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SURVIVAL TIME AND INCAPACITATION IN SUPRALETHALLY IRRADIATED DOGS

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ABSTRACT

Incapacitation and resultant times of death have been studied with dogs following supralethal doses of either ^{60}Co gamma or pulsed TRIGA reactor radiations. The nominal doses delivered were 4500, 9000, 13,500, or 18,000 rad. The exposure rates were 190.25 R/min from the ^{60}Co sources and $3.4 - 11.5 \times 10^7$ rad/min from the TRIGA reactor.

The two lower doses (4500 and 9000 rad) produced gastrointestinal deaths, with survival times ranging from 67 - 97.5 hours. These animals first exhibited signs of incapacitation at 48 - 72 hours.

The two high doses (13,500 and 18,000 rad), on the other hand, produced central nervous system deaths, with survival times of 16 - 90.5 hours. With the exception of one animal, all dogs receiving 18,000 rad died within 29 hours. The dogs exposed to 13,500 rad had a much greater spread in survival times, indicating that doses in this range may cause either a gastrointestinal or central nervous system syndrome in dogs. All dogs in these two dose groups were incapacitated by 100 minutes.

There was no evidence in the dogs of any recovery after the initial signs of incapacitation. The rate and severity of incapacitation was generally

related to dose; the lower doses produced a slower onset and gradual incapacitation, while the higher doses caused a more rapid, severe clinical syndrome.

Of the comparable exposures to either ^{60}Co gamma or pulsed reactor radiations, no differences in clinical response were noted. Thus, in the dog, under these experimental conditions, no differences in clinical response were seen with regard to the type of radiation, and no exposure-rate dependency was observed for either incapacitation or survival times.

SUMMARY

Problem:

Incapacitation following supralethal irradiation, whether measured clinically or as decrement in performance, has been studied primarily in the subhuman primate. By studying these parameters in other species, extrapolation to man may be made more feasible. Knowledge of man's capabilities, whether complex or relatively simple, after large doses of radiation, will be of prime importance in many military and civil defense situations.

Findings:

Dogs were exposed to ^{60}Co gamma or pulsed TRIGA reactor radiations. All doses (4500, 9000, 13,500, or 18,000 rad) were in the supralethal range and caused deaths in both the gastrointestinal and central nervous system syndromes.

Doses of 4500 and 9000 rad caused gastrointestinal death in the dog, with resulting survival times of 67 - 97.5 hours.

13,500 rad is in the dose range in which the dogs exhibit gastrointestinal and central nervous system deaths. Clinical signs and survival times varied according to the death syndrome in which the dogs succumbed. Survival times ranged from 19 - 90.5 hours.

All dogs receiving 18,000 rad exhibited central nervous system syndrome signs and, with one exception, died within 29 hours.

Incapacitation, briefly defined as an inability to maintain normal posture or make purposeful defensive actions, was a permanent phenomenon in the dogs, as once they showed signs of incapacitation, their clinical status progressively degenerated until death.

Time of onset and the rate and degree of incapacitation were dose related. The lower dose dogs remained essentially normal until 48 - 72 hours after exposure. Their capabilities then slowly degenerated until death.

The dogs receiving 18,000 rad were totally incapacitated by 100 minutes, remaining prostrate and in a spasmodic state until death.

The animals exposed to 13,500 rad varied greatly. Although incapacitation was evident by 100 minutes, it was less severe than in the higher dose groups. Their clinical course followed either the gastrointestinal or central nervous system syndromes and their survival times were indicative of the type of death.

Of the comparable exposures to either ^{60}Co gamma or pulsed reactor radiations, no differences in clinical response were noted. Thus, in the dog, under these experimental conditions, no differences in clinical response were seen with regard to the type of radiation, and no exposure-rate dependency was observed for either incapacitation or survival times.

What appeared to be clinical blindness was observed in several of the reactor-irradiated dogs. This is based on the observation that movement of an object to within several millimeters of the animal's eyes elicited no defensive or blinking response.

Thus, both gastrointestinal and central nervous system deaths were seen in dogs following 4500 - 18,000 rad of either ^{60}Co gamma or reactor radiations. Incapacitation became permanent upon onset, as no recovery of function was observed in any of the dogs.

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INTRODUCTION

The dose-survival time curve for the acute radiation syndrome in man as estimated from scattered clinical data and extrapolated from animal experiments contains three "plateaus" (1). These "plateaus" are attributed to three different pathogenetic mechanisms or syndromes; the low-dose region characterized by hematopoietic depression, the mid-dose region characterized by gastrointestinal disturbances, diarrhea, and electrolyte imbalance, and the high-dose region characterized by a "central nervous system syndrome".

This central nervous system syndrome in monkeys was examined in detail by Allen et al. (2). Animals receiving doses of 3000 R exhibited hyperirritability and scratching movements during the first 3 - 4 minutes. At doses above 7000 R this was followed by a period of progressively severe debilitation, nystagmus, ataxic movements, and convulsive seizures. Their animals also showed progressive symptomatology with meningismus and a markedly opisthotonic posture as well as ataxia and tremors, which were difficult to distinguish from convulsions. Shortly before death, the animals lost consciousness, showed opisthotonus, spasmodic gasping respirations, persistent tremors, and convulsive movements. This pattern

was described in all animals in the 9000 - 40,000 R range. Death occurred within the first three days after irradiation.

Histopathological examination showed that animals dying of the central nervous system syndrome had foci of cerebral vasculitis and focal acute meningitis. There was also acute pyknosis of the granular cell layer of the cerebellum and the pituitary basophiles. Also, other systems were obviously involved. Lymphoid tissue, bone marrow, and the spleen were practically devoid of their characteristic cells. In addition, there was degeneration of the parietal cells of the gastric mucosa as well as degeneration of the islet cells of Langerhans.

More recently, attention has been drawn to a fourth radiation syndrome, which is attributed to cardiovascular collapse (3). Karas and Stanbury (4) described cardiovascular collapse in man ensuing as early as four hours after accidental exposure to approximately 8000 rad. Kundel (5) studied the effect of similar dose ranges of radiation on the cardiovascular system of the rhesus monkey and showed progressive hypotension as radiation dosage increased. Because not all experimental animals show such cardiovascular collapse in response to this dose range of radiation, this syndrome has received relatively little attention.

Immediate incapacitation and debilitation following such high doses of radiation is primarily the result of damage to the central nervous system.

The contribution of hypotension and cerebral anoxia to incapacitation has not been clearly defined, although it appears that cardiovascular collapse and secondary hypoxia occur somewhat later and are not major contributory causes of immediate incapacitation (4).

Such incapacitation or debilitation following high doses of radiation was studied in monkeys by Seigneur and Brennan (6). Their data indicated that doses of 25,000 - 80,000 rad produced early transient incapacitation followed by a period of relative recovery of varying lengths in the lower dose ranges. This period of recovery was again followed by a plateau of partial recovery and then a rapid second decline to permanent complete incapacitation.

Such early transient incapacitation followed by a period of variable recovery was found up to doses of 30,000 rad. In addition, they stated, "The relative vigor, agility, and general physiological reserve that some animals demonstrated, even one hour after 50,000 rad of pulsed reactor radiations, were unanticipated."

Because of the high dose necessary to produce complete incapacitation within 30 minutes in their animals, it seemed that further investigation of incapacitation and death times in another species was indicated. We hope that this comparison will help with the difficult problem of extrapolation to man based on the radiation responses of primates and other species. Furthermore, studies at these dose levels may give insight into the response

to the cardiovascular system of the dog to high doses of radiation.

