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EMESIS ED₅₀ OF NEUTRON IRRADIATION AND PROPHYLACTIC EFFECTIVENESS

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NOTICES

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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19. ABSTRACT (continued)

group at 0.75 Gy/min, 20 were exposed in the undrugged neutron group at 1.62 Gy/min, and 19 were exposed in the drug-treated neutron group. The drugged group received, 40-min preexposure, a combination of thiethylperazine, promethazine, and cimetidine which was previously shown to raise a 60 Co gamma ED₅₀ by 85%. The drugs were ineffective against neutron irradiation.

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EMESIS ED50 OF NEUTRON IRRADIATION AND PROPHYLACTIC EFFECTIVENESS

INTRODUCTION

Military planners have long been interested in protecting personnel by negating the radiation effects of nuclear weapons. Initial experimental efforts to reduce or eliminate the lethal effects of supralethal radiation were essentially unrewarded. More recently, efforts at this laboratory have been directed at finding a procedure or treatment to decrease the acute radiation illness problems. In this manner, performance of the recently irradiated individual would be improved in comparison to that of a similarly exposed but untreated worker.

Effects of midline absorbed radiation between approximately 2 - 8 Gy (1 Gy = 100 rad) are in the range of most importance in U. S. Air Force operations. Less than 2 Gy is expected to have little effect in the absence of additional insults. Absorbed doses greater than 8 Gy, in most cases, mean that the individual was closer to the detonation and would be significantly injured by blast or heat. The range between 2 and 8 Gy causes most people varying degrees of distress which would commence within 1/2- to 6-h postexposure. Symptoms which occur in this time period include any, or any combination of the following: anorexia, nausea, vomiting, hypotension, diarrhea, and fatigue. These symptoms are collectively known as the prodromal syndrome (1).

Animal research at this laboratory has been toward both categorizing and predicting radiation effects and reducing prodromal effects of ionizing radiation which was generated by radioactive cobalt (^{60}Co) (2-5). Experimentation has been concentrated on the emetic effect because of its significance in combat operations and therapy patients, and because it is easily measured in animals compared to the rest of the prodromal syndrome. In dogs, Cooper and Mattsson (4) significantly raised (p<0.05) the ED₅₀ (dose of radiation at which 50% vomited). In that experiment undrugged, gamma-irradiated dogs (the controls) received 1.7 Gy midline tissue dose for their ED_{50} while the radiation tolerance of the most effectively treated group was extended to 4.02 Gy. Further testing by Mattsson et al. (5) used the same drugs, but at somewhat different doses and in all possible combinations. That study was much larger, with at least 25 dogs The ED₅₀ of the control group was 2.57 Gy. in each group. The ED_{50} of the group receiving the most effective treatment was 4.73 Gy; dogs in that group had been injected with all 3 drugs: cimetidine, promethazine, and thiethylperazine.

Gamma radiation studies produce important information for military application and radiation therapy procedures. Military planners also need information pertaining to neutron effects. Depending on many variables such as weapon construction, weapon yield, distance from ground zero, height of burst, and shielding, the neutron component of exposure from a weapons detonation could be as high as 60% (6).

Textbooks most frequently give the neutron relative biological effective-This neutron RBE most likely originates from ocular lens ness (RBE) as 10. effects because the lens is very sensitive to neutron exposure. With more experience we have learned that the source and type of radiation, animal or tissue irradiated, and the physiologic or functional endpoint chosen, play a very large role in the resultant RBE. For instance, with exposures at supralethal levels, the following neutron studies led to RBEs of less than 1 when endpoints related to prodromal effects: (1) a study of early transient incapacitation (ETI) in monkeys had an RBE of 0.68, and (2) in another study the RBE was 0.23 for causing performance decrement in miniature pigs (7.8). These two experiments were each performed with neutron-to-gamma ratios (n:Y) of 10:1 compared to 0.1:1. In contrast, another study demonstrated no significant difference for the incidence of vomiting in monkeys exposed to supralethal doses of radiation with n:Y ratios of 3:1 compared to 0.4:1 (9).

Even though a neutron: gamma emesis study has been conducted and reported in monkeys (9), these data may not be meaningful for man since the monkey radioemetic threshold is much higher than that of man and dogs (10). Much of the existing monkey emesis data was obtained at higher radiation levels. Also, primates can conceal vomitus in their cheek pouches so that an observer might not realize that they have been affected. Data from dogs may be more useful since there are several radiobiologic and biochemical similarities which we see between dogs and man. For instance, normal plasma histaminase levels are similar between man and dogs, but lower than that of monkeys. Also, dog and man's response to emetics (apomorphine, etc.) are similar. When irradiated, the canine radioemetic threshold (level at which emesis begins), time to onset, and duration of effect are all quite similar to those of man.

This study is divided into two experiments and reported in two phases: Phase I was a comparison of the emetic responses in dogs which were exposed to either neutron or gamma radiation from a reactor. Phase II (with a larger sample size) was to confirm the results of Phase I, and also to determine the degree of benefit which could be expected of certain drugs against radiation effects of neutrons. The animals exposed and group structure by phases are described in Table 1.

	Gamma	Neutron Salíne	Neutron drugged
Phase I	12*	13	-
Phase II	19	20	19

TABLE 1. ANIMALS EXPOSED AND GROUP STRUCTURE

*Number of dogs exposed.

METHOD AND MATERIALS

Exposures were conducted at the Armed Forces Radiobiology Research Institute (AFRRI) TRIGA MARK F Reactor in exposure room 1. The enhanced neutron field (ENF) was obtained by placing a movable $.91 \times .91 \text{ m}$ (3 ft. x 3 ft.) 15.25 cm (6 in.) thick, lead shield in front of the reactor tank protrusion, and straddling the sides with boron- and lead-impregnated Masonite slabs. The Masonite was used to minimize scattered neutrons and gamma-rays.

An enhanced gamma field (EGF) was obtained by positioning the reactor core 30.5 cm (12 in.) from the tank protrusion in exposure room 1. The neutron component was minimized by thermalization of the neutrons by the 30.5 cm (12 in.) of water between the core and the exposure room. The thermalized neutrons were subsequently captured in the gadolinium-cadmium on the tank wall.

