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**INFLUENCE OF EXPOSURE ASPECT
ON RADIATION LETHALITY IN SHEEP**

**NAVAL RADIOLOGICAL
DEFENSE LABORATORY**

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ADMINISTRATIVE INFORMATION

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ABSTRACT

The effect of exposure aspect has been studied with sheep exposed to 1 MVP X-rays. The conventional bilateral exposure $LD_{50/60}$ was 258R, while the unilateral exposure $LD_{50/60}$ was 17% higher, 303R. Other exposure aspect studies done with dogs and swine are summarized for comparison purposes.

The sheep data was evaluated according to a hematopoietic stem cell survival model developed by Bond and Robinson. In addition, the model is used to predict the effect of animal width upon stem cell survival and the LD_{50} . For unilateral exposure, the model predicts a significant effect of animal width among sheep widths ranging from 20.5 - 30.5 cm. As the model is predicated upon stem cell survival kinetics for the mouse, the possible reasons for species differences relative to the mouse data are discussed within the limits of the assumptions upon which the model is based.

SUMMARY

The Problem :

The comparison of exposure aspect is important in military, civil defense, and radiation accident situations. Exposure of personnel to penetrating radiation in the field would most likely be unilateral in nature if received from a weapon detonation or from an accidental radiation exposure. On the other hand, if it were necessary to traverse a fallout area or work in the presence of a large radiation field, the exposure would be omni-directional. The present study was undertaken to evaluate the difference in radiation response for sheep exposed bilaterally and for those irradiated from one side only, using 1 MVp X-rays.

The Findings:

Previous studies with dogs and swine showed unilateral exposure $LD_{50}'_s$ to be 20-48% greater than those resulting from conventional bilateral exposure. The present study with sheep found the unilateral exposure $LD_{50/60}$ to be 17% greater than that for the bilateral configuration, 303 R vs. 258 R. The mean survival times for both sheep groups were practically identical. All decedents experienced weight loss after irradiation, while survivors and controls maintained or slightly increased

their body weight.

A stem cell survival model based on depth-dose distribution, as formulated by Bond and Robinson, was used to evaluate the mortality responses for the two exposure configurations used in the sheep experiments. The calculated stem cell survival at the LD₅₀ level, for both groups did not appear to be different. This is in agreement with the basic assumption of the model, that survival is dependent upon a minimal level of stem cells. If this is the case, the unilateral and bilateral dose depositions should yield the same total survival of stem cells at the LD₅₀ level.

Further computations showed that calculating responses with sheep widths from 20.5 - 30.5 cm, resulted in total stem cell survivals differing by almost a factor of 2. This indicated the protection afforded the contralateral side of the animal during unilateral exposure. The differences among the three large animals as compared to the mouse, regarding calculated stem cell survival are discussed from the standpoint of the various radiosensitivities and/or cellular kinetics which could account for the species variations. With the sheep LD₅₀ being one of the lowest mammalian LD_{50's} and the sheep having body diameters quite similar to those of man, bone marrow studies with this species

following non-uniform irradiation might lend themselves to operational requirements for predicting human response under similar exposure conditions .

INTRODUCTION

The radiation experiments conducted with large domestic animals at this laboratory have included whole-body exposures to both 1 MVp X-rays and gamma radiation from ^{60}Co . Most experiments using whole-body exposures are designed around the concept of delivering as uniform a dose as possible to the mass of the animal. Thus, with the larger animals, a bilateral method is commonly used. The body size of a man is indeed large enough that the direction and energy of the imparting radiation could influence the physiological responses under study.

The comparison of exposure aspect is important in military, civil defense, and radiation accident situations. Exposure of personnel to penetrating radiation in the field would most likely be unilateral in nature if received from a weapon detonation or following a radiation accident. On the other hand, if it were necessary to traverse a fallout area or work in the presence of a large radiation field, the exposure would be omni-directional. The present study was undertaken to evaluate the difference in radiation response between sheep exposed bilaterally and those irradiated from one side only using 1 MVp X-rays. Comparisons were made between the $\text{LD}_{50/60}$'s, mean survival times, and changes in body weight after exposure.

MATERIALS AND METHODS

The sheep for this study were Western range-bred Columbia-Rambouillet castrated male yearlings. Their body weight averaged 34.5 kg, shoulder height 67 cm, and body width 21 cm.

After receipt at the NRDL farm, the sheep were given three prophylactic doses of sodium sulfamethazine and two administrations of anthelmintic. The sheep were retained in quarantine for a minimum of 14 days under veterinary supervision. The animals grazed on pasture with supplemental alfalfa hay daily. Trace mineral salt block and water were available ad libitum.

During the experimental phase, the sheep were transported to holding pens adjacent to the laboratory and held for a minimum of 14 days prior to irradiation. These pens are concrete with adequate shelter for 35 sheep per pen. Alfalfa hay and commercial pelleted supplement was fed daily, with salt block and water available at all times. The animals remained in these pens for the 60-day observation period following irradiation.

Body weights and dimensions were measured prior to irradiation and weights recorded weekly and at death after exposure. Due to the nature of this experiment, the animals were selected according to their

body dimensions, thereby allowing as homogeneous a population as possible for each exposure group.

Irradiation Facility:

The radiation source for this study was the radial beam of a GE Resotron 1000 1 MVp X-ray machine. The machine is operated at 1000 kilovolts at 3 milliamperes. The beam has an effective energy of 330 keV and the half-value layer is 2 mm of lead. All filtration is inherent, being 4 mm H₂O and 5.4 mm copper.

Exposures were made with the centerline of the animal on an isodose curve 200 cm from the target. Four sheep were exposed simultaneously at an exposure rate of 7.6 R/min (midline air) as measured and monitored by a Phillips dosimeter. Unless otherwise specified, all exposures and exposure rates will be expressed as roentgens (R) measured in air at a location corresponding to the animals midline.

The animals were held in exposure boxes constructed of 1/4" plywood with 2" x 4" supports. 1/4" plywood spacers were positioned behind the animals to minimize sideward movement during the exposures.

All unilateral exposures were made with the animal's left side facing the beam. The bilateral exposures were done in the conventional manner, i.e., one-half of the exposure given to one side, the animals rotated 180° and the remainder of the exposure delivered to the other side.