Pursuant to this, dogs have been exposed to 4500 - 18,000 rad of either ^{60}Co gamma or pulsed reactor (gamma ray + neutron) radiation in an effort to determine dose-survival time responses and to determine the extent to which the time to incapacitation and the dose required for incapacitation in the dog compares with the results obtained in the monkey.

MATERIALS AND METHODS

Animals used in the study were female Beagles ranging in age from 6 months - 1 year and weighing 6.26 - 11.5 kilograms. Dogs were preconditioned in laboratory cages for at least 4 weeks to stabilize the leukocyte counts. Animals received no medication from the time of preconditioning to the end of the experiment. Water and feed were provided ad libitum during the preconditioning period. The animals were fasted for 12 hours before irradiation, and following irradiation, food and water were offered at 8 hour intervals.

Details of both ^{60}Co gamma-ray and pulsed reactor exposures and their dosimetry are presented in the appendix. In brief, for ^{60}Co radiation, exposures were performed at the Camp Parks Radiation Range (7). Two ^{60}Co sources were used, and two dogs were exposed simultaneously in

boxes made of 1/2 inch plywood (Figure 1). Sixteen animals were divided into groups of four which received either 4500, 9000, 13,500 or 18,000 R^a. The exposure rate was 190.25 R/min, and exposure times varied from 23 - 95 minutes. All exposures and exposure rates are expressed in R, as measured in air at a point corresponding to the midpoint of the animal volume.

Immediately following exposure the animals were taken out of the exposure boxes and placed in holding cages for observation. Due to the remote operation of the ⁶⁰Co sources and the type of exposure boxes used, direct observation of the animals was not made during actual exposure time.

The exposure room of the University of California, Berkeley, TRIGA reactor was used for pulsed reactor irradiation (Figure 2). The reactor was "pulsed", thereby delivering the desired total dose at rates of 3.4 - 11.5 x 10⁷ rad/min. Animals were restrained by a collar chain to one end of the plywood exposure boxes, which measured 20.3 x 58.4 x 41.9 cm.

^a The ⁶⁰Co study consisted of simultaneous bilateral exposure to ⁶⁰Co gamma rays. Hereafter, these animals will be referred to as gamma-irradiated dogs.

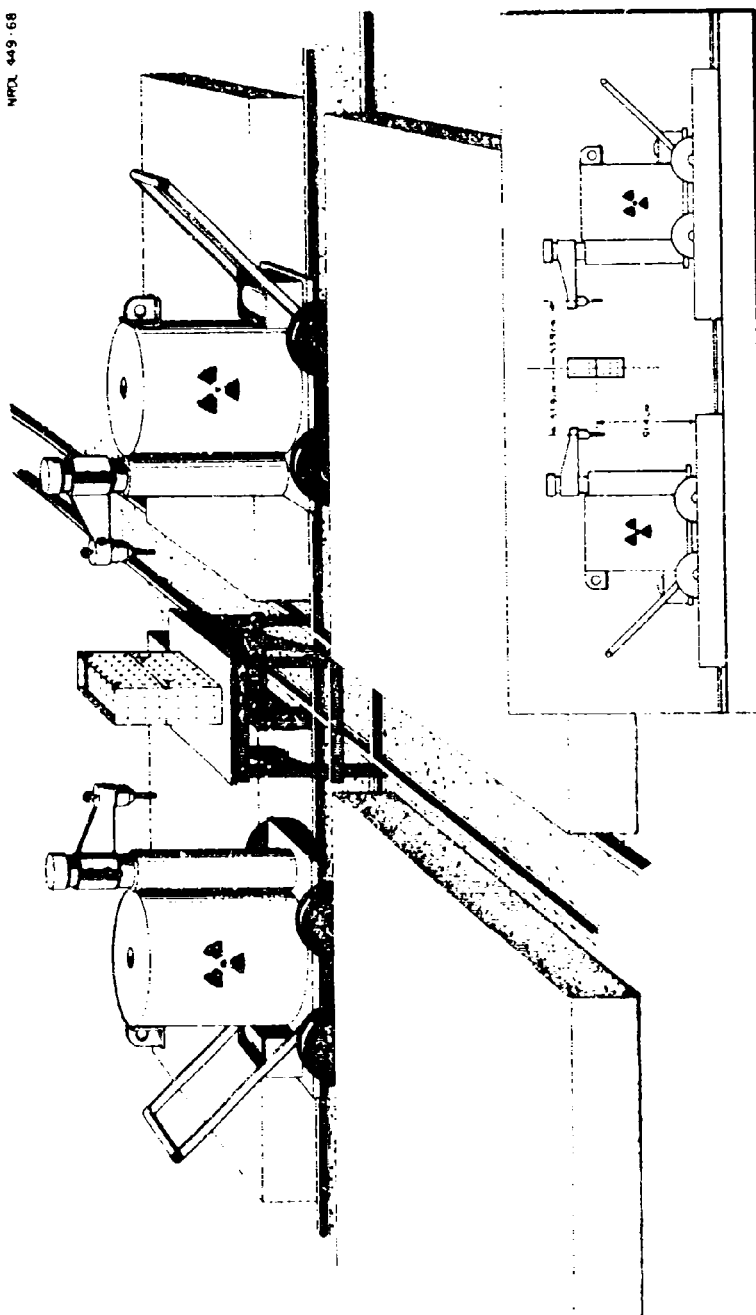


Figure 1. Exposure configuration for ^{60}Co gamma irradiations - 190 R/min.

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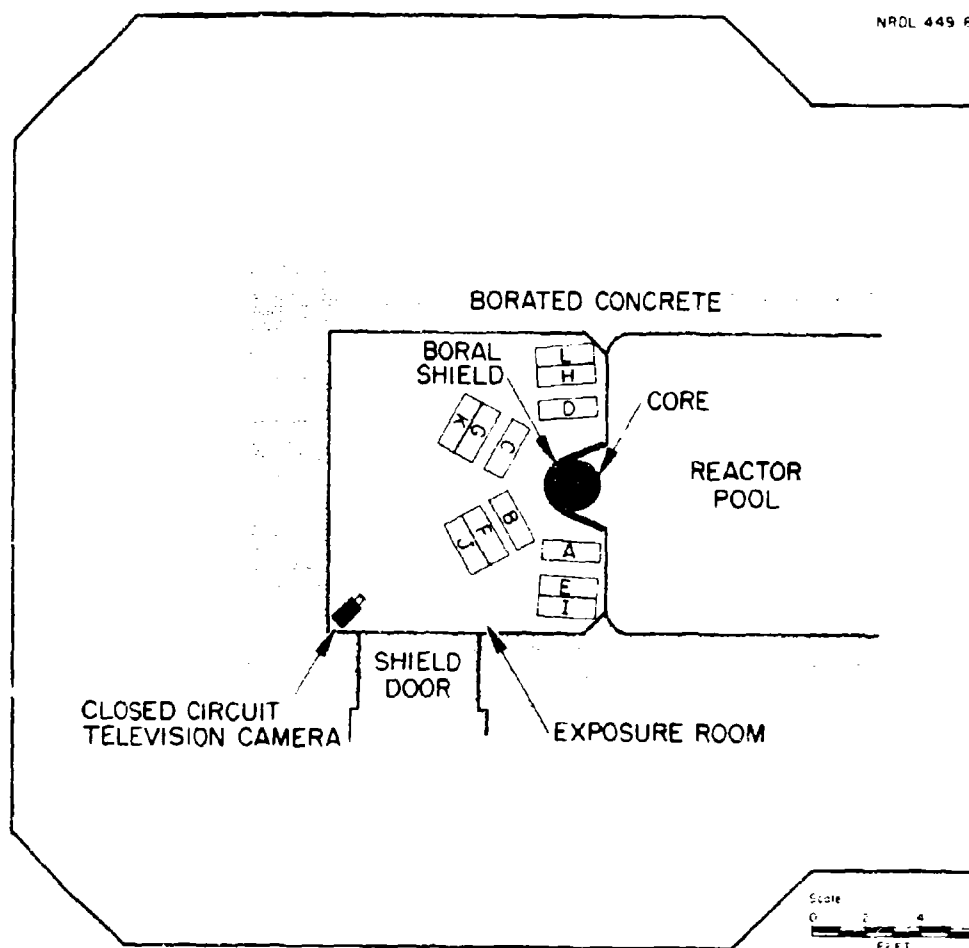


Figure 2. Schematic representation of TRIGA facility. The lettered boxes depict the different exposure positions; see Table VI.

