

Active Bone Marrow Dose Related to Hematological Changes in Whole Body and Partial Body ⁶⁰Co Gamma Radiation Exposures'

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INTRODUCTION

~~The depletion of formed circulating blood elements following exposure to ionizing radiation has been known for some time. Furthermore, It has long been recognized that uniform whole-body exposure is more effective than nonuniform exposure for the production of these hematological changes.~~ Currently, the University of Cincinnati has a program for whole body exposures and for partial body exposures (either upper body, lower body, or complete trunk) of patients for the treatment of cancer. In connection with this program, we have been extremely interested in finding an approach to allow the prediction of the hematological changes to be expected following the uniform and the nonuniform exposures used in our specific study. ✓

A quantitative approach to the evaluation of effects of nonuniform exposure has been proposed by Bond and Robinson (1,2). They have shown this model to apply to survival prediction of several mammalian species but suggest that it would be expected to apply under other circumstances in which the biological effect scored is related to marrow stem cell survival. The object of the present paper is to extend this model to human survival for the specific uniform and nonuniform exposure procedures used in our program and to test the validity of ^{its use} using this model to predict the nadir ⁱⁿ peripheral _{cell} blood ^λ levels resulting from the various exposure conditions.

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METHODS

The Model

The model proposed by Bond and Robinson is based on the fact that survival in the $LD_{50(30)}$ range depends on the survival or proliferative integrity of a critical number or fraction of the stem cells in the total active bone marrow mass. Mammalian studies suggest that with uniform whole body exposure (same dose to all bone marrow) the number of surviving stem cells in the bone marrow decreases exponentially with dose over a range of exposures that more than spans the $LD_{50(30)}$. Thus, under nonuniform irradiation the unequal distribution of dose to the bone marrow should permit a higher rate of survival than if the same average dose were distributed uniformly.

In their approach, Bond and Robinson assume that sub-units of bone marrow act independently of other sub-units and are subject to the same exponential dose-effect relationship as that for the total marrow. Thus, given the dose to a number of sub-units of bone marrow and the fraction of bone marrow stem cells in that sub-unit, one can determine the relative number of surviving stem cells for each sub-unit. Summing over the entire marrow yields the total relative number of stem cells in the body that would survive the exposure. This value can then be used in estimating the biological effect based on the uniform exposure necessary to produce the same relative stem cell survival. The dose survival curve they propose for human bone marrow stem cells for high energy gamma radiation is shown in Figure 1. The ordinate on the left shows the mortality levels for man corresponding to a given dose of radiation delivered uniformly to all of the marrow. Since no dose - survival curve was available for human bone marrow stem cells, the slope of the survival curve for mouse bone marrow was used. The mouse survival curve used by Bond and Robinson is based on the work of McCulloch and Till⁽³⁾

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The Model - continued

dose

who used the spleen colony technique and obtained a D_0 of 95 rads and an extrapolation number of 1.5. As mentioned above, the slope of the mouse curve has been shown to apply fairly well to several mammalian species (4,5,6). Since the shape of the curve at lower doses is not well known for man, the curve shown in Figure 11 has been normalized such that the relative number of stem cells ^{at} the LD_{50} for man is 1.0. In a recent paper, Senn and McCulloch (7) have shown by the colony-forming ability in culture technique that the sensitivity of human bone marrow to irradiation is of the same order as that predicted on the basis of experiments in mice. The survival curve they obtained for a class of human hemopoietic cells has a D_0 of 137 rads and an extrapolation number of 1.0.

To In apply this model, one has to know the distribution of bone marrow (assumed to parallel that of stem cells) and the radiation dose distribution throughout the bone marrow. ^{using the} ~~for a~~ detailed distribution of the active bone marrow ^{as given} ~~the paper~~ by Atkinson was consulted (8). ~~The percentage of total~~ bone marrow distribution times the cellularity factor for the principle bone groups at age 40 ^{was calculated, data from} ~~were taken from Atkinson paper~~. Table I gives a summary of the distribution of active marrow weights in "Standard Man" at age 40. In the absence of any large scale study of the distribution of active marrow in man, ^{all are} ~~this~~ data ~~is~~ considered to be the best ~~data~~ available at the present. The radiation dose distributions throughout the bone marrow for our specific conditions of uniform and nonuniform exposure were measured in a tissue equivalent phantom as described below.