Dosimetry:

In vivo and cadaver dosimetry was done using lithium-flouride thermoluminescent powder.^a The in vivo study consisted of three 40 mg samples attached to each flank of 20 sheep, half of which were exposed bilaterally and the other half unilaterally. The dosimeter location used was 20.5 cm ventral to the spinal midline (immediately in front of the ischial crest) as measured along the body contour. This location was chosen to minimize possible loss of the dosimeter packet due to the animal's rubbing against the exposure box.

The cadaver dosimetry consisted of one sheep with a total of eighteen 58 mg LiF packets attached to or inside the sheep. Eight dosimeters circumscribed the sheep at the sternum and eight more circumscribed the cadaver around the abdomen just anterior to the ischial crest. Internally, a two-dosimeter packet was attached just ventral to the lumbar vertebrae.

Data Analysis:

The median lethal doses (LD_{50} 's) were computed from a maximum likelihood regression of the normal equivalent deviate (probit minus 5.0)

a. Harshaw Chemical Co., Cleveland, Ohio

of percent mortality on the radiation exposure in roentgens (R). These were calculated using an NRDL program, based on probit analysis (1) as adopted by Aitchison and Brown (2), using a Univac 1108 computer.

RESULTS

Lethality and days of death for both bilateral and unilateral exposures are listed in Table I. The $LD_{50/60}$ for the bilateral exposures is 258 R while that for the unilateral exposures is 303 R. The data used in determining the bilateral LD_{50} are a combination of our original mortality data (3), additional animals at 177 R (4) and two subsequent exposures, 250 and 300 R, to verify that the radiation response of this group of sheep is comparable to our previous sheep data (Figure 1). The mean survival times for both bilaterally and unilaterally exposed decedents is 22 days.

Routine necropsies were performed on 25% of the decedents for observation of gross lesions. The lesions seen were typical of those reported in other lethally irradiated sheep, i. e., petechial and ecchymotic hemorrhages throughout the thoracic and abdominal organs. No gross distinction could be made between those irradiated bilaterally or unilaterally except for the leftside alopecia that was noted in approximately 30% of the unilaterally irradiated sheep. There was no observed relationship between unilateral exposure over the dose range

TABLE I

MORTALITY DATA FOR LD 50/60 DETERMINATIONS OF
UNILATERALLY AND BILATERALLY X-IRRADIATED SHEEP

UNILATERAL EXPOSURE

<u>Exposure (R)</u>	<u>Mortality</u>	<u>Days of Death</u>
250	2/10	22, 36
300	4/10	24x3, 26
375	9/10	18x2, 19, 20, 21, 22x2, 24, 25
400	10/10	19x2, 21x2, 22x2, 23x3, 24

$$LD_{50/60} = 303 \text{ R } (270 - 331)^a$$

BILATERAL EXPOSURE

<u>Exposure (R)</u>	<u>Mortality</u>	<u>Days of Death</u>
177	2/48	23, 31
198	3/15	19, 28, 46
243	4/15	8, 16, 20, 27
250	4/10	20, 24, 25, 28
300	8/10	18, 19x2, 20, 23 24, 25, 43
325	19/20	8, 16x2, 17, 18x4, 19x2, 20x2, 21x3, 22, 26, 31, 33