This allowed considerable freedom of movement but did not allow the dog to turn within the closed box. One side of the exposure boxes was spring-hinged and could be released by a remote-switch mechanism. After release of the door catch, the side was allowed to fall open. Observations of the dogs could be made by closed-circuit television within one second after exposure^a.

This method of observation was used during the first 20 - 25 minutes after exposure, and when the radiation level in the exposure room ceased to be a personnel hazard and it was possible to enter the exposure room, the animals were examined, removed, and placed in holding cages for further direct observation and testing.

^a The exposures and exposure rates for the TRIGA reactor experiments are expressed as midline air values, consisting of fission neutron rad and the accompanying gamma component in roentgens (R). For simplicity, the reactor exposures will be referred to in rad, while the ⁶⁰Co exposures will be described in R. When direct comparisons are made between the reactor exposures and the ⁶⁰Co gamma-ray exposures, the symbol rad (R) will be used, to avoid repetition and explicit definition each time a comparison is made.

Sixteen animals were divided into four nominal dose groups of four animals each^a. The first group received 13,500 rad of reactor radiation divided into two pulses of 6500 rad delivered to each side of the animal. The second group received 18,000 rad in one unilateral pulse; the third received 18,000 rad total irradiation divided into two pulses of 9000 rad delivered to each side of the animal (time between pulses was approximately 25 minutes). The fourth group also received a total of 18,000 rad divided into two doses of 9000 rad given to the same side of the animal (time between pulses was approximately 25 minutes). All dogs receiving unilateral exposures were positioned with their right side adjacent to the reactor core.

Animals were observed every 4 - 6 hours from the time of irradiation until death. White blood counts and hematocrits were measured daily as well as before and four hours after irradiation. The clinical status of each animal was evaluated by physical examination as well as by the animal's response to a noxious stimulus. Noxious stimuli used were either a threat or a loud noise. The animal's ability to stand and walk as well

^a The TRIGA reactor study involved placement of the animals, in standing position, on arcs of varied distance from the reactor core. These animals will be referred to as reactor-irradiated dogs.

as maintain a normal sitting position was tested at each examination.

Definition of Incapacitation

Because of the obvious difficulties in establishing exactly when an experimental animal became incapacitated, certain arbitrary standards were used to define incapacitation. Stimuli such as a loud noise or threatening movements were used to establish if an experimental animal was able to respond in a purposeful voluntary fashion. A total inability to respond to a noxious stimulus, either by a purposeful attempt at rising or a purposeful attempt at assuming a defensive posture were taken as an indication of incapacitation. When such incapacitation was present, the dogs showed prostration, generalized neuromuscular irritability with tonic-clonic movements, and occasional spontaneous convulsive seizures. Often ataxia was severe enough so that the animals could no longer maintain a normal or near-normal posture. At this point the animal was no longer able to assume any effective defensive movements and was considered to be incapacitated. Because of the possibility that some animals which were initially incapacitated might possibly show some return of function and some return to a more normal state, the animals were carefully evaluated for signs of decreasing incapacitation.

RESULTS

In general, the results indicate that incapacitation following exposures to either pure gamma or mixed reactor radiation of 13,500 rad (R) or more occurred between 30 and 90 minutes after irradiation. No exposure rate dependency was observed for either incapacitation or survival times. Animals given less than 13,500 rad (R) showed no incapacitation for at least 24 hours. An exposure-survival time relationship was noted, both for ^{60}Co and pulsed TRIGA radiation.

Incapacitation Following ^{60}Co Gamma and Pulsed TRIGA Reactor Irradiation

Data indicating elapsed time from the end of radiation exposure to incapacitation for the four gamma-ray doses are listed in Table I. Comparative data for the two doses delivered from the pulsed TRIGA reactor are listed in Table II; in the groups in which two pulsed irradiations were sustained, the incapacitation times are measured from the second pulse. Dogs which received either 13,500 or 18,000 R of gamma radiation already exhibited nystagmus, tonic-clonic movements, ataxia, incoordination, inability to stand, and vomiting at the end of radiation time. Since the dogs were not observed during exposure to gamma radiation, the exact time of onset of their clinical symptoms is not known.

TABLE I
Incapacitation and Mortality Following ^{60}Co Gamma Irradiation

Exposure Rate 190.25 R/Min

Dose (R)	Dog Number	Incapacitation	Death
18,000	1	< 95 min*	19 hr
	2	< 95 min*	19 hr
	3	< 95 min*	21 hr
	4	< 95 min*	25 hr
13,500	1	< 30 min*	19 hr
	2	< 30 min*	67 hr
	3	30 min	90.5 hr
	4	30 min	39 hr
9000	1	65 hr	67 hr
	2	24 hr	67 hr
	3	69 hr	76 hr
	4	69 hr	92 hr
4500	1	72 hr	97.5 hr
	2	72 hr	92 hr
	3	70 hr	77 hr
	4	77 hr	93 hr

*These figures represent the end of exposure times. When first observed after exposure, these dogs already were incapacitated.

These signs were most severe in dogs which had received 18,000 R. All animals which had received this high dose were totally incapacitated at the end of the exposure. In contrast, of the four dogs which received 13,500 R, two were transiently able to stand unaided at the end of the exposure, although they stood with difficulty and swayed from side to side. Any rapid, aggressive stimulus resulted in a generalized tonic rigidity with spasms in all dogs which received 13,500 R or more.

There was no evidence of recovery of function between the end of the exposures and death. All dogs receiving either 13,500 or 18,000 R never regained the ability to sit or stand. All showed continued spastic rigidity of the limbs, truncal ataxia, and occasional, spontaneous tonic-clonic movements. Any noxious stimuli, such as prodding or loud noises, resulted in generalized tonic-clonic movements and an abortive effort to assume a sitting position. One to two hours before death, the dogs became totally unresponsive.

There was a dramatic difference in dogs given 9000 R. At the end of the exposure to gamma radiation (a total of 45.6 minutes) the dogs were able to walk and stand with no difficulty. They appeared alert and were able to respond appropriately to noxious stimuli by moving away. This normal response continued until 48 hours after irradiation. Between 48 and 72 hours, all dogs became prostrate and two showed truncal ataxia. They remained in this state until death.

Similarly, dogs receiving 4500 R were alert, able to walk, and were well coordinated immediately following irradiation. They remained in a stable clinical condition until 48 hours, when one of the dogs in this group was found prostrate and responded to noxious stimuli only by turning its head. The remaining three animals in this group continued to be alert and active at this time. At 72 hours a second dog in this group demonstrated similar unresponsiveness to stimuli. The remaining two showed slight ataxia and difficulty in walking, but were up and alert. Between 72 and 96 hours, however, these latter two dogs showed increasing ataxia and difficulty in walking. Finally, they became prostrate and showed no evidence of recovery until the time of death.