The AFRRI reactor was chosen because the radiation is similar to a nuclear weapon spectrum. Exposures were not made in a pulse as would occur with a weapon detonation and the percentage of high energy neutrons was not quite as great from the reactor as from a weapon. However, the average energy was similar to a weapon and was also close to the average energy of the cascade disintegrations of 60 Co. We also attempted to standardize with procedures which had been established in previous testing of dogs to cobalt radiation.

Preexperimental dosimetry estimated the free-in-air (FIA) exposures incident at the midline level as 7.9:1 n:Y ratio in the ENF and 1:14 in the EGF. Tissue-to-air ratios (TAR) varied considerably. At midline level, inside the restraint box, the TAR for ENF was 0.49 and for the EGF it was 0.84. Dosimetry was conducted using a cylindrical phantom filled with tissue-equivalent fluid; 0.05 cm³, 0.5 cm³, and 50 cm³ ionization chambers; and sulfur foils. Ionization chambers and sulfur foils were also exposed during each animal exposure for comparison to the phantom exposures in order to establish the midline dose for each animal. Appendixes A and B contain a full description of dosimetry procedures and results.

Experimental subjects were random-source adult male dogs which averaged 18 kg. The dogs were procured through sources of the AFRRI, held in quarantine at a nearby location for 21 days, and shipped to the AFRRI vivarium to be used within 1 week.

Food was withheld from each animal in the evening prior to the test day. On the morning of the procedure, each dog was fed one can (454 g) of dog food and given approximately 50 min to eat. The dogs were then removed from the cage, weighed, and 2 ml of blood was drawn for serum blochemical determination (to be conducted at a later date). The average time from presentation of food to the end of irradiation was 100 min.

For exposure, the dog was secured, usually seated, in a box constructed of 0.95 cm (3/8 in.) Plexiglas. The box was 63 cm (24.8 in.) long, 49 cm (19.3 in.) high, and could be adjusted between 16 (6.2 in.) and 24 cm (9.4 in.) in depth. The dogs were restrained fully conscious with their heads protruding through a hole in the front of the box. The dogs were secured so they could not move excessively by placing 0.95 cm (3/8 in.) Plexiglas rods around the dog through holes predrilled in the box. The rods had a Plexiglas flange glued on one end and were secured on the other end with a Plexiglas locking nut. This arrangement provided additional side-to-side strength for the box.

To achieve bilateral exposure, the box was placed on a rotating platform in the exposure room so the midline of the dog was 125 em (49.2 in.) from the

core center. As one-half of the exposure was completed, a solenoid was activated to cause the box to rotate 180° .

Each dog was confined in the box for at least 30 min during room closure, relocation and activation of the core, and room reopening. The dog was observed by closed circuit television during this time.

As quickly as possible following irradiation, the dog was retrieved from the exposure room, released from the box, had another blood sample taken, and was placed in an individual observation cage. The observation cage was large enough to allow free movement. The cage floor was wire mesh which allowed easy quantification of emetic episodes. Examination of the cage floor for emesis was conducted at a minimum of every 15 min during the first 6 h postirradiation. No food or water was available during the observation period. Each dog also received a third venipuncture for withdrawal of 2 ml of blood immediately following the 6 h of observation. The dogs were euthanized within 24 h postexposure. A necropsy was conducted on each animal to be sure there was no physical condition to compromise results obtained.

The exposure paradigm was a sequential Up-Down technique (11). A radiation dose for the first dog in each group was established based on previous experience. Thereafter, each exposure within each group was determined solely by the emetic response of the previous dog. A dog having emesis at its radiation dose resulted in a one step decrease in radiation for the next dog in that group. A dog having no emesis at its given dose caused an increase of one step for the next dog in that group. Step size was established as 0.045times the natural log (ln) of 200 which resulted in approximately a 27% change in regular dose units from any one step to the next.

Early in our experimentations logarithmic treatment of step sizes was seen to be very beneficial. When transposed back to regular units, the step sizes are smaller in the lower doses, but become separated further as dose increases. The net result is that fewer dogs are required to be irradiated at higher doses before the effect is seen. Calculations of dose and step sizes were the same as those made for previous 60 Co studies (computed in rad or cGy). However, those results were reported in midline absorbed dose. Because there are two different radiations used in this experiment, these results are given in terms of FIA dose at midline level.

Phases I and II used the same log step size, but different starting doses. Table 2 shows how target dose levels were established on a midline absorbed basis. These values must be multiplied by their respective TARs to establish exposure targets for each type of radiation.

TABLE 2. ESTABLISHMENT OF RADIATION DOSE LEVELS

a)	natural log (ln) of 200) = 5.2983		
b)	step size: (0.045) (1r	1 200) = 0.2384		
2)	(Phase I)	x(ln dose)	Dose = e ^x	(rad or cGy)
		5.2983	200	-
	add to above $x: 0.2384$	= 5.5367	254	
	add to above $x: 0.2384$	= 5.7752	322	
	etc.	= 6.0136	409	
		6.2520	519	
		6.4904	659	
		6.7289	836	
	(Phase II)	x(ln dose)	Dose = e ^X	(rad or cGy)
		5,3936	220	•••
	add to above $x: 0.2384$	= 5.6321	279	
	etc.	= 5.8705	354	
		6.1089	450	
		6.3473	571	
		6.5857	725	

During Phase I, gamma exposures were made at the rate of 0.69 Gy/min, and neutron exposures were 1.2 Gy/min. During Phase II, gamma exposures were 0.75 Gy/min and, because Phase I exposures were quite lengthy to attain an effect, neutron exposures were increased to 1.62 Gy/min in Phase II. A second group of animals was exposed to neutrons in Phase II. This group was injected with a combination of three drugs which was determined to be an effective antiemetic to gamma radiation. The average time between the feeding and drug injections was 50 min. The time spent between drug injections and the end of radiation averaged 44 min. Pertinent drug information is given in Table 3.

	TABLE 3. DRUG INJECTI	ON SCHEME FOR PHASE II	
Group	Treatment	Quantity	Route
1, 2	Saline	0.5 ml	im
3	Thiethylperazine Promethazine Cimetidine	5.57 mg/m ² 13.93 mg/m ² 167.14 mg/m ²	im im iv

Drug doses were calculated using the canine body surface area (12) which was determined by the formula $m^2=(10.1)$ (weight in grams)^{2/3} (10⁻⁴). This formula was to better equate drug doses to those of man and represented thie-ethylperazine 10 mg; promethazine 25 mg; and cimetidine 300 mg.