$$LD_{50/60} = 258 \text{ R } (243 - 276)^a$$

a) 95% confidence intervals

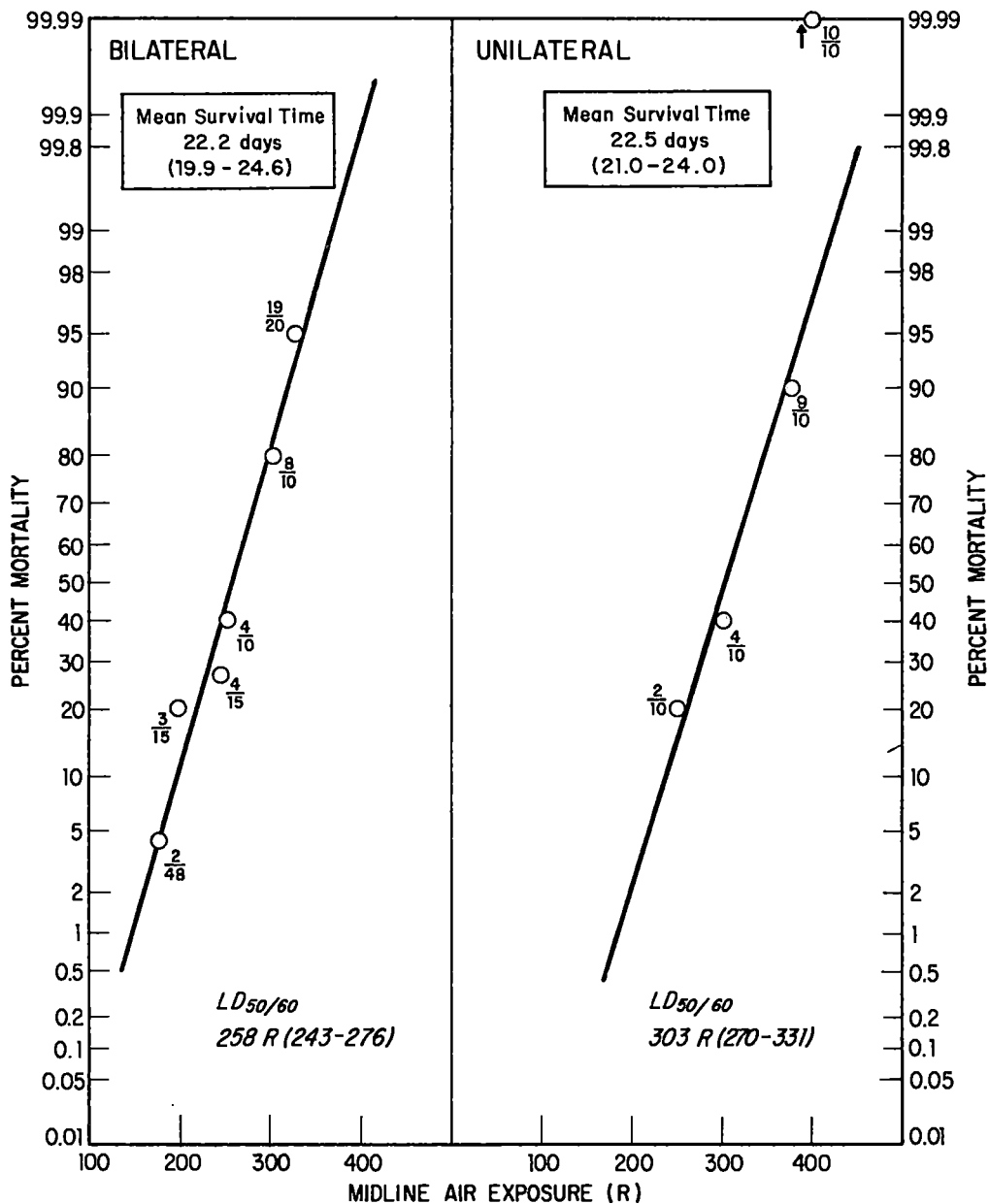


Fig. 1. Dose-response curves for bilateral and unilateral X-irradiation of sheep. The fraction by each point represents the number dying over the number exposed. The 95% confidence intervals are enclosed in parentheses.

for this study, and degree of alopecia, as it was seen in sheep from all four exposure groups. The alopecia was complete and remarkably well delineated along the midline, both dorsally and ventrally, and involved the trunk, neck, and limbs to an equal degree.

Body weights were measured prior to and at weekly intervals following irradiation. All but three of the decedents were weighed shortly after death. The only group showing any significant weight changes were the decedents. The 35 decedents weighed shortly after death had a mean weight of 30.3 kg (29.1-31.6)^a, as compared to their mean pre-irradiation weight of 34.1 kg (33.2-34.8)^a.

The in vivo and cadaver dosimetry measurements agreed quite well with the phantom measurements previously reported by Menkes (5). These comparisons are shown in Figure 2. For cadaver comparisons, only the entrance, exit, and midline measurements are included. The entrance measurements for the in vivo and cadaver studies of 129 and 138% of midline air values, respectively, are in reasonable agreement with the phantom curve. The exit measurements for the sheep do not vary significantly from what would be expected based on the curve

a. 95% confidence intervals

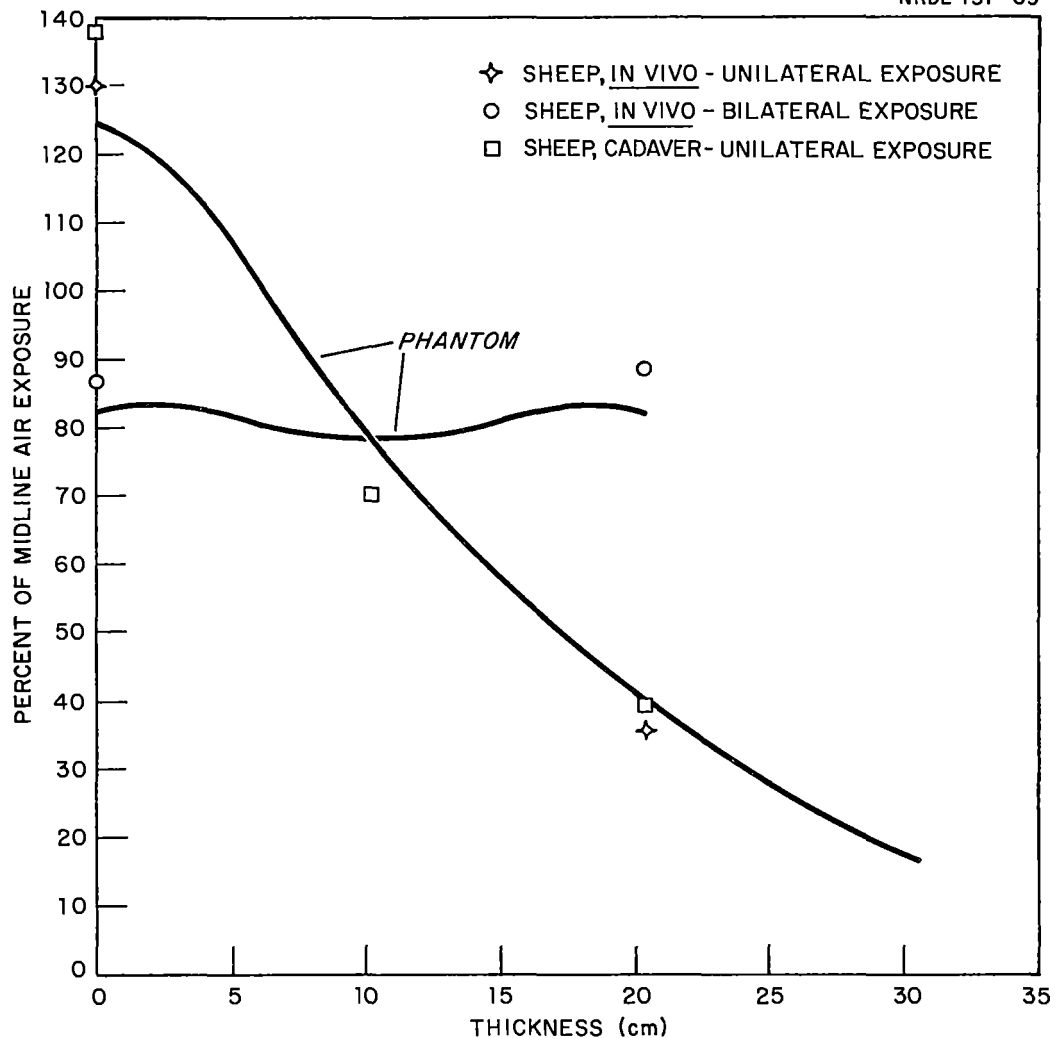


Fig. 2. Depth-dose determinations for 1 MVp X-rays. The phantom^a was exposed at a distance of 2.5 meters (target to midline) while the in vivo and cadaver sheep were exposed at a distance (TML) of 2.0 meters. The phantom bilateral curve was derived from the unilateral exposure data. The data are presented as percent of midline - air with no inverse-square effect corrections.