In the experiments with pulsed reactor radiation, closed-circuit television was used to observe the dogs immediately after the exposure. Times of incapacitation are listed in Table II. The length of time needed to develop incoordination, ataxia, inability to stand, and tonic-clonic movements was similar for all dogs which received either 13,500 or 18,000 rad (dose rate approximately 10^7 rad/min). Between 60 and 100 minutes following exposure, all dogs in these groups showed incapacitation with the symptoms mentioned above. At no time before death was there any evidence of recovery in these animals.

TABLE II

Incapacitation and Mortality Following TRIGA Reactor Irradiations

Exposure Rate $3.4-11.5 \times 10^7$ rad/min.

<u>Dose</u>	<u>Dog Number</u>	<u>Incapacitation</u>	<u>Death</u>
<u>18,000 rad</u>			
Unilateral	1	30-60 min	24-27 hr
1 pulse	2	30-60 min	18-21 hr
	3	30-60 min	15-18 hr
	4	30-60 min	27-29 hr
Unilateral	5	40-80 min	25-27 hr
2 pulses	6	40-80 min	25-27 hr
9000 rad ea.	7	40-80 min	13-16 hr
	8	40-80 min	16-19 hr
Bilateral	9	40-100 min	20-21 hr
2 pulses	10	40-100 min	24-26 hr
9000 rad ea.	11	40-100 min	58-66 hr
	12	40-100 min	15-18 hr
<u>13,500 rad</u>			
Bilateral	13	40-80 min	27-31 hr
2 pulses	14	40-80 min	26-27 hr
6750 rad ea.	15	40-80 min	50-53 hr
	16	40-80 min	74-77 hr

Survival Times After ^{60}Co Gamma and Pulsed TRIGA Reactor Radiation

Data indicating elapsed time from the end of radiation exposure to death for the four gamma-radiation groups are listed in Table I. Comparative data for dogs exposed to pulsed reactor radiation doses of 13,500 and 18,000 rad are listed in Table II.

Dogs that received a total of 13,500 R of gamma radiation exhibited survival times after irradiation of 19 - 90.5 hours. Dogs which received the same total dose of reactor radiation showed quite comparable survival times of 27 - 77 hours. Similarly, dogs which received a total of 18,000 R of gamma radiation survived 19 - 25 hours; dogs which received a similar dose of reactor radiation showed survival times of 16 - 29 hours, with the exception of one animal which survived 66 hours after exposure. Thus, for a given dose, the range of survival times following irradiation at the two different exposure rates were very similar.

The question then arises as to what relationship exists between survival time and the exposure level. The exposure-survival time relationships for each animal are shown in Figure 3. Regression lines have been fitted to these groups as follows: the two lower ^{60}Co gamma-ray exposures (4500 and 9000 R); the two higher ^{60}Co gamma-ray exposures (13,500 and 18,000 R), and the two reactor exposures (13,500 and 18,000 rad). The data was divided in this manner that a more meaningful comparison

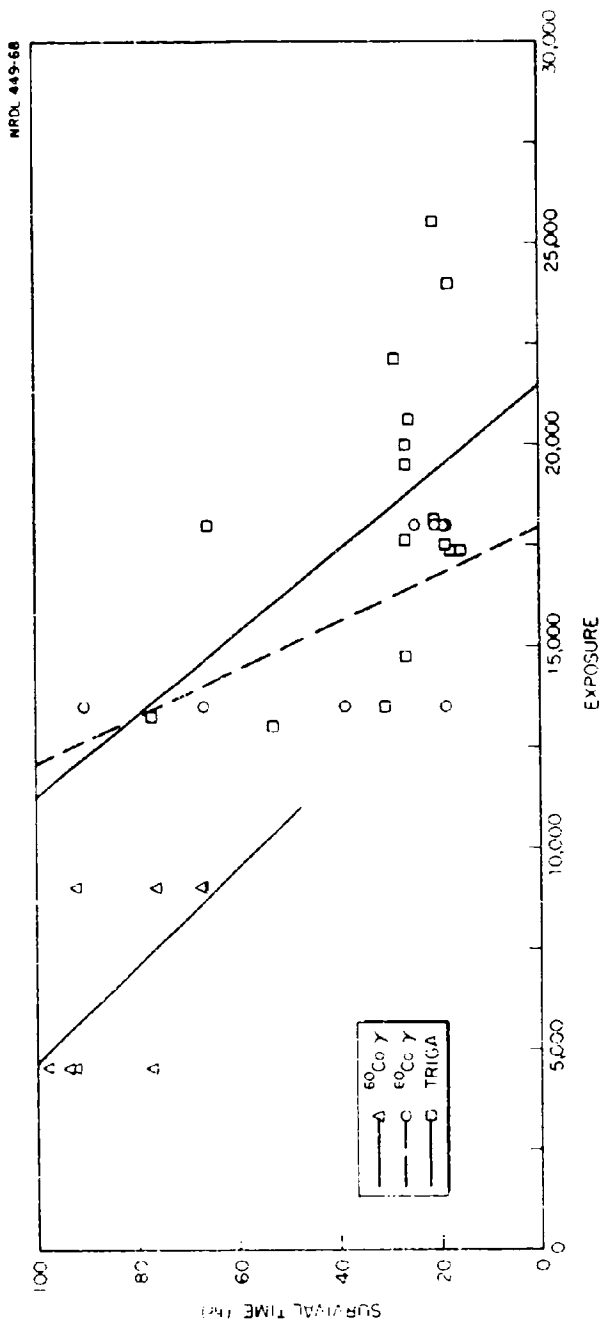


Figure 3. The relationships between exposure (R or rad) and survival time. The three lines were computed by least squares regression analysis. The data have been grouped as follows: 1) 4500 and 9000 R, ^{60}Co gamma rays; 2) 13,500 and 18,000 R, ^{60}Co gamma rays; 3) 13,500 and 18,000 rad reactor radiations.

could be made between the ^{60}Co and reactor studies, as only the two higher exposures were common to both groups. Due to the wide spread in the survival times and the small number of points within each group, none of the regression lines are significantly different from zero.

The survival times can be divided into two distinct groups: (1) survival times of dogs dying within 50 hours after irradiation, and (2) survival times of dogs dying more than 50 hours after irradiation. For this evaluation of the data, the animals are pooled by time of death only, whether exposed to ^{60}Co gamma or reactor radiation. Such a subdivision arbitrarily divides those dogs which died exhibiting a central nervous system syndrome (less than 50 hours from irradiation to death) and those dogs which died exhibiting a gastrointestinal-type of syndrome. The latter is defined as consisting of nausea, vomiting, loss of appetite, and diarrhea (occasionally bloody), resulting in dehydration and death in from 50 - 97.5 hours. Such a subdivision of data enables a breakdown of the curves in Figure 3 into two separate curves, both computed by least-squares regression. These regressions are shown in Figure 4. The upper line represents the regression for all dogs dying of the so-called gastrointestinal syndrome, while the lower line represents the regression for all dogs dying of the central nervous system syndrome. Such a division seems to be a more valid method of treating the survival data, since the mode of death of the two groups of dogs

