, and 1067 mm in height were used for restraint of the monkeys, and glass-plastic squeeze-type cages 813 mm in width, 711 mm in depth, and 924 mm in height were used to restrain the dogs during conditioning and challenge exposures. The animals were restrained to one-half the cage depth during the relatively short fractionated conditioning doses and were given the comfort provided by maximum cage dimensions during the continuous challenge exposure. Restraint cages were positioned at 4.56 m for conditioning fractions and 4.8 m for challenge exposures. Dose rates were measured in air at the center of the restraining cage with 0.25-, 1.0-, and 2.5-R high-energy Victoreen chambers. Dose measurements were corrected for pressure and temperature and converted to tissue dose in rad by the conversion factor 1 R = 0.96 rad. The comparative response of hematopoietic tissue of dogs and monkeys to dose protraction by fractionation and continuous

low dose-rate exposure was observed from blood samples obtained by venipuncture. Blood volumes of 2 ml or less were taken prior to and at 7-day intervals during and/or following gamma-ray exposure.

III. RESULTS AND DISCUSSION

The ameliorating effects of dose protraction by the fractionation method used in this investigation were less obvious in dogs than in monkeys. Six of the 12 dogs started on the fractionation exposure regime succumbed to radiation injury from the eighth through the thirteenth 100-rad exposure. One monkey died 18 days after the eighth 100-rad gamma-ray exposure.

Packed cell volumes (PCVs) and leucocyte counts observed in monkeys and dogs 27 days after each of the thirteen acutely delivered conditioning exposures are shown in Figs. 1-4. Dog and monkey PCVs

Fig. 1. Mean packed cell volume (PCV) of dogs 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The numbers indicate the animals included in the means; 12 were started.

Fig. 2. Mean packed cell volume (PCV) of monkeys 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The number indicates the animals included in the means; 12 were started.

Fig. 3. White blood cell (WBC) counts of dogs 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The numbers indicate the animals included in the means; 12 were started.

Fig. 4. White blood cell (WBC) counts of monkeys 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The number indicates the animals included in the means; 12 were started.

remained at about the preexposure level through the seventh exposure (Figs. 1 and 2). Following the seventh exposure, dog PCVs declined steadily to 60 to 70% of the preexposure value after accumulating 1100 rad (Fig. 1). Recovery following conditioning doses in dogs was at about the same rate as the decline, and PCVs reached approximately 85% of the preexposure value 84 days after the thirteenth 100-rad dose. One of the 6 dogs surviving the conditioning exposure kept the PCV mean of the group down with a value of 13. The PCVs of monkeys remained within about 95% of the preexposure value through the eleventh 100-rad dose, then dropped to a low of approximately 85% of the base-line value. Eighty-four days after the thirteenth gamma-ray exposure, the monkey PCVs had returned to about 90% of preexposure values.

White blood cell (WBC) numbers in dogs dropped to about 18% of preexposure values during the fractionation regime. At the end of the 84-day period

allowed for recovery, leucocyte numbers returned to only 24% of preexposure values (Fig. 3). The initial WBC decrease in monkeys was comparable to that of dogs but leveled off at about 40% of the preexposure value and returned to approximately 60% of the base-line value during the 84-day recovery period (Fig. 4).

Differential leucocyte counts were done to observe the comparative response of neutrophils, lymphocytes, and eosinophils from dogs and monkeys exposed under the same conditions. Neutrophil, lymphocyte, and eosinophil values for the dogs and monkeys are plotted in Figs. 5-9.

The neutrophil/lymphocyte (N/L) ratio increased from the preexposure value of approximately 2.0 to approximately 2.75 during the first 5 acute exposures. This N/L increase was followed by a similar decrease, approaching 1.0 during the sixth through the tenth acute exposure. The N/L ratio returned to approximately 1.4 (somewhat less than

Fig. 5. Neutrophils of dogs 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The numbers indicate the animals included in the means.

Fig. 6. Lymphocytes of dogs 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The numbers indicate the animals included in the means.

Fig. 7. Neutrophils of monkeys 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The number indicates the animals included in the means.

Fig. 8. Lymphocytes of monkeys 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The number indicates the animals included in the means.

Fig. 9. Eosinophils of dogs and monkeys 27 days after each of thirteen acute 100-rad gamma-ray exposures and during 84 days of recovery. The numbers indicate the animals included in the means.

the base-line ratio of approximately 2.0) during the 84-day recovery period (Figs. 5 and 6). The N/L response of monkeys was similar to that of dogs following the first 2 exposures but returned

to the base-line value of approximately 1.0 after the third exposure. Unlike dogs, the N/L ratio of monkeys was generally less than 1.0 during the last 10 acute gamma-ray exposures and somewhat higher than the base-line value after the 84-day recovery period (Figs. 7 and 8).