- a. The phantom was a 30.5 cm diameter masonite cylinder with Landsverk ionization chambers positioned 3.81 cm apart.

of the thicker phantom material. The measurements obtained from the ten bilaterally exposed sheep resulted in the averages of the two sides agreeing within 3%, with a maximum difference of 10% on any individual animal. Visual extrapolation of the phantom bilateral depth-dose curve between these two points indicates a midline tissue dose of approximately 80-85% of midline air exposure. The one dosimeter packet placed at the cadaver abdominal midline indicated a midline tissue dose of 70% which is in reasonable agreement with the phantom measurements. The phantom exposures from this laboratory are in good agreement with other "large animal" phantom studies done with various photon energies (97keV - 1.25 MeV). Detailed discussions of exposure geometries and dose distribution patterns are contained in the report by Bond et al (6).

The sheep used throughout the radiation studies at this laboratory have varied between 32-57 kg. Observations from earlier studies have shown no patterns indicating that smaller sheep tend to experience greater mortality than larger animals. The 20 sheep exposed bilaterally during the present study, although averaging 31.8 kg, responded as predicted by the established LD₅₀ curve derived from heavier animals. This variation in animal size would indicate different depth dose patterns; thus, an attempt has been made to determine how size might show some effect on the LD₅₀. A comparison of the current in vivo dosimetry

to that with the masonite phantom indicate extrapolation to varying sheep thicknesses should yield good approximations of actual tissue depth-doses. Table II lists depth-dose extrapolations for sheep widths from 20.5-30.5 cm. The resulting midline tissue values range from 81 to 58% as the thickness increases. Based on a plot of sheep widths versus body-weight, Figure 3, it is possible to obtain a reasonable estimate of body width of 18-27 cm for animals ranging in weight between 32-57 kg, the weight range of animals used in this study. Therefore, midline tissue dose estimates would most probably range between 81 and 65% of midline air values, for bilateral exposure to 1 MVp X-rays. The average dose concept can be used to point out that slight differences in depth-doses due to animal size are within the limits of the normal variability encountered in LD₅₀ determinations. Computation of the average doses sustained by a 24 cm wide sheep, exposed to the upper and lower confidence limits of the bilateral LD₅₀, Table II, indicate compatibility with the doses received by the individual widths from 20.5 to 28 cm. The concept of average dose would be meaningless for unilateral exposure, as cellular damage is much higher on the side closest to the beam, while the contralateral side receives less dose due to inverse square falloff and tissue attenuation and absorption by the remainder of the body mass.

The comparisons made in this study logically led to their evaluation

TABLE II

Sheep Depth-Dose Calculations - Based on Phantom Exposure to 1 MVp X-rays^a

UNILATERAL EXPOSURE - AS % OF MIDLINE AIR^b

Dose Distribution

<u>Sheep Width (cm)</u>	<u>Entrance</u>	<u>Midline</u>	<u>Exit</u>
20.5	124.4	81	41
23	124.4	75.7	33.5
24	124.4	72	30
25.5	124.4	69	26.75
28	124.4	64	23.6
30.5	124.4	58.5	16.6

BILATERAL EXPOSURE - AS % OF MIDLINE AIR^b

Dose Distribution

<u>Sheep Width (cm)</u>	<u>Entrance</u>	<u>Midline</u>	<u>Exit</u>	<u>Average</u>	<u>Average dose^c as received at LD₅₀ Level</u>
20.5	82.7	81	82.7	82	205
23	79	75.7	79	78	195
24	77.2	72	77.2	75	188 (177-201)
25.5	75.6	69	75.6	73	183
28	74	64	74	71	178
30.5	70.5	58.5	70.5	67	168

a) Menkes (5)

b) As extrapolated from phantom curve - see Figure 2

c) Computed by using 258 R (midline air exposure)
X 0.97 (R to rad conversion) x average % dose
for each width.

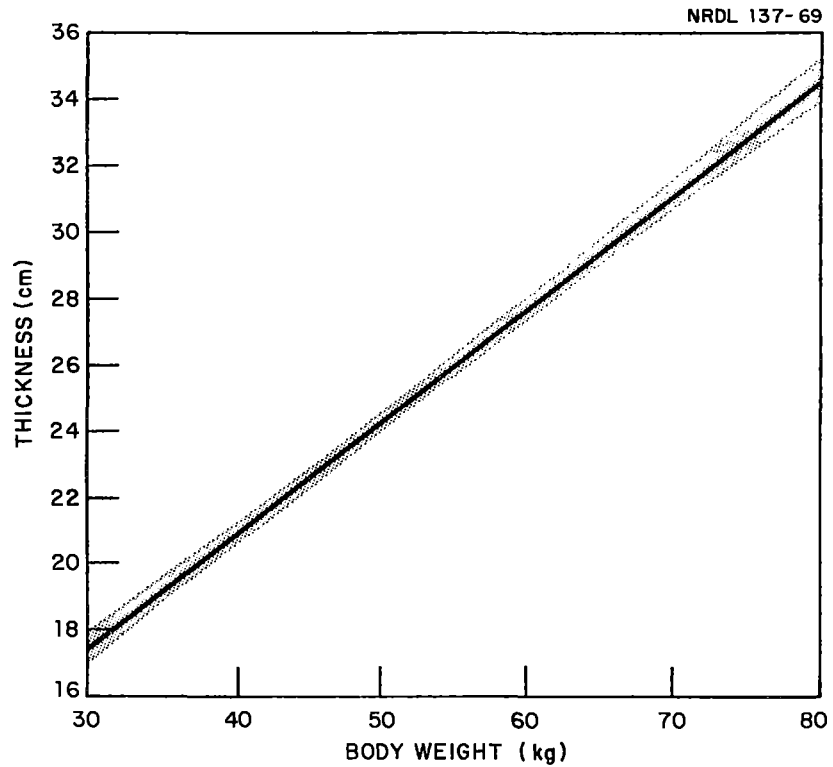


Fig. 3. The relationship between body width and body weight for sheep, as determined by least-squares regression analysis. Body widths were measured at the widest portion of the trunk, disregarding wool growth. The shaded area represents the 95% confidence intervals of the computed line.

by the dose distribution model proposed by Bond and Robinson (7). Briefly, their model consists of relating predicted bone marrow doses to dose-survival curves for bone marrow stem cells. Survival from midlethal whole-body irradiation is primarily dependent upon maintenance of a minimal level of stem cells capable of repopulating the bone marrow and thus the peripheral blood elements (7). The model has several basic assumptions: (1) stem cells are uniformly distributed throughout all hematopoietically active bone marrow; (2) all stem cells, regardless of location, have the same dose-effect relationships; (3) the surviving stem cells will furnish mature peripheral blood elements at the same rate, and (4) active marrow distribution throughout the skeletal system for large animals resembles that estimated for man. The surviving fraction of stem cells is then calculated to ascertain the relative number of surviving stem cells for each 1/3 body segment.