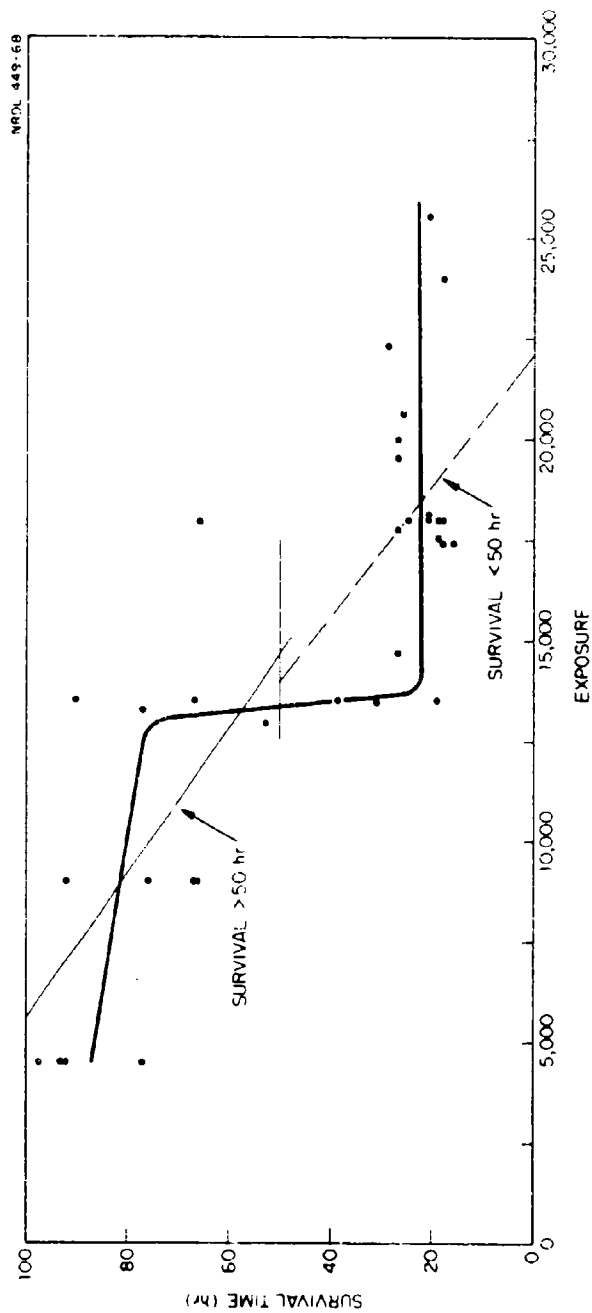


Figure 4. The relationships between exposure (R or rad) and survival times less than or greater than 50 hours. The points represent all dogs, exposed to either ^{60}Co gamma or reactor radiation. The two lighter lines were fitted by least squares regression analysis, and the heavy line is a subjective eye-fitted curve through all the data points. The 50 hour survival time arbitrarily separates the central nervous system and gastrointestinal syndromes.

is entirely different. A dose of 13,500 rad (R) appears to be the threshold above which the central nervous system syndrome predominates and below which the gastrointestinal syndrome is operative. Of eight dogs receiving 13,500 rad (R), five died before 50 hours and three died at later times. The heavy curve is a subjective eye-fitted curve through all the data points. The data seem to indicate a slight reduction in the survival time as the exposure increases from 4500 - 9000 R. Then at 13,500 rad (R), there is a transitional stage, characterized by an extreme spread in the survival times. These very variable dose responses were manifested as either a typical central nervous system involvement or a syndrome with a gastrointestinal-central nervous system combination. At the highest doses, the relationship seems linear, as the survival times appear not to decrease any further with increasing exposure. At this point, all animals exhibited a clear central nervous system involvement, with the most severe incapacitation of all dogs under study.

Hematology and Clinical Observations

White blood counts were performed on all dogs at various times after either gamma irradiation or pulsed reactor irradiation. The data are listed in Tables III and IV. The severe leukopenia that occurred between 48 and 72 hours after exposure in the gamma-irradiated dogs given lower radiation doses was not seen in the reactor group, because all of the dogs in this

TABLE III
Hematological Changes Following TRIGA Reactor Irradiation

	<u>LEUKOCYTES</u>			<u>HEMATOCRIT</u>		
Dog	<u>HOURS AFTER EXPOSURE</u>					
Number	Pre-	4	24	Pre	4	24
<u>18,000 rad</u>						
1	7655	13592	-	45	53.5	-
2	8588	13975	-	48	50.5	-
3	8785	16056	-	43	46	-
4	9772	11718	-	42	41.5	-
5	13142	21818	-	45	47.5	-
6	6380	13506	-	41	46.5	-
7	8391	14693	-	46	50.5	-
8	7986	13241	-	48	52.5	-
9	4187	11253	-	45	49.5	-
10	10362	18702	-	38	47	-
11	6524	11976	6431	42	46	53
12	9173	20647	-	44	50	-
<u>13,500 rad</u>						
13	9006	15038	8808	46	49	59
14	8096	12489	9196	41	46	65
15	7498	12608	14754	43	45	53
16	9012	21911	11003	46	53.5	53

TABLE IV

Hematological Changes Following ^{60}Co Gamma Irradiation

Dog Number	<u>LEUKOCYTES</u>					<u>HOURS AFTER EXPOSURE</u>					<u>HEMATOCRIT</u>		
	Pre	7	20	44	68	Pre	7	20	44	68			
<u>4500 R</u>													
1	10397	17794	13157	9869	323	-	56	44	52	59			
2	12255	10489	7440	7037	297	-	50	-	43	49			
<u>9000 R</u>													
3	10555	7642	7542	1774	-	-	55	48	50	50			
4	7049	10491	8917	3985	-	-	52	44	44	56			
<u>12,500 R</u>													
5	11669	12834	14786	5107	-	-	49	55	53	54			
6	10367	16756	15316	-	-	-	57	58	-	-			
<u>12,000 R</u>													
7	11211	15292	12621	-	-	-	57	66	-	-			
8	7038	12430	11985	-	-	-	52	57	-	-			

group were either dead or moribund by 24 - 26 hours after exposure. In general, white blood cell counts and blood differential data were relatively noncontributory and little new information could be gained from them. As expected, white counts rose briefly and then fell sharply as granulocytopenia and lymphopenia set in following irradiation.

Hematocrits of the same dogs are also listed in Table III. The clinical impressions of dehydration seen in all of the dogs following exposure is corroborated by the progressive rise in hematocrits. Further corroboration is found in the dog weights (Table V). All dogs in the TRIGA group were weighed before exposure and after death. The loss of weight experienced by all dogs reflects their severe dehydration. This is due presumably to their lack of voluntary fluid intake. Of interest is the fact that the hematocrits of these dogs rose approximately 10% within four hours after irradiation. Because of the rapidity of this response, it can probably be best explained by intravascular-extravascular fluid shifts, rather than to pure dehydration (8).

During the general clinical examinations of the reactor-irradiated dogs, it was noted that several of the dogs had apparently developed blindness. This was manifested by the lack of a withdrawal or blinking response when an object was moved to within several millimeters of the cornea. This lack of response followed either slow or rapid movements towards the eye.

TABLE V

Body Weight Changes Following TRIGA Reactor Irradiation

Dog Number	Weights (Kg)		Difference	Death Times (Hrs)
	Pre- Exposure	Death		
1	8.5	7.1	-1.4	24-27
2	9.5	8.1	-1.4	18-21
3	10.0	7.9	-2.1	15-18
4	9.5	7.5	-2.0	27-29
5	10.5	8.3	-2.2	25-27
6	10.5	8.1	-2.4	25-27
7	9.0	7.2	-1.8	13-16
8	7.5	6.7	-0.8	16-19
9	6.3	5.0	-1.3	20-21
10	10.0	7.6	-2.4	24-26
11	8.0	7.0	-1.0	58-66
12	11.0	9.5	-1.5	15-18
13	9.5	7.8	-1.7	27-31
14	7.5	5.3	-2.2	26-27
15	7.8	6.6	-1.2	50-53
16	11.5	9.1	-2.4	74-77

This was noticed as early as 3.75 hours after exposure in one animal and out to 24 - 48 hours in several others.