The eosinophil response of the two species to acute gamma-ray fractionation was quite different. The dog, being the more radiosensitive to acute doses of ionizing radiation, showed a steady decrease in eosinophils (to zero in some animals) after the ninth exposure. Following 84 days of recovery, the number of eosinophils remained below the base number of approximately 33% (Fig. 9). In contrast, eosinophil counts in monkeys, the more radioresistant of the two species to acute x- and gamma-ray exposures, increased steadily during the first 6 acute gamma-ray exposures to approximately 280% above the base-line number. Although the number declined from the sixth through the thirteenth exposure, it remained above the preexposure level throughout the exposure series and was a factor of 2.0 above the base-line value 84 days after the thirteenth acute dose (Fig. 9).

An observation of at least academic interest is shown in Fig. 10. An early concept of radiation injury and recovery proposed by Blair^{15,16} and used by the National Committee on Radiation Protection and Measurements¹⁷ to estimate the effects of exposure to radiation in an emergency suggested that radiation injury can be relegated to two components: reparable and irreparable. In man, the recovery half time (RT_{50}) of the reparable component was set at approximately 28 days, and approximately 10% of

Fig. 10. Theoretical equivalent residual dose from thirteen 100-rad exposures separated by 28-day periods for recovery. One monkey and 6 dogs died from radiation injury at the times indicated.

any whole-body exposure was presumed to induce an undefined irreparable lesion which would ultimately be seen as a dose-dependent reduction in normal life span. Earlier work with mice showed this concept to be useful in predicting the consequences of gamma-ray exposure within a limited range of exposure conditions if animal subjects are not prone to some dose- and/or dose-rate-dependent neoplasia.¹⁸

When the two-component concept and the factors $RT_{50} = 28$ days and irreparable lesion = 10% of exposure are applied to the fractionation exposure regime used to provide conditioning doses to dogs and monkeys in this study, the theoretical equivalent residual gamma-ray dose builds up in the manner shown in Fig. 10. The residual dose from 1300 rad delivered in thirteen acute fractions peaked at slightly over 300 rad. This dose is approximately one-half of the LD_{50-30} of the monkey,²⁻⁵ and only 1 of 12 (8%) monkeys died from gamma-ray injury. The LD_{50-30} of the dog (300 rad)⁶⁻⁸ was reached by the equivalent residual dose of 1300 rad delivered in thirteen equally spaced acute doses, and 6 of 12 (50%) dogs succumbed to radiation injury. Without exception, dog and monkey deaths were the result of failure of the hematopoietic system. Under this same radiation exposure regime, we would predict approximately 25% lethality in man with survivors exhibiting few, if any, acute syndrome effects.

Response of the hematopoietic system of conditioned and nonconditioned dogs and monkeys to dose protraction by low dose-rate, continuous gamma-ray exposure (invariant 35 rad/day) is shown in Figs. 11-19. Nonconditioned dogs and monkeys showed similar response patterns for PCVs and WBCs during continuous terminal exposures (Figs. 11, 12, 15, and

Fig. 11. Packed cell volume (PCV) of gamma-ray conditioned (1300 rad) and nonconditioned dogs during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

Fig. 12. Leucocytes of gamma-ray conditioned (1300 rad) and nonconditioned dogs during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

Fig. 13. Neutrophils of gamma-ray conditioned (1300 rad) and nonconditioned dogs during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

Fig. 14. Lymphocytes of gamma-ray conditioned (1300 rad) and nonconditioned dogs during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

16). Dog PCVs were slightly higher than monkey PCVs prior to exposure and started to drop sooner. However, from the twenty-first day on after exposure, PCV response in both species was very similar (see Figs. 11 and 15). Preexposure leucocyte levels were about 60% higher in the monkeys than in the dogs; however, the WBC loss pattern was quite steep from onset of exposure in both species and followed the

Fig. 15. Packed cell volume (PCV) of gamma-ray conditioned (1300 rad) and nonconditioned monkeys during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

Fig. 16. Leucocytes of gamma-ray conditioned (1300 rad) and nonconditioned monkeys during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

same pattern during the course of terminal exposure (Figs. 12 and 16).