Calculations of stem cell survival at the measured $LD_{50}'s$, 303 R unilateral and 258 R bilateral, were made for sheep widths of 20.5-30.5 cm. The model predicts that, for animals of equal width, the stem cell survival should be the same at the measured $LD_{50}'s$. Tables III and IV and Figure 4 show the results of these calculations. Using the measured LD_{50} values for all widths, the following indications were noted: for 25.5, 28 and 30.5 cm widths, a slightly greater

TABLE III

Calculated Stem Cell Survival for Varied Animal Widths Exposed Unilaterally to X-radiation^a

Animal Width (cm)	Body Segment	Dose ^b (rad)	S/S ₀ ^c	Relative Number of Stem Cells Surviving ^{d,e}	Average Nonuniform Dose ^f (rad)	Uniform Dose to Yield Same Stem Cell Survival	DEF ^h	1/DEF (%)	
<u>Sheep</u> 20.5	P (Proximal)	366	.03165	1.29	15.98	262	212	.809	123.6
	M (Middle)	238	.12225	3.79					
	D (Distal)	121	.41925	10.90					
23	P	366	.03165	1.29	19.61	251	193	.769	130.0
	M	223	.14310	4.44					
	D	98	.53400	13.88					
24	P	366	.03165	1.29	21.71	246	184	.748	133.7
	M	212	.16065	4.98					
	D	88	.59400	15.44					
25.5	P	366	.03165	1.29	23.76	241	175	.726	137.7
	M	203	.17685	5.48					
	D	79	.75355	16.99					
28	P	366	.03165	1.29	26.59	233	164	.704	142.0
	M	188	.20700	6.42					
	D	69	.72600	18.88					
30.5	P	366	.03165	1.29	32.18	223	146	.655	152.7
	M	172	.24525	7.60					
	D	49	.89580	23.29					
<u>Swine</u> 27.9	P	563	.00398	.17	12.45	369	236	.640	156.3
	M	302	.06165	1.94					
	D	126	.39780	10.34					
<u>Dog</u> 14	P	469	.01073	.46	7.82	353	280	.793	126.1
	M	339	.04215	1.31					
	D	177	.23250	6.05					

a Based on Model proposed by Bond and Robinson (7).

b Using % distribution of dose as listed in Table II x 294 rad. Exposure to the unilateral LD_{50/60} of 303 R (midline air) x 0.97 = 294 rad. For swine and dog data see Table VI.

c $S/S_0 = E \times e^{-D/D_0}$, where E = extrapolation number of 1.5, D = dose (rad) to each body segment and D₀ = 95 rad.

d The model uses the following bone marrow distribution for unilateral exposure:

Proximal third 43%
Middle third 31
Distal third 26
100% of bone marrow

e S/S₀ x relative number of stem cells for each body segment.

f Average nonuniform dose equals the sum of each body segment dose times the relative number of stem cells for that segment.

g Solve for D: $S/S_0 = E \times e^{-D/D_0}$

h Distribution effectiveness factor (DEF): $DEF = \frac{\text{equivalent uniform dose}}{\text{average nonuniform dose}}$

TABLE IV

Calculated Stem Cell Survival for Varied Animal Widths Exposed Bilaterally to X-radiation^a

Animal Width (cm)	Body Segment	Dose ^b (rad)	S/S ₀ ^c	Relative Number of Stem Cells Surviving ^{d,e}	
<u>Sheep</u>					
20.5	(E)Entrance	207	.16950	5.85	17.18
	(M)Middle	203	.17685	5.48	
	(E)Entrance	207	.16950	5.85	
23	E	198	.18615	6.42	19.19
	M	189	.20475	6.35	
	E	198	.18615	6.42	
24	E	193	.19650	6.78	20.54
	M	180	.22500	6.98	
	E	193	.19650	6.78	
25.5	E	189	.20475	7.06	21.63
	M	173	.24225	7.51	
	E	189	.20475	7.06	
28	E	185	.21225	7.32	23.31
	M	160	.27975	8.67	
	E	185	.21225	7.32	
30.5	E	176	.23475	8.10	26.18
	M	146	.32205	9.98	
	E	176	.23475	8.10	
<u>Swine</u>					
27.9	E	271	.08655	2.99	9.88
	M	235	.12615	3.91	
	E	271	.08655	2.99	
<u>Dog</u>					
14	E	270	.08715	3.01	8.43
	M	281	.07785	2.41	
	E	270	.08715	3.01	

a Based on model proposed by Bond and Robinson (7).

b Using % distribution of dose as listed in Table II x 250 rad. Exposure to the bilateral LD_{50/60} of 258 R (midline air) x 0.97 = 250 rad. For swine and dog data, see Table VI.

c $S/S_0 = E \times e^{-D/D_0}$, where E = extrapolation number of 1.5, D = dose (rad) to each body segment and D₀ = 95 rad.

d The model uses the following bone marrow distribution for bilateral exposure:

Entrance/exit	34.5%
Middle third	31.0
Entrance/exit	<u>34.5</u>
	100.0% of bone marrow

e S/S₀ x relative number of stem cells for each body segment.