Emetic results derived from both phases are given in Table 4. A total of 40 of the 86 subjects had one or more emetic episodes. Onset time was defined as the length of time after completion of irradiation at which a responder had his first emetic episode. Similarly, offset times were the length of time following irradiation at which the subject had his last emetic episode. For those animals with more than one episode, duration times are the span of time between the first and last emetic episode. Only one responder had emesis after the observation period and none of the nonresponders.

	Phase I		Phase II		
	Gamma group	Neutron group	Gamma group	Neutron saline group	Neutron drug group
Responders (subjects)	5 (12)	5 (13)	9 (19)	11 (20)	10 (19)
Mean onset time (min) Range (min)	185 150-200	163 110-195	156 88-199	163 128-210	187 135-227
Mean time duration(mir Range (min)	1) 17 1-60	53 1-165	38 1-110	49 1-180	27 1-80
Mean of episodes Range	1.8 1-3	3.8 1-7	2.7 1-6	2.9 1-6	2.1 1 - 5

TABLE 4. EMETIC RESULTS

In Phase I, both groups had 5 responders. In the gamma-irradiated group. subjects had a total of 9 emetic episodes (average of 1.8) with the least episodes being 1 and the most episodes being 3. When there was only 1 episode, duration was listed as 1 min. The shortest onset time was 2.5 h postirradiation. The neutron-irradiated group had a total of 19 episodes with 1 being the least number of episodes while 1 of the dogs had 7 episodes during the 6 h observation period. Most of the data in Table 4 is quite similar across groups. This finding should further demonstrate that the identified endpoints were obtained similarly in the groups. However, the quantity of radiation necessary to reach these endpoints was different. Figures 1 through 3 illustrate the amount of radiation given, and the occurrence of emesis in both phases.



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Figure 1. Phase I neutron emesis ED₅₀ results. Each point represents one subject. A "O" indicates that the dog did not vomit at that radiation level; an "X" depicts a dog with at least one episode of emesis during the observation period.



Figure 2. Phase II neutron emesis ED₅₀ results (undrugged). "X" and "0" indicate results as given in Figure 1.





For each phase and radiation type, the $ED_{50}s$ and 95% confidence intervals (CI) were calculated. Those $ED_{50}s$ and 95% CI (Table 5) were based on the FIA dose at the level of the midline. Although these values appeared dissimilar within the same radiation type comparing Phase I to Phase II, statistical evaluation (t-test) showed that the results could be from the same population of individuals. Therefore, the results were combined on a weighted average basis (Table 5).

TABLE 5. ED50 AND 95\$ CONFIDENCE INTERVALS IN GRAY

Weighted average
4.89
46 4.22 - 5.67
8.83
0.14 7.57 - 10.30
1.62
,

(Incident Radiation)

Comparing the weighted FIA doses statistically, demonstrates that more neutron radiation is required than gamma to cause vomiting in 50% of test subjects. Also, using these figures and their neutron-to-gamma ratios, RBE is calculated (Fig. 4) to be 0.48.

The combined, weighted (Phase I & Phase II) ED so values are:

gamma $ED_{10} = 4.89 \text{ Gy}$ Neutron $ED_{10} = 8.83 \text{ Gy}$

Both resulted from mixed exposures as described. In the EGF, exposure consisted of 93.3% gamma and 6.7% neutron radiation. In the ENF, exposure consisted of 88.8% neutron and 11.2% gamma radiation. In other words:

Gemma ED₁₀ = (4.89)(.933 gemma) + (4.89)(.067 neutron)= 4.56 gemma + 0.33 neutron

Neutron $ED_{10} = (8.83)(.112 \text{ gamma}) + (8.83)(.888 \text{ neutron})$ = 0.99 gamma + 7.84 neutron

Both are the same effect, emesis in 50% of the subjects. Therefore, the two are equal as follows:

7.84 neutron +0.99 gamma = 4.56 gamma + 0.33 neutron

By transposing like values and subtracting:

7.51 neutron = 3.57 gamma

The neutron:gamma RBE is:

$$\frac{3.57}{7.51} = 0.48$$

Figure 4. Calculation of neutron:gamma RBE.

DISCUSSION

The Up-Down technique was employed because it required 30-40% fewer subjects than standard probit procedures to depict a mean (11). This reduction in sample size was beneficial even though the sampling procedure reduces the ability to estimate low or high effectiveness ranges (ED₁₀ or ED₉₀).

Dosimetry analyses (Appendixes A and B) point out the marked drop-off of neutrons during penetration of the restraint box and the animal. This drop-off was the basis for rotation of each animal. However, during ENF irradiations in Phase I, three animals failed to rotate 180° as the castors of the rotating platform were jiggled into a locked position prior to platform release by the solenoid. Emetic results of these unilateral exposures were not

used for ED₅₀ determinations even though the irradiation data is present in the dosimetry analysis. After each failure to rotate, the next animal in the neutron group was repeated at the same dose. Conversely, gamma-irradiated dogs do not have such a marked drop-off in penetration to the midline. Also, previous experiments were conducted with unilateral exposures (4,5). Therefore, the two unilateral irradiations which occurred were used as data points from the EGF.

Prior to Phase II exposures, the rotating platform was modified from gravity power to positive power (electric motor) to assure rotation. Therefore, in Phase II no animals were lost to nonrotation at exposure as had occurred in Phase I. However, one vomited while being irradiated. Two others were lost when it was discovered at necropsy that one dog was immature. The immature one was eliminated because all subjects were to be standard adult males. Prior to necropsy and discovery of the immature dog, the following dog had been irradiated and was eliminated too. The following day, that group was restarted at the dose which had been received by the immature dog.

More than 250 random-source dogs have been used in previous experiments of emetic effects (4,5). In these experiments, a total of 135 responders have resulted. Unlike primates, in no case have the dogs had retching without some amount of productive emesis. In fact, when an episode immediately followed the previous one, the dog moved so each result was easily quantifiable. This event was the basis for our decision to observe at least every 15 min rather than continually.