Patient and Phantom Dosimetry

The radiation is delivered by a cobalt-60 teletherapy unit under the following exposure conditions. The radiation beam is directed horizontally at a wall 342 ^{cm} centimeters away with the ~~patient~~ ^{of the patient} midline at 286 ^{cm} centimeters from the source. For whole body exposures, the ^{radiation} beam area ^{size} for the 60% isodose curve at the patient midline distance is a square approximately 120 ^{cm} centimeters x 120 ^{cm} centimeters. The patient is placed in the sitting position with legs raised and head tilted slightly forward. Radiation is given by delivering half the specified exposure laterally through one side of the patient; the patient is then turned and the other half exposure delivered laterally through the other side. The variation of air exposure with distance from the source indicated that no correction was required for a possible dose contribution to the patient due to backscatter from the wall.

The exposure to the patient is determined using the percentage depth dose table for a 400 sq. ^{are cm} ~~centimeter~~ ^{size} field at 80 cm source-to-skin distance corrected for the source-to-skin distance used for the patient. Using the corrected depth dose at patient midline (1/2 lateral dimension at the trunk in the plane of the ~~Xiphoid~~ ^{Xiphoid}) and a conversion factor of 0.957 rads/Roentgen for cobalt-⁶⁰ gamma radiation, ~~in~~ the midline air exposure required to give a desired midline absorbed dose in rads is calculated. The validity of ~~this~~ ^{an Alderson Rando} of this procedure was established with measurements in a ~~mesonite~~ phantom using thermoluminescence dosimeters (see Figure 2). ~~In our program thus far,~~ ^{-GR} air exposure rates at the distance indicated above have varied from 3 R per minute ~~to 6 R per minute~~. The combined dose to homogeneous tissue for bilateral exposure is shown in Figures 3 and 4 for various lateral dimensions. Figure 3 shows that for a given midline exposure there is considerable variation in dose over the patient. For a given midline absorbed dose, Figure 4 shows the dose extremes and the average lateral absorbed dose received in the plane of the ~~Xiphoid~~ ^{Xiphoid} over the range of lateral dimensions of patients. ~~in our program.~~

For individuals receiving partial body radiation, the teletherapy collimator is used to restrict the beam. The lateral dimension in the plane of the ~~Xiphoid~~ ^{Xiphoid} is again used for calculating the desired midline dose. As for whole body exposure, the dose is delivered bilaterally. For partial body radiation, the ~~Xiphoid~~ ^{Xiphoid} is used as the boundary of the field for upper and lower body exposures. (see Figure 5).

A tissue equivalent phantom (Rando) containing a human skeleton and simulated lung cavities was used to ~~experimentally~~ ^{measure} determine the active bone marrow dose under simulated whole body and partial body cobalt-60 exposure conditions. Figure 5 shows the exposure ^{of} in the Alderson phantom ~~to the cobalt beams~~ to simulate the actual whole body and partial body exposure to humans.

Capsules filled with lithium fluoride (LiF) were placed in bone cavities as demonstrated by radiographs of each phantom section. The cavities selected were based on locations of active bone marrow spaces as indicated by the work of Atkinson. For each exposure condition, 222 capsules were utilized. The majority of these capsules were placed in bone cavities with the remainder being distributed along the midline of the phantom and in various body organs. Following exposure, the thermoluminescent dosimeters (TLD) were read on an Eberline TLR-5 Reader (Eberline Instrument Corporation, Santa Fe, New Mexico). The phantom received 300 R midline air exposure for each exposure condition. This exposure corresponds to an average lateral absorbed dose in the plane of the ziphoid of about 200 rads as calculated by the procedure indicated above.

Clinical Information

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The peripheral blood counts of the patients receiving whole body exposure or partial body exposure in this program were obtained prior to irradiation and were followed for as long as practical following exposure. The data reported in this paper were obtained from patients shown to have normal blood counts prior to exposure.