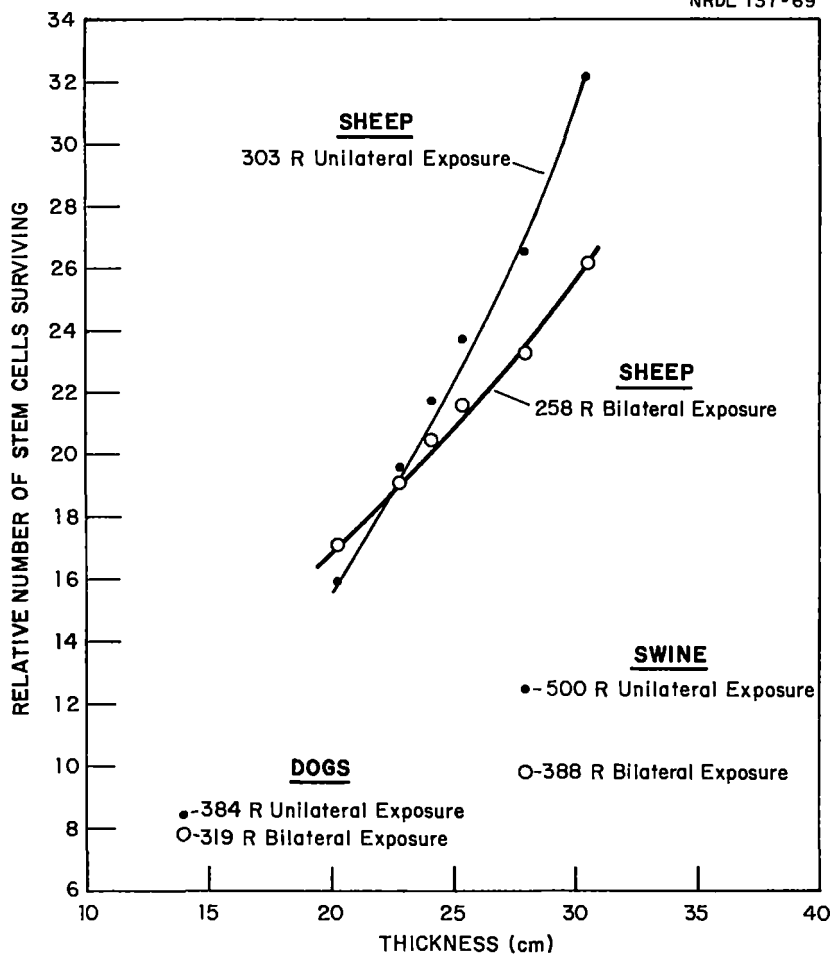


Fig. 4. Stem cell survival as a function of radiation-depth doses. Based on exposure at the LD_{50} level for unilateral and bilateral configurations. Data points were extracted from calculations presented in Tables III and IV.

stem cell survival was shown for unilateral exposure than that for bilateral exposure; 23 and 24 cm widths, the stem cell survival was essentially equal for both configurations; the 20.5 cm width calculations showed a slightly lower stem cell survival for unilateral exposure. Due to the number of assumptions and generalizations upon which the model is based, it is doubtful that the differences between the sheep calculations at each animal thickness are significant, except perhaps for the widest animals. The more rapid increase in relative stem cell survival for unilateral exposure with increasing thickness indicates the protection afforded the contralateral side of the animal.

Further computations based on Bond and Robinson's hypothesis include calculation of the "distribution effectiveness factors" (DEF's). The averaged nonuniform dose was calculated for 20.5-30.5 cm sheep (Table III). The "relative stem cell survival percentages" were then used to derive the uniform dose (bilateral exposure) which would produce the same percent survival for each animal thickness. Thus, the DEF serves to numerically compare the decreased effectiveness of unilateral exposure to that of the uniform bilateral exposure. The lower DEF's associated with the wider sheep point out the greater increase in nonuniformity of dose distribution accompanying unilateral exposure to that seen with bilateral exposure. Taking the reciprocal

of the DEF restates the dose-distribution inequities as the expected ratio by which the unilateral exposure must be increased above the bilateral exposure to produce equal morality. The DEF (and its reciprocal) for 20.5 cm wide sheep are in reasonably good agreement with the measured LD_{50} values. The sheep bilateral exposure $LD_{50/60}$ was determined by exposure of animals of varied widths, with no apparent effects upon morality or survival times due to body size. However, the sheep exposed unilaterally were quite uniform in size and averaged 20.3 cm in width. The question naturally arises as to what the unilateral exposure $LD_{50/60}$ might be for sheep averaging 30.5 cm in width. The calculation of the DEF requires a priori knowledge of the unilateral depth doses from which the equivalent uniform bilateral exposure dose is calculated. To make predictions for unilateral responses, baseline uniform or bilateral exposure data must be used. Thus, the calculated stem cell values for a 24 cm wide sheep were used, to be representative of bilaterally exposed animals. The assumption was made, for this mathematical treatment, that a relative number of 20.5 surviving stem cells was the critical minimum at the LD_{50} level for sheep. Then by trial and error, the projected unilateral dose can be calculated which will decrease the stem cell survival to the same level. The calculations (Tables III and IV and Figure 4) indicated a greater effect of body

thickness with unilateral exposure, thus projected unilateral exposure doses were calculated for 20.5 cm, 24 cm and 30.5 cm widths to indicate the maximum possible spread. These calculations are shown in Table V. Similar unilateral and bilateral exposure data for dogs (8) and swine (15) are evaluated in Tables III and IV and Figure 4. The doses used for the calculations were those reported by the authors. The calculated stem cell survival percentages for the dog and swine studies were practically identical to those cited by Bond and Robinson (7). Exposure and mortality data for all three species are listed in Table VI.

DISCUSSION

Studies of the effect of exposure aspect on the radiation response of large animals have several important ramifications. Depth-dose patterns under different conditions of exposure geometry and differences in the energy deposition in target organs in large animals and man would be expected to influence morality, hematological responses, and survival time. Operational requirements for the military and civil defense agencies involve hazard predictions and evaluations of personnel responses in nuclear environments involving a variety of exposure conditions. Therefore, there is a need to clarify these effects for operational use.