Duration determinations are approximate. As described, observations were not continuous, but were accomplished every 15 min, so it's possible that the same reported observations could be made for two pairs of results which actually occurred as much as 30 min apart. Similarly, some onset determinations could have been a few minutes sooner (no more than 15 min) than were actually recorded.

The following observations were consistently made: Dogs irradiated in the enhanced gamma group acted much as those in previous 60 Co experiments, becoming generally quiet in the observation cages. Dogs in the enhanced neutron group were more active and alert, usually for the entire observation period. Conversely, the neutron-exposed dogs without warning, on the third or fourth day postirradiation, became rapidly moribund. This occurrence led to the decision to euthanize within 24 h.

CONCLUSIONS

Three very important observations were made from these experiments: First, neutron irradiation was not as efficient in causing vomiting as was gamma radiation. This observation was based on the requirement to double the FIA neutron dose at the subject to show the same emetic result. However, while animals exposed to greater proportions of neutrons received more radiation, in a subjective evaluation of alertness, they seemed much less severely affected. Second, with exposure to sufficient neutron radiation to initiate vomiting, there was no benefit from antiemetics which we have tried thus far. Third, while subjects receiving high percentages of neutrons may have been more alert immediately postexposure, the final effects were more dramatic and earlier.

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APPENDIX A

PHASE I EXPERIMENT

Dosimetry Analysis

All dogs in this study were irradiated in exposure room 1 of the Armed Forces Radiobiology Research Institute (AFRRI) TRIGA MARK F Reactor. Twenty-nine irradiations were conducted during the month of October 1979. Enhanced gamma field irradiations are summarized in Table A-1 and ENF irradiations in Table A-2. The average dose delivered while coming to power was 0.1 Gy in the EGF and 0.24 Gy in the ENF. The average dose rate during the irradiations was 0.693 Gy/min EGF with a maximum variation (from average) of 4% (excluding the irradiation of 10 October) and 1.204 Gy/min ENF with a maximum variation of 5%. Sulfur monitors indicated that within their precision (6%, 2 σ) all irradiations received the same neutron fluence per kilowatt-minute.

TABLE A-1. ENHANCED GAMMA FIELD IRRADIATION

	FIA	Average	Rise		\$ Dose
	dose	dose Rate	dose		delivered
Date	(Cy)	(Gy/Min)	(Gy)	Dog position	at rotation
Oct 10	2.92	3.480		Lying flat	Unilateral
Oct 11	3.75	0.702	0.11	Various; standing sitting, lying	49
Oct 12	4.78	0.679	0.08	Sitting	73
Oct 15	3.76	0.679	0.09	Squatting & sitting	49
Oct 16	4.76	0.710	0.09	Sitting	50
Oct 17	3.73	0.665	0.10	Standing	Unilateral
Oct 18	2.93	0.717	0.11	Sitting corner	49
				to corner	
Oct 19	3.82	0.674	0.08	Sitting forward	50
Oct 22	2.94	0.714	0.11	Sitting corner to corner, arched	49
Oct 23	3.93	0.693	0.10	Sitting forward	48
Oct 24	4.73	0.676	0.07	Sitting & lying	50
Oct 26	6.18	0.695	0.12	Sitting; corner to corner & forward	48

(Tissue-to-Air Ratio = .84)

Enhanced Gamma Field

An EGF was obtained by positioning the reactor core 30.5 cm (12 in.) from the tank protrusion in exposure room 1. The neutron component is minimized by thermalization of the neutrons by the 30.5 cm (12 in.) of water between the core and the exposure room. The thermalized neutrons are subsequently captured in the gadolinium-cadmium shield on the tank wall. Free field measurements determined the neutron-to-gamma dose ratio at the centerline of the experiment (121.5 cm (47.8 in.) from the centerline of the core) to be 0.07 \pm 1095.

Based on the estimates from the study by Chapman and Burrus (A-1) on the spectrum of gamma rays from the Bulk Shielding Reactor II for 35 cm (13.7 in.) of water, it is estimated that for the AFRRI TRIGA Reactor about 55% of the photons penetrating the 0.635 cm (1/4-in.) aluminum reactor tank are less than 1 MeV and about 16% are of the energy range near 2.2 MeV. The 2.2-MeV photons are capture photons produced by thermal neutron capture in the hydrogen of the water. The photon energy spectrum extends up to about 10 MeV with the large quantity of photons less than 1 MeV arising from fission and subsequent scattering of the higher energy photons from fission and 2.2-MeV capture photons. The average energy of the photon beam based on a weighted average by number of No corrections were made to the chamber responses for photons is 1.13 MeV. the relatively large number of lower energy photons, but the calculations based on the Chapman and Burrus (A-1) data indicate that such corrections are less than 3% of the chamber response.

TABLE A-2. ENHANCED NEUTRON FIELD IRRADIATIONS

	FIA	Average	Rise		% Dose
	dose	dose rate	dose		delivered
Date	(Gy)	(Gy/Min)	(Gy)	Dog position	at rotation
Oct 10	5.23	1.184		Sitting centered	52
Oct 11	6.66	1.234	0.19	Standing centered	49
Oct 12	8.39	1.163	0.15	Lying	51
Oct 15	10.60	1.163	0.19	Sitting	50
Oct 17	8.45	1.218	0.19	Sitting forward	50
Oct 18	10.77	1.190	0.20	Sitting forward	50
Oct 18	8.43	1.237	0.19	Standing	50
Oct 19	6.67	1.255		Sitting corner to corner	Unilateral
Oct 22	6.64	1.265	0.24	Sitting corner to corner	Unilateral
Oct 23	6.51	1.202	0.16	Various	50
Oct 24	8.45	1.212	0.28	Sitting	Unilateral
Oct 24	8.42	1.190	0.17	Sitting forward	50
Oct 25	10.72	1.198	0.22	Sitting squatted	50
Oct 25	13.64	1.216	0.47	Sitting arched	50
Oct 26	17.29	1.190	0.47	Sitting forward	50
Oct 26	13.50	1.176	0.19	Sitting	50

(Tissue-to-Air Ratio = .49)

Enhanced Neutron Field

An ENF is obtained in the AFRRI exposure room 1 by placing a movable .91 x .91 cm (3 x 3 ft), 15.25 cm (6 in.) thick, lead shield in front of the reactor tank protrusion and straddling the sides with boron and lead-impregnated Masonite. The Masonite is used to minimize the scattered neutron and gamma-ray component. Free field measurements indicate a majority of the gamma dose is caused by room return of capture photons. Free field measurements determined the neutron-to-gamma dose ratio at the centerline of the experiment from the centerline of the core at 121.5 cm (47.8 in.) to be 7.9 ± 15 %.