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RESULTS

A summary of the integral dose distribution to the bone marrow of the phantom as obtained from the LiF measurements for 300 R midline air exposure are shown in Table II. Several of the larger bones were arbitrarily divided with several LiF capsules placed in each section. The divisions were made to approximate equal masses of bone and hence an equal weighting factor for the bone marrow within each divided portion. The doses for each section were then averaged and multiplied by the total grams of active bone marrow in the

Results - continued

portion under consideration. The active bone marrow integral doses for upper body, lower body, and complete trunk under simulated human exposure conditions are 48%, 61% and 75%, respectively, of that determined for whole body exposure under the radiation exposure conditions given above. The integral ^{bone marrow} absorbed dose for ^a whole body ^{midline air} exposure of 300 R divided by the total bone marrow weight yields a marrow weighted average dose of 204 rads to the bone marrow. The average midline dose within the primary field area for each exposure condition appears in Table III. The average dose to various organs for each exposure condition is given in Table IV.

Using the radiation dose distribution to the active bone marrow, we proceeded to calculate the weighted stem cell survival for the various exposure conditions. For mortality in the $LD_{50(30)}$ range, the normalized stem cell survival curve as shown in Figure 1 was utilized. An example of the procedure as applied ^{a portion of} ~~to~~ the pelvic region for ~~whole body and lower body exposure~~ is shown in Table V. The sum over all active bone marrow yields the weighted relative stem cell survival. The calculations were extended to midline air exposure other than 300 R by multiplying the dose to each bone portion by the ratio of ^{the next exposure level to 300 R} ~~the next exposure level to 300 R~~. The results of this procedure appear in ^{Figure} ~~Figure~~ 6. Thus, for any of the given nonuniform exposures, ~~we can determine from Figure 6~~ the dose of uniform whole body irradiation that ^{can be determined} ~~would result in the same mortality rate~~. The corresponding "doses" thus ~~derived~~ derived for uniform whole body exposures can be thought of as being "dose equivalent," rather than absorbed dose. This is because in the averaging process for nonuniform exposure, each increment of dose was weighted by the amount of bone marrow irradiated at that dose level and by the relative effectiveness

Results - continued

of the dose increment to destroy the stem cells. The dose equivalents for 300 R and 600 R midline exposures are shown in Table VI.

In extending this model to the circulating fractions of the peripheral blood elements at the nadir point, the un-normalized mouse bone marrow stem cell survival was utilized ($D_0 = 95$ rads) as well as the survival curve for human ^{etc} hemopoietic cells ($D_0 = 137$ rads). It is assumed ^{of the} this extension of the model that the nadir ^{of the} circulating fraction for a given blood element is equal to the surviving fraction of marrow stem cells for the given exposure.

The model was applied as above and the results appear in Figure 7, and 8. ^{order?}

~~We tested~~ ^A The validity of this extension of the model ^{was tested} by comparing the predicted and measured nadir ^{of the} circulating fractions of white blood cells and platelets for several groups of patients. ~~We grouped~~ ^{were grouped} the patients by the type of exposure and the midline dose received. Table VII shows the comparison for three groups of patients who received whole body exposures to achieve 100, 150, and 200 rads midline absorbed dose respectively, and two groups of patients who received lower body exposures to achieve 200 and 300 rads midline absorbed doses, respectively. A small number of patients in ^{the} ~~our~~ study received trunk and upper body exposure but not in sufficient number to group them for an adequate comparison with the proposed model.

DISCUSSION

Figure 4 reveals that ^{the extent of the} ~~considerable~~ variation ^{observed} in dose to bone marrow ^{submits} ~~is expected~~ for a given midline air exposure to Cobalt-60 radiation delivered bilaterally. ^{difference} In spite of this, ~~it is interesting to note that the~~ average lateral absorbed dose in the plane of the phantom's ^{the} ~~lateral~~ sigmoid calculated from the percentage depth dose curve yields a value which is very close to

the marrow weighted average dose based on the thermoluminescence dosimetry measurements and the effective dose based on the stem cell survival model for whole body exposure. Thus, ^{it is felt} ~~we~~ feel that the calculated average lateral absorbed dose in the plane of the ^Xiphoid provides a means of comparing patients with ^{the} our phantom studies, ~~provided the patient is neither extremely obese nor extremely thin.~~

The approach to nonuniform exposure proposed by Bond and Robinson is based on an exponential survival curve for bone marrow stem cells. Thus, under nonuniform irradiation, the unequal distribution of dose to the bone marrow should permit a higher rate of survival than if the same average dose were distributed uniformly. This point was made ^{it is here} abundantly clear in ^{the} our phantom studies. For example, an upper body exposure of 600 R would result in a marrow weighted absorbed dose of about 200 rads, yet the "dose equivalent" of 600 R upper body exposure is only about 95 rads.