Several earlier studies have been conducted with large animals to compare responses produced by bilateral X-irradiation with unilateral

TABLE V

Calculated LD₅₀ Values, Using 20.5 Relative Number of Surviving Stem Cells as Critical Minimum Level at the LD₅₀^a

<u>UNILATERAL EXPOSURE</u>				<u>BILATERAL EXPOSURE</u>	
Sheep Width (cm)	Body Segment	Dose (rad)	Relative Number of Stem Cells Surviving	Midline Air Exposure ^b (R)	Midline Air Exposure ^c (R)
20.5	P (Proximal)	332	1.94	20.4	275
	M (Middle)	216	6.05		
	D (Distal)	109	12.38		
24	P	380	1.21	20.2	315
	M	220	4.59		
	D	92	14.43		
30.5	P	573	0.17	20.2	475
	M	270	2.70		
	D	77	17.37		

a See Table III for explanation and format of calculations.

b Exposure (R) determined by trial and error to yield ~20.5 relative number of stem cells surviving.

c The 20.5 and 30.5 cm values based on the 24 cm data; ie $258 \text{ R} \times 0.97 \times 0.755 = 189 \text{ rad}$. 189 rad yields 20.5 relative number of surviving stem cells, thus solve for R using the appropriate average dose (Table II) for the two widths.

TABLE VI

Selected Mortality and Exposure Data for Three Species - Influence of Exposure Aspect

Species	Radiation Source	Effective Energy	Exposure Rate (R/min)	Manner of Exposure	Average Body Weight ^a (kg)	Average Body Width ^a (cm)	LD ₅₀ ^b (R)	Entrance Dose	Midline Dose	Exit Dose	Reference
Dog	1 MVp X-ray	540 keV	8 - 10	Bilateral	7 - 13	14	319	269	280	269	8
	1 MVp X-ray	540 keV	8 - 10	Unilateral	7 - 13	14	384	469	339	177	8
	1 MVp X-ray	450 keV	55	Bilateral	7 - 15	-	310	-	250	-	9, 10
	1 MVp X-ray	600-650 keV	10	Dorsal	6 - 23	-	460	480	357	196	6, 10
	⁶⁰ Co	1.25 MeV	6	Bilateral	8 - 19	-	376	-	325	-	11
	⁶⁰ Co	1.0 MeV	15	Bilateral	10.55 (6.65-16.15)	13.5 (11-17)	323	273	285 ^c	273	12
Swine	1 MVp X-ray	540 keV	9 - 10	Bilateral	102-113	29-31	399	325	263	325	13
	⁶⁰ Co	1.25 MeV	11.8	Quadrilateral	91-113	27	382	263	226	263	14
	2 MVp X-ray	450 keV	15	Bilateral	61.7 (51.3-73)	28	339	271	234	271	15, 16
	2 MVp X-ray	450 keV	15	Unilateral	61.7 (51.3-73)	28	437	563	302	126	15
	1 MVp X-ray	370 keV	30	Bilateral	54-109	28	423	373	264	373	17
	⁶⁰ Co	1.25 MeV	18-29	4 π	34	20 x 25	335	273	211	273	18
	⁶⁰ Co	1.25 MeV	18-29	4 π	68	26 x 33	393	301	221	301	18
Sheep	1 MVp X-ray	330 keV	7.5	Bilateral	34-57	20-25	258	178	145	178	3
	1 MVp X-ray	330 keV	7.5	Unilateral	35	21	303	See Table III			Present Study
	⁶⁰ Co	1.25 MeV	11	Quadrilateral	45-59	27	237	165	140	165	Present Study
	250 kVp X-ray	97 keV	7.5	Bilateral	34-50	30 (27-33)	389	-	238	-	19
	⁶⁰ Co	1.25 MeV	11	Bilateral	46 32-57	-	367 ^d	259	231	259	20, 21

a The average or range cited by the authors. Figures in parentheses are the cited range.

b The exposure as listed, or calculated from the authors data, as measured at midline air of the exposure volume.

c 258 rad is the average absorbed dose for the average whole body diameter.

d The differences observed in ⁶⁰Co-irradiated sheep LD₅₀'s between NRDL and AFWL are currently being studied.

X-irradiation. Pertinent data listed in Table VI indicate that in dogs and swine, unilateral exposure was less effective in producing mortality than the more conventional bilateral configuration, i.e., the unilateral LD_{50} 's, were higher than the bilateral by 20 - 48%. The LD_{50} difference observed in the present experiments with sheep was somewhat less, 17%, than with the other species, however, the results with all the species point to the significance of exposure aspect when measuring a physiological response following whole-body irradiation.

When comparing the effects of bilateral and unilateral or other types of nonuniform exposure in large animals, the dose distribution through the animals appears to be the principle determinant of biological effect. At X-ray energies below 250 kVp there is a marked effect on the LD_{50} of dogs. Alpen reported that the LD_{50} for 100 kVp X-rays was 664 R as compared with a value of 281 R for 250 kVp X-rays (22). In this case the LD_{50} difference is undoubtedly attributable to different depth-dose relationships rather than to photon energy per se. This is in contrast to the comparisons in dogs and other species involving effective photon energies over the range of 97-1250 keV, since photon studies over this range of energies show quite similar depth-dose relationships.

Significant differences between bilateral and unilateral LD₅₀ values have been shown in dogs and swine, and the present sheep data strongly indicate a difference, as the 95% confidence intervals overlap only slightly. The influence of exposure aspect is thought to be a function of the ability of the contralateral side of the unilaterally exposed animal to maintain sufficient levels of hematopoietic function. Survival following uniform or nonuniform whole-body irradiation is primarily dependent upon survival of a minimal level of stem cells which are capable of repopulating the bone marrow and thus the peripheral blood elements (7). Bond and Robinson have proposed a stem cell model with which a dose distribution-effectiveness factor may be computed for the purpose of comparing or predicting the hazards of uniform and nonuniform exposure of X- or gamma radiation (7)^a. In brief, their model concerns the prediction of total stem cell survival in animals based on the following considerations: 1) depth-dose relationships 2) stem cell distribution throughout the animals, and 3) radiation sensitivity (D₀) of the stem cell. The present LD₅₀ data have been evaluated, using this model, and the

a. The distinction is made for photon exposures, as studies with dogs and sheep indicated no significant differences in LD₅₀'s between unilateral and bilateral exposures to reactor radiations (8,23).

results show good agreement between the measured difference in unilateral and bilateral LD₅₀ and the difference in LD₅₀ predicted by the model.