Field uniformity as established by activation foils at 121.5 cm (47.8 in.) was a 12.7 cm (5 in.) radius uniform field. Beyond 12.7 cm (5 in.) the field fell off linearly to about 75% of the dose at the centerline of the array at 40.6 cm (16 in.).

The individual irradiations were monitored by three independent systems. Two sets of chambers (two 0.5 cm³ tissue-equivalent (TE) chambers and two 0.05 cm³ TE chambers) and 2.54-cm (1-in.) dia monitor sulfur tablets were employed. All monitor chambers and monitor sulfurs were placed such that they were free from significant changes in the scattered radiation from minor changes in the placement of the animal. During the FIA measurements, a calibration factor for each individual monitor chamber was established so that the voltage collected on the monitor could be related to the actual dose delivered. Similarly, the sulfur monitors located on the experiment and on the reactor tank were calibrated and a sulfur fluence per unit dose established for the particular experimental setup.

During the irradiations the monitor chambers began to record the dose as soon as the reactor began coming to power since a slight dose is deposited as reactor power is obtained. For the EGF the average dose coming to power was 0.1 Gy and 0.24 Gy for the ENF. When the dose deposited as indicated by the 0.5 cm³ monitor chambers was just under 50% (about 2 s in time), the rotator was activated to rotate the dog and establish a bilateral irradiation. At approximately 99% of the dose delivered, the reactor was scrammed and backed away from the tank protrusion in exposure room 1 to reduce the dose deposited by fission fragment decay. During the irradiation the primary active monitors were the 0.5 cm³ TE chambers since their larger volume allows for increased sensitivity. The two 0.05 cm³ TE chambers acted as an active backup system. After irradiation the passive monitor sulfurs were counted to assure that the neutron fluence delivered was consistent. No inconsistencies between any of the monitoring systems were found throughout all irradiations, and agreement was within the errors of the detection systems.

Measurement Techniques

General dosimetry techniques employed at AFRRI can be found in AFRRI Contract Reports 65-4 and 65-6 (A-2,A-3). Descriptions and diagrams of the AFRRI exposure rooms and various neutron field modifications can be found in AFRRI Contract Report 65-6, and AFRRI Technical Notes 71-2 and 73-16 (A-3 - A-5).

Presently, the AFRRI paired chamber technique is the primary method of separating the neutron and gamma-ray components of the mixed field. A brief discussion of this method is found in the International Commission on Radiation Units and Measurements (ICRU), Report #26 (A-6). All ionization chambers employed at AFRRI are calibrated in a 60 Co field which is calibrated with the National Bureau of Standards (NBS) semiannually to within 2%. Reproducibility of all doses as determined by chambers (precision) in the various reactor fields is 5%.

Two sets of paired chambers were employed in this experiment. A set of $50-cm^3$ chambers were used to establish initial free field parameters. The $50-cm^3$ chamber set is an AFRRI-designed set consisting of a TE plastic (A-150)

chamber with a TE gas mixture as recommended in the ICRU report #26 (A-6), and a graphite chamber with carbon dioxide gas $(G/CO_2$ chamber). The TE gas mixture used consisted of 3.08% nitrogen (N), 32.8% carbon dioxide (CO₂), and the balance methane (percentages are by partial pressures). The 50-cm³ free field measurements are summarized in Table A-3. The very large uncertainty in the neutron component behind the water shield (109%) and the large uncertainty in the gamma component behind the lead shield (38%) are due to: (1) the small doses measured for these components; (2) the large value of the neutron sensitivity coefficient for the G/CO_2 chamber; and (3) the uncertainty of the coef-Since the sensitivity coefficient has a reasonably sized neutron ficient. energy dependence and the neutron spectrum behind the 15.25 cm (6 in.) of lead and 30.5 cm (12 in.) of water has not yet been determined, a worse case ± 50% variation for this coefficient was used in the accuracy error analysis. The data obtained using the $50-cm^3$ chambers was in excellent agreement with pre-The vious irradiations in exposure room 1 (A-3).

	TABLE A-3.	FREE FIELD MEASUREMENTS	
.!	EGF <u>cGy</u> kW-min	ENF <u>cGy</u> kW-min	ENF <u>cGY</u> kW-min
	50 cm ³ Chambers	50 cm ³ Chambers	0.5 cm ³ Chambers
Total dose per kW-min	4.35 ± 8.1%	4.16 ± 8.1≸	4.13 ± 6.1%
G amm a dose per kW-min	4.09 ± 4.6\$	0.40 ± 38%	0.47 ± 13.8%
Neutron dose p er kW- min	0.28 ± 109\$	3.76 ± 8%	3.66 ± 6.1%
n Dose Y Dose	0.07 ± 109\$	9.40 ± 39%	7.90 ± 15%

All errors are 2g accuracy/precision not included.

Table A-3 also contains the FIA ENF measurements made with the 0.5-cm³ paired chamber set. The $0.5-cm^3$ chamber set was designed by Shonka. The set consists of a 0.5-cm³ TE plastic (A-150) and the same mixture of TE gas as used in the 50-cm³ TE chamber and the neutron insensitive chamber is a magnesium (Mg) chamber with argon (Ar) gas (Mg/Ar chamber). The errors on the gamma dose (13.8%) and subsequent n:Y ratio (15%) are smaller since the neutron sensitivity coefficients for the Mg/Ar chamber are much smaller than those of the G/CO2 chamber. Although the gamma dose measured is still small and uncertainty in the coefficient is larger than in the G/CO₂ chamber, the overall uncertainty is substantially reduced since the physical properties of the Mg and Ar in the chamber make it a much better neutron insensitive chamber than the G/CO₂ chamber. The uncertainty in the Mg/Ar chamber includes a worse case coefficient variation of 100%. A 100% neutron sensitivity coefficient uncertainty was chosen since prior history at AFRRI on the 0.5-cm³ paired The 0.5-cm³ FIA data includes a correction term inchamber set is limited. corporated into the Mg/Ar chamber coefficients to account for the overresponse due to 88-keV X-ray from the lead shield (A-7).