The ^model ~~as~~ proposed by Bond and Robinson assumes that, for a man to survive the hematopoietic crisis, his supply of the critical type (or types) of mature cells during this period (descended from surviving stem cells) must exceed the minimum required for survival. In these terms, the model they propose is based on the assumptions: (a) that the total number of mature cells is proportional to the total number of surviving stem cells, whatever their distribution in the body; and (b) that the requirement for mature cells following ^{any non-uniform exposure is the same as that following the uniform exposure} ~~the uniform exposure~~ equivalent to it with respect to total stem cell survival. In extending this model to the nadir ^{of} peripheral blood levels ^{of irradiated humans}, an additional assumption was made: that the nadir ^{of the} circulating fraction of the given blood element is equal to the surviving fraction of marrow stem cells. These assumptions as well as the application of the mouse stem cell survival

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curve to man appear to yield fair agreement between the proposed model and the average clinical findings. ~~Because of the wide range in our clinical findings, however, additional clinical data are obviously needed.~~ Also, more work is needed on the specific dose-effect curve for human stem cells. If the value for D_0 or extrapolation number for man in vivo is marked different from those used in the calculations, the model as applied to our phantom measurements would have to be altered.

Our observations may be affected to some degree by the fact that ~~the patients~~ ~~patients~~ had cancer ~~which was~~ being treated by palliative radiation. Although their initial hemograms ~~to~~ were within normal ranges, it is possible that the radiation effect may be different from normal by an ~~unknown~~ degree to a degree as yet not well defined.

TABLE I: MARROW DISTRIBUTION OF THE AVERAGE MALE ADULT

SITE Site	Marrow WEIGHT g	Fraction Red Marrow (Age 40)	Red Marrow WEIGHT (Age 40)	% TOTAL RED Marrow
← Head	250.9	0.75	188.2	14.2
Upper Limb Girdle	150.6	0.77	115.9	8.8
← Sternum	50.0	0.65	32.5	2.4
← Ribs	265.7	0.354	94.0	7.1
← Vertebrae				
Cervical	64.5	0.75	48.3	3.7
Thoracic	263.9	0.75	198.0	15.0
Lumbar	203.1	0.75	152.3	11.5
← Sacrum	226.6	0.75	170.0	12.9
Lower Limb Girdle	431.5	0.75	323.6	24.4

pringle
pringle

TABLE II: TOTAL GRAM-RADS TO THE ACTIVE MARROW OF A "STANDARD MAN"
AGE 40

SKELETAL ANATOMY <i>Skeletal anatomy</i>	WHOLE BODY (g-rads)	PARTIAL BODY (g-rads)		
		Upper	Lower	Trunk
Head				
Cranium	44,508	41,590	1,185	1,787
Mandible	4,248	4,254	141	329
Upper Limb Girdle				
Humerus , head and neck	6,012	5,407	485	4,789
Scapulae	11,705	11,573	1,384	8,686
Clavicles	3,767	4,128	193	890
Sternum	5,896	6,360	620	4,753
Ribs (1-12 pair)	18,585	11,999	12,288	18,203
Vertebrae				
Cervical	9,892	10,113	426	1,586
Thoracic	38,176	29,315	22,827	38,744
Lumbar	31,615	2,572	30,781	32,300
Sacrum	33,652	1,308	32,241	32,751
Lower Limb Girdle				
Os Coxae	55,278	1,985	53,972	54,027
Femoral heads and necks	10,197	314	10,212	6,174
<i>Total g. rads</i>	273,531	130,918	166,755	205,019