Heart rates, breathing rates, and temperatures were recorded for the dogs receiving gamma radiation, but no significant correlations could be established between these measurements and time after exposure or the dose received. Survival times or changes in clinical status could not be correlated with or predicted by any of these parameters.

DISCUSSION

The present experiments were designed to evaluate (1) the exposure-survival time responses, and (2) the extent of incapacitation in dogs exposed to supralethal doses of ^{60}Co gamma radiation or pulsed reactor radiation from a TRIGA reactor. No exposure-rate effect was observed since the times to incapacitation and death were quite similar in dogs exposed to gamma radiation at 190.25 R/min and in dogs exposed to pulsed reactor radiations at $3.4 - 11.5 \times 10^7$ rad/min.

Other exposure rate comparisons, although involving the hematopoietic syndrome, have been done in mice and dogs. Ainsworth et al. (9, 10) found no dose rate dependence for lethality in mice or dogs exposed to fission neutrons at either 40 or $0.37 - 1.27 \times 10^6$ rad/min. They also compared

reactor-gamma radiation ($\gamma/n = 49:1$) at either 100 or $0.9 - 4.0 \times 10^6$ rad/min, and found the resulting lethality in mice to be independent of exposure rate. Spalding et al. (11) also showed the $LD_{50/30}$ for mice to be independent of exposure rate, when exposed at 10 or 2×10^8 rad/min, using the LASL Godiva critical assembly. The results of this current study, designed to compare clinical responses from two different radiation sources at exposure rates differing by a factor of approximately 10^5 rad/min, did not indicate any major differences in response, and, therefore, the data will be considered together.

The survival times over the dose range of 4500 - 18,000 rad (R) fell into two distinct categories. Doses below 13,500 rad (R) produced the so-called gastrointestinal-type syndrome with nausea, vomiting, progressive dehydration, coma, and death; whereas, doses higher than 13,500 rad (R) produce a clear-cut central nervous system-type syndrome with nystagmus, ataxia, convulsions, coma, tonic-clonic movements, and death. The time course as well as the clinical picture of these two syndromes is entirely different. The results obtained at 13,500 rad (R) were of particular interest in that the dogs which received this dose exhibited a classic central nervous system syndrome initially. However, while the earlier deaths were typical of the central nervous system syndrome, the three later deaths appeared to be caused by a combination of the central nervous system

involvement with dehydration and gastrointestinal-type signs. Of the eight dogs having received a total of 13,500 rad (R), five died before the arbitrary cutoff time of 50 hours, which, in these studies, would indicate a central nervous system-type syndrome, and three died at later times, which would indicate exitus via the gastrointestinal-type syndrome. Thus, a dose of 13,500 rad (R) might be considered the minimum dose at which the central nervous system syndrome is seen in a reasonable number of dogs. This is a lower value than other numbers established with monkeys, for a dose of 20,000 rad was needed to produce 50% deaths of monkeys in less than 50 hours following irradiation. The certainty of this lower threshold for the central nervous system syndrome in dogs cannot be established clearly from these data, since the number of animals is small and more experiments are needed to clearly establish this difference.

The incapacitation in the dogs following both gamma and reactor radiations was quite striking. Despite the fact that in these experiments no animals were immediately incapacitated, it is quite apparent that from 40 - 60 minutes after the end of the exposure, all animals having received more than 13,500 rad (R) and some animals that received 13,500 rad (R) total were totally incapacitated. At this point they all exhibited significant ataxia, seizures, tonic-clonic movements, and inability to stand and were obviously incapable of maintaining a defensive posture or reacting in

a purposeful manner to any noxious stimulus. The blindness that was noted in several of the reactor-irradiated animals was an unexpected phenomenon. Although specific tests for blindness were not carried out on all the dogs, nystagmus was noted in the majority of the animals, regardless of the dose received. This blindness was not noticed in the gamma-irradiated dogs, although specific testing for blindness was not carried out with these animals. Thus, whether this phenomenon is an exposure rate or radiation-type related syndrome, can only be borne out by further study. It is important to note that none of the animals which were incapacitated after one hour showed any tendency to regression of the symptoms or a so-called "return of function". The early transient incapacitation found in monkeys was not found in the dogs in these experiments. Throughout the experiment it was apparent that the dogs were severely incapacitated and were totally unable to move. Because of this, it seems likely that even a relatively small improvement in condition which might have been detected by sophisticated testing would have made little overall difference in their ability to respond to noxious stimuli or in their ability to move purposefully, i.e., in evaluating the degree of incapacitation. In addition, no dogs that had received the highest dose range, i.e., 18,000 rad (R), were invulnerable to the complete incapacitation which occurred at 40 - 60 minutes following irradiation. Despite the fact that dogs given less than 13,500 rad (R)

appeared clinically normal, a more sophisticated testing of these animals might have shown a decrement in ability to perform complicated functions. Our data indicate that on a gross clinical basis, these dogs appeared entirely normal and showed no incapacitation or tendency toward incapacitation.

It can be concluded that dogs may have a lower threshold than monkeys for the appearance of the central nervous system syndrome, but this point is equivocal; however, the clear distinction between the responses of these species is that the dogs did not show any tendency toward recovery, nor any exposure-rate dependence for the parameters measured in this study.

DOSIMETRY APPENDIX

⁶⁰Co Gamma Irradiations:

For gamma irradiation, two dog restraint boxes were placed on top of one another and positioned midway between two 1260 Curie ⁶⁰Co sources (Figure 1). The vertical positioning was such that the horizontal plane between the two exposure boxes was equal in height to the center of each ⁶⁰Co source when in the raised position. Each source was positioned 53.9 cm from the center point of the exposure boxes.

The exposure boxes, made of 1/2 " plywood with ventilation holes were 63.5 x 22.9 x 31.8 cm; the dogs were held in kneeling sternal recumbency.

Gamma-ray dosimetry to determine exposure rate and exposure geometry was accomplished using lithium-fluoride (TLD-100)^a passive dosimeters (14). The lithium-fluoride dosimeters were placed, in air, in each box at three locations; one at center midline and one at each end to simulate the positions of the head, diaphragm, and pelvis (Figure 1). One additional dosimeter was placed between the two boxes; the position was at the midpoint on the horizontal plane between the two ⁶⁰Co sources. The dosimeters consisted of 40 mg of lithium-fluoride powder hermetically sealed in polyethylene tubing, 1.5 cm in length and 0.3 cm in diameter. All dosimetric points consist of at least three dosimeters at each location. The average midline-air exposure rate was 190.25 R/min with a 9% falloff at either end of the box.

Pulsed TRIGA Reactor Irradiations:

Preliminary neutron and gamma-ray dosimetry was accomplished in the exposure room at various distances from the reactor core and at several output power levels in the pulse mode of the reactor (Figure 2).