Base-line N/L ratios in nonconditioned dogs and monkeys were approximately 2.7 and 1.8, respectively (Figs. 13, 14, 17, and 18). These ratios remained about the same during the first 21 days of exposure in both dogs (Figs. 13 and 14) and monkeys (Figs. 17 and 18). Following 21 days of exposure, dog N/L ratios gradually decreased to

Fig. 17. Neutrophils of gamma-ray conditioned (1300 rad) and nonconditioned monkeys during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

Fig. 18. Lymphocytes of gamma-ray conditioned (1300 rad) and nonconditioned monkeys during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

Fig. 19. Eosinophils of gamma-ray conditioned (1300 rad) and nonconditioned dogs and monkeys during a continuous 35 R/day gamma-ray stress. The numbers indicate the animals in the mean values.

approximately 1.0 at 49 days and were less than 1.0 from the sixtieth day (Figs. 13 and 14). Monkey N/L ratios declined more sharply than dogs and were less than 1.0 from the twenty-eighth day of exposure (Figs. 17 and 18). The majority of deaths occurred after the N/L ratio was less than 1.0 in both species.

Eosinophils in nonconditioned dogs and monkeys exposed continuously at 35 R/day showed similar responses (Fig. 19). This was in contrast to the eosinophil response of the two species to dose protraction by the acute fractionation method (Fig. 9). In this study, eosinophil response early in the two exposure regimes used (Figs. 9 and 10) seemed to forecast the comparative radioresistance of the two species. As stated earlier, the dog is a factor of approximately 2.0 more radiosensitive to single acute doses of ionizing radiation in the LD₅₀₋₃₀ range than the *Macaca mulatta* monkey. Our investigation shows that this difference in sensitivity persists when the dose is protracted by the acute fractionation method but does not hold when the continuous low dose-rate method of dose protraction is used. We have shown in earlier studies¹⁹ that dose protraction by fractionation with relatively low dose-rate fractions (4 R/h) is more biologically damaging than dose protraction by continuous low dose-rate exposures totaling the same dose over the same time period. Thus, as seen here, the comparative response among different species to a specific set of exposure conditions may not be predictive over a wide range of conditions. A species cannot be categorized as radiosensitive or radioresistant without exposure condition qualifications.

The results of this and earlier studies¹¹⁻¹⁴ suggest that dose protraction by low dose-rate invariant exposure brings the radiosensitivity of the blood-forming tissue of the beagle and *Macaca mulatta* monkey (widely different when acute exposures are used) to nearly the same response level at approximately 35 R/day. With lower dose rates, there is evidence¹² that the dog becomes more radioresistant than the monkey. We believe that the response of normal man to whole-body x- or gamma-ray exposure would fall within the response limits of the dog and monkey over a wide range of dose-rate

and total-dose conditions ranging from single acute to very low dose-rate exposures.

Mortality distributions and mean survival times of nonconditioned dogs and monkeys exposed continuously to gamma rays at 35 R/day are shown in Figs. 20 and 21, respectively. Mean survival

Fig. 20. Cumulative plot of mortality data and mean survival time (h) with standard deviation of nonconditioned dogs exposed continuously to gamma rays at 35 R/day.

Fig. 21. Cumulative plot of mortality data and mean survival (h) time with standard deviation of nonconditioned monkeys exposed continuously to gamma rays at 35 R/day.

times and standard deviations for dogs and monkeys were 1387 ± 258 h and 1445 ± 207 h, respectively. Neither mortality slopes nor mean survival times of nonconditioned dogs and monkeys differed significantly. This is in sharp contrast with the approximately 2-fold difference in acute LD₅₀₋₃₀ of these mammalian species. The survival times of non-conditioned dogs at 35 R/day are in good agreement with the work of Norris.⁹ Mortality distributions and mean survival times of dogs and monkeys conditioned with 1300 rad of gamma rays and exposed continuously to gamma rays at 35 R/day are shown in Figs. 22 and 23, respectively. Mean survival times and standard deviations were 3258 ± 1535 h and 1942 ± 644 h for dogs and monkeys, respectively. Mortality curve slopes and mean survival times for conditioned dogs and monkeys (Figs. 22 and 23) were

Fig. 22. Cumulative plot of mortality data and mean survival time (h) with standard deviation of gamma-ray conditioned (1300 rad) dogs exposed continuously to gamma rays at 35 R/day.

Fig. 23. Cumulative plot of mortality data and mean survival time (h) with standard deviation of gamma-ray conditioned (1300 rad) monkeys exposed continuously to gamma rays at 35 R/day.

significantly different, with dogs having a greater mean survival time than monkeys.

The attempt to measure the more persistent radiation-induced injury in dogs and monkeys as a reduction in mean survival time in a continuous gamma-ray stress environment (35 R/day) was not successful because the conditioned dogs and monkeys had significantly greater mean survival times than their control counterparts. Although the reduction in mean survival time method has been used successfully with mice,^{20,21} an earlier attempt to measure the residual injury in dogs and monkeys, conditioned with 660 rad of gamma rays in a 10-day continuous gamma-ray exposure with a gamma-ray stress challenge of 24 R/day, was inconclusive, with the dogs showing residual injury but not the monkeys.¹²

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