TABLE III: AVERAGE MIDLINE DOSE FOR VARIOUS
IRRADIATION PROCEDURES - Δ
300 R MIDLINE AIR EXPOSURE

<u>Exposure Conditions</u>	<u>Average Dose rads</u>
<u>Whole Body</u>	212.8
<u>Partial Body</u>	
Upper	198.2
Lower	198.6
Complete Trunk	207.2

TABLE IV: AVERAGE DOSE TO VARIOUS ORGANS
(300 R MIDLINE AIR EXPOSURE)

Organ	Whole Body	Partial Body (rads)		
	rads	Upper	Lower	Trunk
Lung	217.3	180.5	81.4	202.3
Liver	223.5	39.9	208.3	218.1
Spleen	229.7	104.4	205.0	227.6
Kidneys	215.2	19.2	203.2	219.1
Ovaries	206.0	7.0	193.8	188.7
Uterus	202.2	6.9	189.4	183.8

TABLE V: RELATIVE STEM CELLS SURVIVAL (WEIGHTED)
300 R Midline Air Exposure

Body Section	Active Marrow Weight g	Portion Total Active Marrow	WHOLE BODY			LOWER BODY		
			Dose rad	Relative Stem Cell Survival (RSCS)	Weighted RSCS	Dose rad	Relative Stem Cell Survival (RSCS)	Weighted RSCS
<u>Pelvic Region</u>								
Sacrum	170.0	.129	198	2.40	.309	190	2.60	.334
R & L Os. ^{Coxae} Oxae	272.0	.206	203	2.30	.474	198	2.42	.499
R & L Femoras ^{Femur}	51.6	.039	198	2.45	.096	198	2.42	.095
					<u>.879</u>			<u>.928</u>

Iluminate Bone

TABLE V: EXAMPLE: ~~FOR~~ CALCULATION OF WEIGHTED RELATIVE STEM CELL SURVIVAL

Body Section - Pelvic Region
 Active Marrow Weight - 170.0g
 Portion Total Active Marrow - 0.129
 Dose - 195 rads
 Relative Stem Cell Survival (RSCS) = 2.40 (from fig.)
 Weighted RSCS = Portion Total Active Marrow x RSCS
 Weighted RSCS = 0.129 x 2.40 = .309

(From Report)

VI
 TABLE ~~IV~~: DOSE EQUIVALENTS FOR VARIOUS
 IRRADIATION EXPOSURES

MIDLINE AIR EXPOSURE	EXPOSURE CONDITION	"DOSE EQUIVALENT"	PERCENT OF WHOLE BODY DOSE	
<i>single</i> { <i>double space</i>	300 R	Whole Body	200 rads	100 %
	300 R	Upper Body	73 rads	36 %
	300 R	Lower Body	98 rads	49 %
	300 R	Trunk	127 rads	64 %
<i>single</i> {	600 R	Whole Body	400 rads	100 %
	600 R	Upper Body	95 rads	24 %
	600 R	Lower Body	133 rads	33 %
	600 R	Trunk	191 rads	48 %

TABLE 4

VIII MEASURED AND PREDICTED NADIR CIRCULATING FRACTIONS OF BLOOD ELEMENTS FOR PATIENT EXPOSURE CONDITIONS

Exposure Conditions	Average Lateral Absorbed Dose Rads	Number of Patients	Measured Average Range (Range)	Nadir Fraction	
				Predicted $D_0 = 95$ rads	Predicted $D_0 = 137$ rads
<u>WHITE BLOOD CELLS</u>					
Whole Body	107	6	.30 (.14-.51)	.43	.45
Whole Body	160	4	.14 (.07-.19)	.26	.30
Whole Body	214	4	.17 (.06-.24)	.15	.21
Lower Body	210	5	.58 (.47-.64)	.45	.47
Lower Body	321	4	.60 (.60-.95)	.37	.38
<u>PLATELETS</u>					
Whole Body	107	6	.47 (.13-.74)	.43	.45
Whole Body	160	3	.14 (.06-.24)	.26	.30
Whole Body	214	4	.18 (.15-.22)	.15	.21
Lower Body	210	5	.78 (.44-1.0)	.45	.47
Lower Body	321	4	.78 (.49-1.0)	.37	.38

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