^a Harshaw Chemical Co., Cleveland, Ohio

These data allowed a choice between either a fixed exposure distance and varied reactor pulse output power levels, or a fixed reactor pulse output and varied exposure distances to achieve the desired doses. This dosimetry was done by exposing the various dosimeters at a location corresponding to the midline of the dog exposure boxes. Standard dosimetry techniques as performed in this laboratory were followed (12 - 16). For neutron dosimetry, sulfur pellets and threshold detectors (plutonium, neptunium and magnesium-thorium alloy) were exposed inside a 2" $^{10}\text{Boron}$ sphere. Beryllium-oxide and lithium-fluoride dosimeters (TLD-700)^a were used for the gamma-ray dosimetry. Sulfur pellets on the outside surface of the box served as a proportional monitoring device during the animal exposures. Because of greater reproducibility, a constant reactor power level (\$3.00 reactivity) and varying exposure distances were used to achieve the desired doses. The calibration measurements were made on arcs of 0.67 and 1.34 meters from the cylindrical wall between the reactor pool and exposure room (Figure 2). These exposures yielded gamma-ray to neutron dose ratios of 2.15 and 2.0 and 0.67 and 1.34 meters, respectively. At these distances, the neutron dose above the 3 MeV threshold for the sulfur reaction varied from 28 to 24% of the total fast neutron dose.

^a
Harshaw Chemical Co., Cleveland, Ohio

Doses for the dog exposures, in terms of tissue rad measured at the midline of the exposure volume, were determined from the monitor sulfur pellet activity as a neutron plus gamma-ray dose per activation count. The values were adjusted for the changes in the neutron and gamma-ray doses for the various dog exposure distances by interpolation between the two calibration values.

TRIGA Reactor Exposures:

Following the calibration dosimetry, appropriate distances were selected to achieve the desired exposures. The four exposure boxes were positioned on plywood tables such that the midline plane of a standing animal would be on the same horizontal plane as the center of the reactor core.

The reactor is a TRIGA Mark III, with pulsing capability (17). After animal placement and closure of the exposure room door, the core was moved into the conical lobe projecting into the exposure room and then pulsed. Immediately following the pulse, the core was moved back to the center of the reactor pool, so that the gamma-ray activity of the core would not add to the dose delivered by the pulse. Core movement from pool center to exposure position took two minutes, followed by a four-minute period to prepare the reactor for pulsing.

Figure 2 is a top view of the exposure room adjacent to the TRIGA reactor pool. The letters refer to the various positions used for exposure

box placement depending upon the dose desired; lack of positional symmetry is due to nonuniformity of the radiation field as determined by preliminary dosimetry. Table VI summarizes the pertinent data relating to the exposure position and dose for each dog.

Dog Phantom Exposure:

A dog phantom, fabricated with the same material as described by Alpen et al. (18), was assembled with the following dimensions: 52 cm length, 12.2 cm height, and 12.9 cm width. This permitted dosimetric measurements on the entrance and exit surfaces and at 2.15 cm intervals along the frontal plane (Figure 5). The following dosimeters were used for the dog phantom exposures: lithium fluoride (TLD-100) for ^{60}Co gamma-ray measurements; lithium fluoride (TLD-700) and sulfur pellets for mixed gamma-neutron measurements.

The dog phantom was exposed both unilaterally and bilaterally to ^{60}Co gamma radiation. This allowed comparison of the depth dose patterns between the ^{60}Co gamma (simultaneous bilateral) and the TRIGA reactor (unilateral) irradiation configurations.

Figure 6 shows the resulting ^{60}Co gamma-ray depth doses. The resulting midline gamma-ray value was 87% of the midline air value.

For TRIGA reactor dosimetry, the dog phantom was exposed at four distances to simulate the three average exposure locations (Positions

TABLE VI

TRIGA Reactor - Exposure Room Dosimetry

Pulse	Group Description	Location	Distance ^a (cm)	Power Output Level Megawatts	Dose ^b (rad)	Average Dose for Pulse
1	18,000 rad, uni-lateral single	A	32.7	1270	19980	23052
		B	37.8		25970	
		C	42.9		23970	
		D	42.9		22290	
2	18,000 rad, uni-lateral 1st pulse 9000 rad	E	75.9	1250	8930	9025
		F	75.9		9730	
		G	88.6		8650	
		H	88.6		8790	
3	18,000 rad, uni-lateral 2nd pulse 9000 rad	E	75.9	1250	8840	9040
		F	75.9		9800	
		G	88.6		8780	
		H	88.6		8740	
4	18,000 rad bilateral 1st pulse 9000 rad	E	75.9	1275	8930	9118
		F	75.9		10150	
		G	88.6		8800	
		H	88.6		8510	
5	18,000 rad bilateral 2nd pulse 9000 rad	F	75.9	1340	9210	9439
		G	75.9		10500	
		H	88.6		9165	
		H	88.6		8880	
6	13,500 rad bilateral 1st pulse 6750 rad	I	96.2	1270	6835	6909
		J	96.2		7470	
		K	108.9		6520	
		L	108.9		6810	
7	13,500 rad bilateral 2nd pulse 6750 rad	I	96.2	1220	6610	6683
		J	96.2		7252	
		K	108.9		6390	
		L	108.9		6480	

a. Distance measured from the boron shield of the reactor pool wall to the center center of the exposure box.

b. Total dose (gamma-rays + neutrons) in rad, as determined by proportional sulfur monitors, and expressed as tissue rad measured at the midline of the exposure volume.

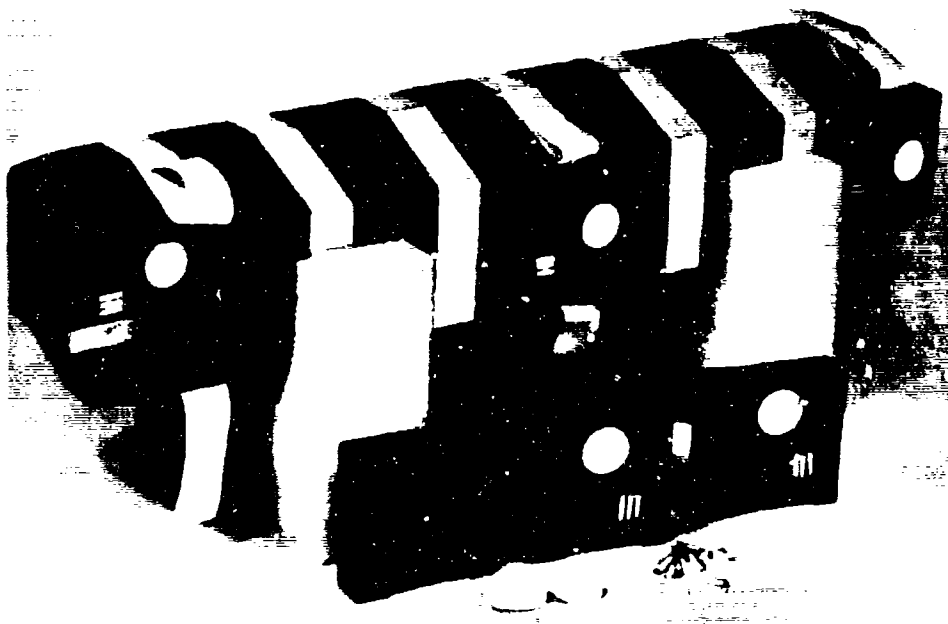


Figure 5. The dog phantom used for depth-dose measurements for both ^{60}Co and reactor irradiations. Also shown are the sulfur pellets and lithium fluoride dosimeters for placement within and on the phantom for reactor fn/γ detection. See the dosimetry appendix for further discussion and specifications.