Due to the increased accuracy of the Mg/Ar chamber, the n:Y ratio established by the 0.5-cm³ chamber set will be quoted as the n:Y ratio of the ENF (i.e., n:Y = 7.9 ± 15% for the ENF).

Tissue-to-Air Ratio Measurements

The TAR for the ENF was established by determining the total dose at depth and comparing it to the dose FIA. The choice of materials for a phantom must allow for the dramatic difference between photon and neutron inter-Photons interact with orbital electrons whereas the main mechanisms actions. of neutron interactions are through elastic and inelastic collisions with the nuclei. Consequently, the elemental composition of the phantom is very important. The TE liquid employed as a phantom is a combination of 65.5% water, 26.8% glycerol, and 7.6% urea by elemental weight as recommended in the ICRU report #26 (A-6) for muscle-equivalent liquid. The actual TE mixture used was in good agreement with the ICRU report. The solution has a density of 1.06 g/ml. The liquid was placed in a 0.32-cm (1/8-in.) thick. 15.25 cm (6-in.) OD Lucite cylinder. A single chamber within a 0.16 cm (1/16-in.) thick, tightfitting, hollow, Lucite tube to prevent the chamber from shorting or being contaminated, was positioned at the center of the cylinder. Calculations indicate the Lucite rod did not substantially perturb the dose measurement. The Lucite/TE phantom cylinder was placed in the Lucite cage used for the dogs during the TAR measurements.

The cylinder diameter was based on a best estimate of the diameter of the average size dog. Calculations based on dog measurements, assuming an elliptical cylinder chest cavity and a tapered elliptical cylinder abdominal cavity (diameter in both ventral-dorsal and lateral directions uniformly decreased from 1 to 0.8) homogeneously filled with a 100-cm^3 air bubble to represent the stomach, indicated that the dogs could be reasonably estimated by a 15.25 cm (6-in.) diameter, cylindrical TE phantom. Table A-4 lists the results of the phantom dosimetry measurements. The large neutron falloff is due to the rapid attenuation and absorption of the neutrons. The increase in the gamma dose is due to the slower attenuation and absorption of the photons and build-up of scattered and capture photons (most predominant reaction is H(n, Y)D).

	TABLE A-4. HIGH	NEUTRON FIELD PHANTOM	TARs*
	FIA (cGy/kW-min)	Midline (cGy/kW-min)	TAR
Total dose rate	4.12 ± 6\$	2.02 ± 7\$	0.49 ± 9%
Neutron dose	3.66 ± 6\$	1.04 ± 12%	0.28 ± 13%
Gamma dose rate	0.466 ± 14%	0.97 ± 5%	2.10 ± 15%
n:Y	7.9 ± 15%	1.1 ± 12 %	

*Errors do not include precision.

Cadaver measurements include three dogs: one large dog (9G74); one small dog (9H11); and a medium-sized thin dog (9G99). Cadaver dosimetry measurements are listed in Table A-5. The marked difference in dog sizes is reflected in the neutron dose which undergoes rapid attenuation in material and is extremely sensitive to small changes in the effective diameter. The gamma dose component is rather consistent since the gamma radiation is more penetrating than neutrons and the gamma component is "built-up" due to accumulated scattered photons, capture photons, and photons from neutron inelastic scatterings.

	TABLE A-5. TAP	DATA FO	R ENF CADAVER	MEASUREMENTS	
Dose ratio	Cylinder	9G74	9H1 1	9699	
Depth:FIA	0.49	0.40	0.64	0.60	
n Depth:n FIA	0.28	0.21	0.47	0.46	
Y Depth:Y FIA	2.1	1.96	1.96	1.71	
n:Y at depth	1.1	0.98	1.89	2.12	
Variations from cylinder phantom	N/A	-18\$	+31%	+22%	

Cadaver body measurements are listed in Table A-6. Effective diameter calculations were made using the elliptical cylinder approximation assuming homogeneous tissue. No corrections were made for bone or tissue density variations, emaciated conditions, and variation of the dog's abdominal region from the tapered elliptical cylinder approximation. A $100-cm^3$ air volume cavity was used to represent the stomach.

TABLE A-6. CADAVER MEASUREMENTS

Dog	Circumference	Ventro- dorsal diameter	Lateral diameter	Effective* diameter
9 67 4	48.3 cm	23.0 cm	14.0 cm	16.7 cm = 6.6 in
9H1 1	45.2 cm	20.0 cm	13.0 cm	14.9 cm = 5.9 in
9699	46.7 cm	21.0 cm	12.0 cm	14.7 cm = 5.8 in

*Effective diameter determined by elliptical cylinder approximation.

Actual measurements of the TAR in the ENF employed the paired chamber technique at midline in the cylinder and midline of the cadavers in the lower Cadavers were x-rayed to assure the chamber was in chest/abdominal regions. In the cadaver measurements, the $0.5 - \text{cm}^3$ the region near the last rib. chamber was slid down the esophagus in a tight-fitting, hollow, Lucite rod to prevent the body fluids from shorting or contaminating the chamber. Separate TE chamber and Mg/Ar chamber measurements were taken and normalized to each other through the monitor chambers. Then doses per kilowatt-minute at depth were determined.

The TAR for the EGF was determined with a similar technique. Placement of the chamber in the phantom and cadaver was identical to the ENF. TE liquid was used in the phantom. Since the FIA neutron component was so small (Table A~3), calculations indicated that it could be neglected and only a comparison of the TE chamber's response FIA and at depth was needed to establish the TAR. The TAR for a 15.25 cm (6-in.) dia TE phantom was $0.84 \pm 7\%$. Measurements for the cylinder and cadavers are listed in Table A-7. The TAR for a 15.25 cm (6-in.) dia cylinder is lower than a similar TAR for a cobalt field in that there is a high component of photons less than 0.5 MeV present. The TAR for a 15.25 cm (6-in.) dia cylinder is in reasonable agreement with that predicted using a photon spectrum for 35 cm (13.7 in.) of water as found in Chapman and Burrus (A-1).