As stated above, the model predicts the same relative number of stem cells should survive at the measured unilateral and bilateral LD₅₀'s and, using the present data, the agreement was within 3% of surviving stem cells for sheep between 20.5 and 28 cm in diameter (Tables III and IV). In the case of the larger 30.5 cm sheep, the difference in surviving stem cells was 6% (26 vs. 32) which means that in larger sheep the difference between the unilateral and bilateral LD₅₀ should be more than the 45 R observed in the present experiments in which smaller sheep were used. The model predicts that the difference between the unilateral and bilateral LD₅₀ should increase as the width (diameter) of the animal increases. For 20.5 cm wide sheep the unilateral LD₅₀ should exceed the bilateral by 24% and for 30.5 cm wide sheep the predicted increment is 53% (Table III). The reason is that with increasing diameter the distal 1/3 of the animal receives an increasingly lower dose in the case of unilateral exposure. The present calculations show that for all diameters considered, the distal 1/3 of the unilaterally exposed sheep contributes 68 - 72% of all surviving stem cells in the sheep. Moreover, the doses sustained by the distal 1/3 are in a range (49 - 121 rad) where

relatively small differences in dose produce relatively large changes in the surviving fraction of stem cells due to exponential killing kinetics.^a

Using the model, the effect of diameters on both bilateral and unilateral LD₅₀'s has been computed (Table V). The calculations predict an increase in bilateral LD₅₀ of 61 R as the diameter increases from 20.5 to 30.5 cm. As mentioned above, there were no indications that the dose responses were influenced by animal thickness in previous bilateral exposure studies. In addition, a calculated difference of 50 - 60 R could probably not be measured using LD₅₀ as the endpoint. For 20.5 cm width, the projected unilateral dose was lower than the observed value, being approximately 275 R. As no significant difference was actually observed, the lower projection indicates that for this width, the dose penetration is sufficient to render sizeable damage to the contralateral side. For the 24 cm width, the projected unilateral dose is only slightly higher than the experimental value. But the

a. Increasing the dose from 100 to 125 R decreases the surviving fraction from 0.523 to 0.402, whereas, increasing the dose from 325 to 350 R decreases the surviving fraction from 0.049 to 0.038. Those calculations are based on the use of 95 rad as the D₀, with an extrapolation number of 1.5.

30.5 cm width figures indicate a sizable difference, i.e., approximately 475 R for a unilateral exposure $LD_{50/60}$, 84% greater than the bilateral exposure $LD_{50/60}$. Until unilateral exposure of very wide sheep could be accomplished, this point obviously remains only theoretical.

Up to this point, all the calculations and predictions for the three large animal species have been based on the stem cell kinetics observed for the mouse. The model has used a D_0 of 95 rad and an extrapolation number of 1.5, as derived from mouse spleen colony-forming unit studies. A review of similar mouse studies by Robinson^a and data reported by Ainsworth et al (24, 25), have established the surviving fraction of stem cells in the mouse to be of the order of $1.5 - 2.0 \times 10^{-4}$ with extrapolation numbers of 1.5 - 2.0 at the LD_{50} level. The data for the large animals have predicted surviving fractions of approximately $7 - 25 \times 10^{-2}$ at the LD_{50} levels, two orders of magnitude greater than the mouse. On the other hand, the LD_{50} values for the large animals are lower than those for the mouse by

- a. C. V. Robinson, Analysis in Terms of Cellular Parameters of Interanimal Variation of Hemopoietic Radioresistance, presented at Joint U.S. - Japanese Seminar "Comparative Cellular and Species Radiosensitivity in Animals," May 20-23, 1968, Kyoto, Japan.

approximately a factor of two. If a direct correlation exists between stem cell sensitivity and the LD_{50} , then the differences among the species might be either different total number of stem cells surviving at the LD_{50} or the same number of surviving stem cells for all species but varying stem cell radiosensitivity, as reflected in the D_0 . As stem cell pool sizes are not known for the large animals, an interspecies comparison might be made by equating the LD_{50} value and stem cell sensitivity for each large animal species to the surviving fraction of stem cells for the mouse. Using the formula $1.5 - 2.0 \times 10^{-4} = Ee^{-D/D_0}$, where E equals 1.5 or 2.0 and D equals the conventional LD_{50} , the D_0 for each species can be calculated. The resulting D_0 's for the three species are as follows: swine, ~ 53 rad; dog ~ 34 rad, and sheep, ~ 27 rad. These values are considerably lower than the 95 rad dose used in the mouse calculations. The possible differences among the species regarding the stem cell theory involving mid-lethal radiation doses are numerous. Among these are bone marrow activity and recuperative ability after irradiation, stem cell pool size, cellular generation times and stem cell radiosensitivity.

The lack of comprehensive bone marrow distribution and kinetics studies with the large domestic animals preclude more specific support

and evaluation of Bond and Robinson's model. Making certain assumptions and generalizations, it has been attempted to correlate existing large animal exposure aspect studies with the bone marrow kinetics of the irradiated mouse. Based on LD₅₀ values and the calculations presented above, it appears that either the sheep stem cells might be one of the most radiosensitive mammalian stem cells, or have radiation-induced maturation and recovery kinetics quite different from other species.

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13. ABSTRACT The effect of exposure aspect has been studied with sheep exposed to 1 MVP X-rays. The conventional bilateral exposure LD _{50/60} was 258R, while the unilateral exposure LD _{50/60} was 17% higher, 303R. Other exposure aspect studies done with dogs and swine are summarized for comparison purposes. The sheep data was evaluated according to a hematopoietic stem cell survival model developed by Bond and Robinson. In addition, the model is used to predict the effect of animal width upon stem cell survival and the LD ₅₀ . For unilateral exposure, the model predicts a significant effect of animal width among sheep widths ranging from 20.5 - 30.5 cm. As the model is predicated upon stem cell survival kinetics for the mouse, the possible reasons for species differences relative to the mouse data are discussed within the limits of the assumptions upon which the model is based.			

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