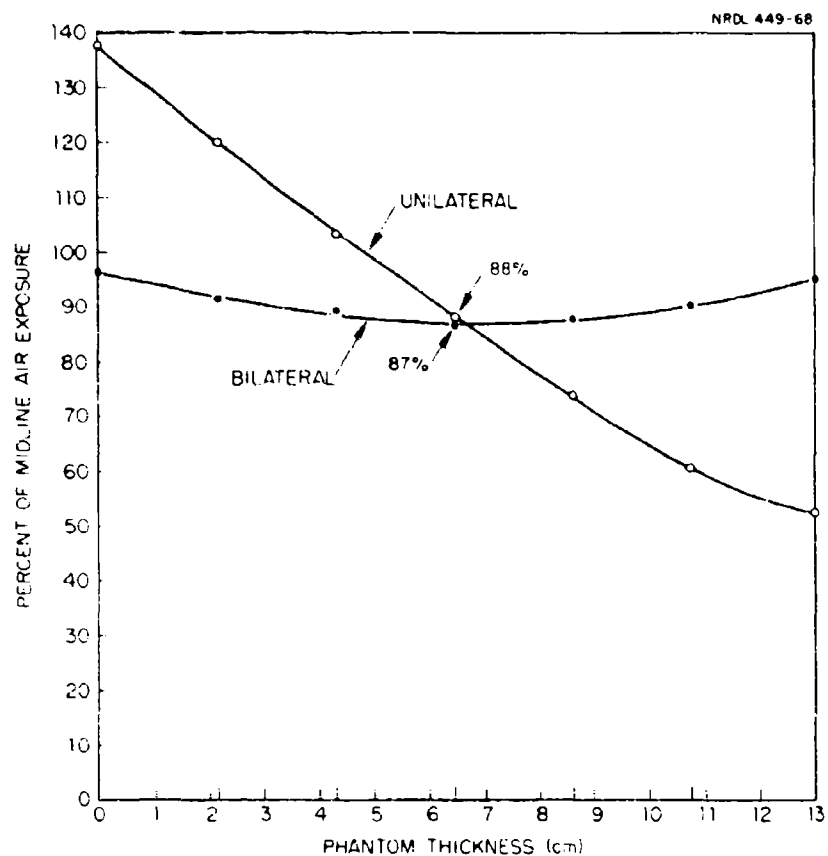


Figure 6. Depth-dose curves, derived by both bilateral and unilateral exposure of the phantom to ^{60}Co gamma radiation. The two percentage values associated with each curve represent the midline tissue doses, expressed as percent of midline air exposure in R.

C, G, K) plus the one very close placement of pulse # 1 (Position A).

Figure 7 shows the total doses, with gamma and neutron doses also plotted, for the four phantom exposure distances. These curves represent the depth doses measured along the horizontal plane bisecting the phantom at the midpoint of its length. The dosimeter locations simulate doses received across the widest portion of a dog's trunk, which would be approximately halfway between the dorsal and ventral surfaces.

The depth-dose patterns at the ends of the phantom were determined at entrance, midline, and exit positions. As would be expected, the falloff at the ends of the phantom became less as the phantom was moved farther away from the core. For example, at Position A (Figure 2), the entrance, midline, and exit doses were 89%, 79%, and 79%, respectively, of the comparable locations at the midpoint of the phantom. As the phantom was moved farther back from the core, Positions C, G, and K, the phantom-end percentages increased from 85% to 95% of the midplane doses. The midline tissue value (expressed as percent of midline air value) did not remain constant at various distances from the reactor. The values ranged from 94 to 78%, but did not fall off proportionately as the distance was increased.

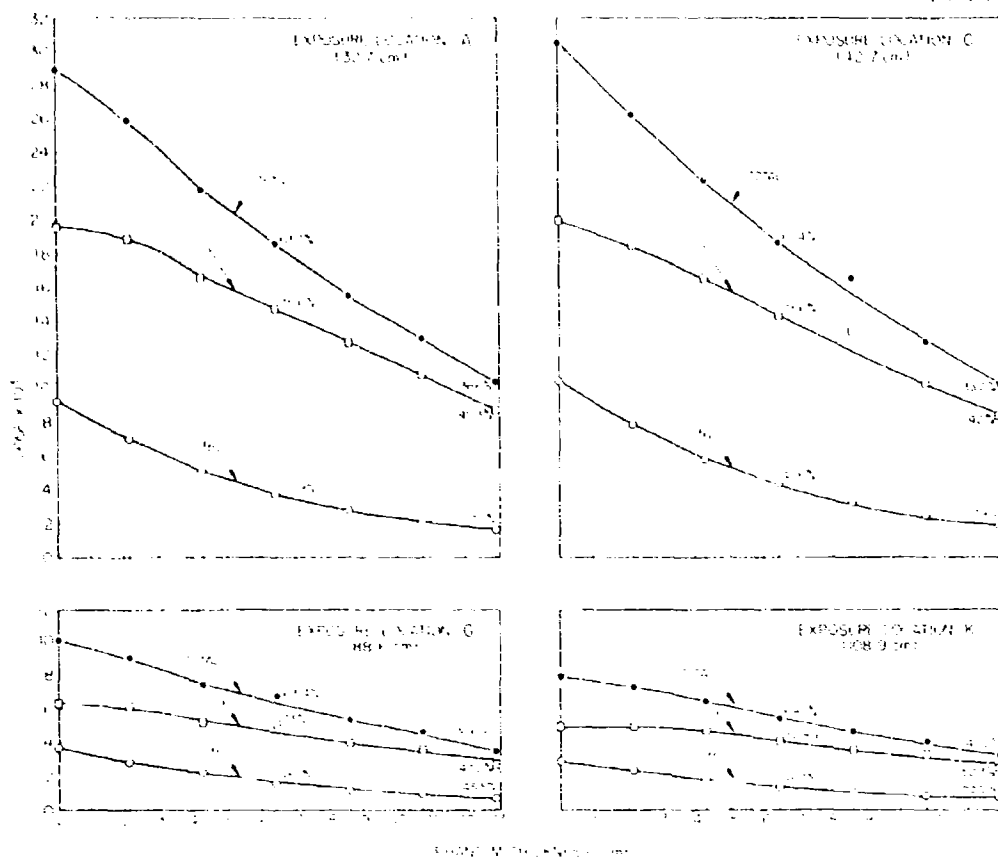


Figure 7. Phantom depth-dose curves for pulsed TRIGA reactor radiations. Four exposure positions were used for phantom irradiations. For further details see Table VI and Figure 2. The percentage values on each curve are the midline and exit doses expressed as percent of surface dose.

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13. ABSTRACT Incapacitation and resultant times of death have been studied with dogs following supralethal doses of either ^{60}Co gamma or pulsed TRIGA reactor radiations. The nominal doses delivered were 4500, 9000, 13,500, or 18,000 rad. The exposure rates were 190.25 R/min from the ^{60}Co sources and $3.4 - 11.5 \times 10^7$ rad/min from the TRIGA reactor. The two lower doses (4500 and 9000 rad) produced gastrointestinal deaths, with survival times ranging from 67 - 97.5 hours. These animals first exhibited signs of incapacitation at 48 - 72 hours. The two high doses (13,500 and 18,000 rad), on the other hand, produced central nervous system deaths, with survival times of 16 - 90.5 hours. With the exception of one animal, all dogs receiving 18,000 rad died within 29 hours. The dogs exposed to 13,500 rad had a much greater spread in survival times, indicating that doses in this range may cause either a gastrointestinal or central nervous system syndrome in dogs. All dogs in these two dose groups were incapacitated by 100 minutes. There was no evidence in the dogs of any recovery after the initial signs of incapacitation. The rate and severity of incapacitation was generally related to dose; the lower doses produced a slower onset and gradual incapacitation, while the higher doses caused a more rapid, severe clinical syndrome. Of the comparable exposures to either ^{60}Co gamma or pulsed reactor radiations, no differences in clinical response were noted. Thus, in the dog, under these experimental conditions, no differences in clinical response were seen with regard to the type of radiation, and no exposure-rate dependency was observed for either incapacitation or survival times.		

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