<u></u>	TABLE A-7. ENHANCED GAMMA	FIELD TAR MEASUREMENTS	
<u></u>	TAR	Variation for cylinder	-
Cylinder	0.84	N/A	
9674	0.75	- 10.7%	
9H1 1	0.89	+ 6.0%	
9699	0.88	+ 5.0%	

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- A-6. Neutron Dosimetry for Biology and Medicine. International Commission on Radiation Units and Measurements, Report #26, 15 January 1977.
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APPENDIX B

PHASE II EXPERIMENT

Dosimetry Analysis

All dogs in this study were irradiated in exposure room 1 of the Armed Forces Radiobiology Research Institute (AFRRI) TRIGA MARK F Reactor. Sixtyone irradiations were conducted during the months of August and September 1980 (19 gamma irradiations and 42 neutron irradiations). The EGF and ENF irradiations are summarized in Tables B-1 and B-2. The average dose rates during the irradiations were .746 Gy/min EGF with a 3.4% (20) variation (excluding the September 17 gamma irradiation) and 1.624 Gy/min ENF with a maximum variation of 4% (2c). The expected precision error on any one dose is as follows:

Gamma 3.6% or less Neutron Dose > 6.80 Gy is 3.6% 4.54 Gy < dose < 6.80 Gy is 4.2% 3.40 Gy < dose < 4.54 Gy is 5.0%

The expected precision error on any one dose rate is as follows:

Gamma 4.1% or less Neutron Dose > 6.80 Gy is 4.1% 4.54 Gy < dose < 6.80 Gy is 5.2% 3.40 Gy < dose < 4.54 Gy is 7.1%

The variations in the neutron dose:dose rate precision errors are due to the short run times involved in these irradiations. Activation foils indicated that within the expected precision of these foils all irradiations received the same neutron fluence per kilowatt minute. The sulfur foils of the August/September 1980 irradiations agreed with the sulfur foils of the October 1979 irradiations within their expected precision errors. The rise and fall dose of the fall 1980 irradiations are of the same relative size as those of the fall 1979 irradiations.

The doses quoted for the neutron irradiations are 3% higher than those quoted on the days of irradiations. At the completion of the irradiations all monitor chambers were compared with the calibration runs to check for overall consistency. It was at this time discovered that the monitor chamber used to control the irradiations consistently underresponded by 3%. This variation was subsequently determined to be due to the chamber's location in the room and the subsequent influence of the scattered radiation from the experiment.

In comparing the actual irradiation configuration of August/September 1980 with that of October 1979 a small modification was necessary. In converting the rotation platform from a gravitational drive to an electrical drive device it was necessary to move the center of the experiment back 6.5 cm (2.6 in.) from the tank wall. This change is insignificant concerning the doses delivered for several reasons. First, the monitor chambers are calibrated relative to the FIA dose received at the center of the apparatus/dog; second, the room is large enough and the returned scattered radiation small enough that a movement of 6.5 cm (2.6 in.) towards the rear of the room is insignificant; and third, the effect of 6.5 cm (2.6 in.) of air will have no serious effect on perturbing either the neutron or gamma spectra. Free-in-air calibrations were in excellent agreement with those of October 1979 when corrected for the 6.5 cm (2.6 in.) change.

Enhanced Gamma Field

The enhanced gamma field (EGF) is described in Appendix A.

Enhanced Neutron Field

The enhanced neutron field (ENF) is described in Appendix A.

Measurement Techniques

The measurement techniques employed are the same as those described in Appendix A. The only change employed is that the 0.05 cm^3 monitor chambers had been replaced by 0.5 cm^3 monitor chambers. Consequently, four 0.5 cm^3 TE monitor chambers were employed at various locations in the room. Table B-3 contains the FIA field calibration dose rate per kilowatt with the estimated accuracy errors. The large errors associated with the gamma measurement in the ENF and the neutron measurement in the EGF are discussed in Appendix A.

Also included in Table B-3 are 50 cm^3 chamber measurements made inside the 1.27 cm (1/2 in.) Lucite cage used to constrain the dogs during irradiation. The results are in excellent agreement to that expected. Very little change is observed in the EGF since the photon field suffers minimal .tenuation through the Lucite. In the ENF, even though no real change has occurred in the total dose rate, the hydrogen content in the Lucite has caused a slight decrease in the neutron component and a corresponding increase in the gamma component. Although the magnitude of these changes is well within the stated accuracy and precision errors, the effect demonstrated is well understood. If a 1.27 cm (1/2 in.) sheet of Lucite is placed in the beam of a 30:1 DN:DG field the neutron-to-gamma ratio will drop to 15:1. A similar dramatic change is not observed here because the original N to G ratio is about three times less than a 30:1 field. The hydrogen in the Lucite acts both as a moderator and absorber (with subsequent gamma production) of the neutrons. Consequently the neutron dose is reduced and the gamma dose increased. It is noteworthy that the FIA measurements without the Lucite cage are used in determining the TAR ratio. If the Lucite cage were not present, one would observe a slight increase in the TAR (i.e., less dose attenuation).

Tissue-to-Air Ratio Measurements

The basic TAR technique is described in Appendix A. No phantom measurements were done during the August and September irradiations. Cadaver dosimetry measurements were made on 4 dogs, and the results are listed in Tables B-4 (ENF) and B-5 (EGF). Cadaver measurements were performed in a manner similar to that employed as described in Appendix A. The only change was that no X-rays were taken as to the position of the chamber in the cadaver. Since a standard size tube was used to slide the chamber down the esophagus, the final position of the chamber was known. Care was taken to insure the spinal

column of the cadaver was straight to prevent the chamber from shifting to one side. Based on the Phase II cadaver measurements the average for the ENF was 0.508 and 0.78 for the EGF. The overall average for all cadaver measurements performed was 0.52 ENF and 0.81 EGF.

To better estimate the size of the dogs irradiated, 54 dogs were measured at the time of necropsy. Based on their measurements and the elliptical cylinder dog model originally used (described in Appendix A) the average effective diameter was 16.0 cm (6.3 in.) with a 13.6% (2g) standard deviation.

				Average		
		Reactor		FIA dose	dose rate	
Date	e	run	Dog	(Gy)	(Gy)	
A1107	18	801154	A~1	4.26	0.75	
Aug	19	80115D	B~1	5.41	0.74	
Aug	20	80115G	C-1	4.26	0.76	
Aug	21	80115K	D-1	5.41	0.75	
Aug	22	80115N	E-1	6.72	0.73	
Aug	25	80115Q	F-1	5.39	0.74	
Aug	26	80115T	G~1	3.69	0.76	
Aug	27	80115W	H-1	3.34	0.74	
Aug	28	80115Z	I-1	4.25	0.73	
Aug	29	80115AC	J-1	3.35	0.72	
Sep	15	80123A	K~1	4.25	0.75	
Sep	16	80123E	M-1	5.09	0.76	
Sep	17	80123L	N-1	6.26	0.68	
Sep	18	801230	P-1	5.41	0.75	
Sep	19	80123W	Q-1	6.85	0.76	
Sep	2 2	80123Z	R-1	8.65	0.75	
Sep	23	80123AC	S-1	6.83	0.76	
Sep	24	80123AF	T-1	8.66	0.76	
Sep	26	80123AQ	W-1	6.85	0.74	

TABLE B-1. ENHANCED GAMMA FIELD IRRADIATIONS (Tissue-to-Air Ratio = 0.84)

	Reactor		FIA dose	Average dose rate	
Date	run	Dog	(Gy)	(Gy)	
Aug 18	80115B	A-2	9,51	1.63	
Aug 18	80115C	A-3	9.55	1.62	Drug
Aug 19	80115E	8-2	12.00	1.68	
Aug 19	80115F	B-3	7.52	1.65	Drug
Aug 20	801158	C-2	9.56	1.67	
Aug 20	801151	C-3*	5.93	1.69	Drug
Aug 20	80115.1	C-4	5 91	1.70	Drug
Aug 21	801151	D-2	4.70	1.69	Drug
Aug 21	80115M	D-3	7 54	1 60	
	801150	F-2	5 92	1 56	
Aug 22	80115P	8-3	3.66	1.72	Drug
Aug 25	801158	F-2	1 67	1 68	Denie
Aug 25	801155	F-2	7 17	1.65	
Aug 26	801150	r-3	[+7] 5 00	1.61	Dana
Aug 26	801150	G-2	9.50	1 62	Drug
Aug 27	80115V	u-3	7.52	1.05	Denne
Aug 27	901158	n-2 N-3	7.50	1 61	Drug
Aug 29	001151	n-3 T 0	[+)U	1.01	
Aug 20	OUIIDAA	1-2	5.92	1.50	 D
Aug 20	00115AB	1-3	9.50	1.05	Drug
Aug 29	80115AD	J-2	7.52	1.05	Drug
Aug 29	BUIISAE	1-3	7.53	1.64	
Sep 15	80123B	K-2	4.72	1.69	
Sep 15	80123C	K-3	9.51	1.61	Drug
Sep 15	80123D	K-4	9.53	1.63	
Sep 16	80123F	M-2	7.54	1.60	
Sep 16	80123G	M-3	12.02	1.56	Drug
Sep 17	80123M	N-2	9.52	1.60	Drug
Sep 17	80123N	N-3	9.55	1.58	
Sep 18	80123R	P-2	7.49	1.62	Drug
Sep 18	801235	P-3	12.05	1.60	
Sep 19	80123X	Q-2	9.53	1.57	Drug
Sep 19	80123Y	Q-3	9.52	1.59	
Sep 22	80123AA	R-2	7.53	1.61	
Sep 22	80123AB	R-3	12.00	1.61	Drug
Sep 23	80123AD	S-2	9.41	1.59	Drug
Sep 23	80123AE	S-3	9.35	1.58	
Sep 24	80123AJ	T-2*	7.54	1.62	Drug
Sep 24	80123AK	T-3	7.53	1.60	
Sep 25	80123AL	U-1*	5.91	1.62	Drug
Sep 25	80123AM	U-2	7.52	1.59	Drug
Sep 26	80123AR	W-2	9.55	1.59	Drug
Sep 26	80123AS	W- 3	5.92	1.61	

TABLE B-2. ENHANCED NEUTRON FIELD IRRADIATIONS (Tissue-to-Air Ratio = 0.49)

* Dogs removed from sample population.

فمنطعتهم

	EGF FIA	EGF in Lucite cage	ENT FIA	ENF in Lucite cage
Total dose: cGy per kW min	3.87 ± 6.5%	3.96 ± 6.5\$	3.57 ± 9.2\$	3.55 ± 9\$
Gamma dose: cGy per kW min	3.67 ± 3.3%	3.76 ± 3.3%	0.37 ± 35%	0.42 ± 32\$
Neutron dose: cGy per kW min	0.2 ± 109%	0.2 ± 98\$	3.2 ± 9.3%	3.13 ± 9.3%
<u>Neutron dose</u> Gamma dose	0.5 ± 109%	0.05 ± 98\$	8.6 ± 38\$	7.5 ± 34%

TABLE B-3. PAIRED CHAMBER MEASUREMENTS(50 cm³)

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TABLE B-4. HIGH NEUTRON FIELD CADAVER MEASUREMENTS

			Dog			
Dose ratio	Cylinder	<u>K-1</u>	N-3	<u>R-1</u>	T-2	Ave.
Depth:FIA	0.49	0.64	0.50	0.51	0.38	0.508
N Depth:N FIA	0.28	0.45	0.30	0.31	0.20	0.32
Y Depth:Y FIA	2.1	2.3	2.2	2.3	2.0	2.2
N:Y at depth	1.1	1.72	1.15	1.20	0.85	1.26
Variation from cylinder phantom	N/A	+31\$	+2 %	+4%	-22\$	+3.7\$

TABLE B-5. ENHANCED GAMMA FIELD TAR MEASUREMENTS

	TAR	Variation from Cylinder	
Cylinder	0.84	N/A	
Dog K-1	0.87	+3.5\$	
N-3	0.72	-145	
R-1	0.81	-3.5%	
T- 2	0.73	-13\$	
Average phase II	0.78	-7.1%	
Average overall	0.81	-3.5%	

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