Active Bone Marrow Dose Related to Hematological Changes in Whole Body and Partial Body ^{60}Co Gamma Radiation Exposures[1]

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INTRODUCTION

The depletion of formed circulating blood elements following exposure to ionizing radiation has been known for some time. ~~appreciated since the turn of the century~~. 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 using this model to predict the ~~radii~~ nadir peripheral blood 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 of 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 uniformally 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 has been used. The mouse survival curve used by Bond and Robinson is based on the work of McCulloch and Till[3] who used the spleen colony technique and obtained

The Model - continued

a D_0 of 95 rads and an extrapolation number of 1.5 [redacted]. As mentioned above, the slope of the mouse curve has been shown to apply fairly well to several mammalian species. ( ) Since the shape of the curve at lower doses is not well known for man, the curve shown in Figure [redacted] has been normalized such that the relative number of stem cells at the LD_{50} for man is 1.0.

In applying 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. For a detailed distribution of the active bone marrow, the paper by Atkinson was consulted ( ). The percentage of total bone marrow distribution times the cellularity factor for the principle bone groups at age 40 were taken from Atkinsons paper. Table [redacted] gives a summary of the distribution of active marrow weights in the "Standard Man" at age 40. In the absence of any large scale study of the distribution of active marrow in man, 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.

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 [redacted] 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.

Patient and Phantom Dosimetry

The radiation is delivered by cobalt-60 teletherapy units under the following exposure conditions. The radiation beam is directed horizontally at a wall 342 centimeters away with the patient midline at 286 centimeters from the source. For whole body exposures, the beam area for the 50% isodose curve at the patient midline distance is a square approximately 120 centimeters x 120 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.

patient is determined using the percentage depth
00 sq. centimeters field at 80 cm source to skin
for the source to skin distance used for the
). Using the corrected depth dose at patient midline
ion at the trunk in the plane of the ziphoid) and a
f 0.957 rads/roentgen for cobalt gamma radiation,
osure required to give a desired midline absorbed dose in r
ed: The validity of this procedure was established
n a masonite phantom using thermoluminescence dosi-
a). The combined dose for bilateral exposure is
igures 3 and 4 for various lateral dimensions. Figure 3 shows
dline exposure there is considerable variation in
nt. For a given midline absorbed dose,
dose extremes and the average lateral absorbed dose
ne of the ziphoid over the range of lateral dimen-
n our program.

receiving partial body radiation, the teletherapy
to restrict the beam. The lateral dimension in the
d is again used for calculating the desired midline
body exposure, the dose is delivered bilaterally.
diation, the ziphoid was used as the boundary of the
body exposure (see Figure 2).
ram thus far, air exposure rates at the distance
e varied from 3 R per minute to 6 R per minute.

A tissue equivalent phantom (Rando) containing a human skeleton and simulated lung cavities was used to experimentally determine the active bone marrow dose under simulated whole body and partial body cobalt-60 exposure conditions. Figure 5 shows the exposure 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 expsoure condition, 222 capsules were utilized. Following exposure, the thermoluminescent dosimeters (TLD) were read on an Eberline TLR-5 Reader (Eberline Inst. Corp., 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.

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.

Clinical Information

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

RESULTS

a summary of the
~~The~~ integral dose distribution to the bone marrow of the phantom as obtained from the LiF measurements for 300 R ~~(effective)~~ midline air exposure are shown in Table ~~I~~ 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 sum of~~ The ~~average~~ dose for from each section were then averaged and multiplied by the total grams of active bone marrow in the 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 average midline dose within the primary field area for each exposure condition appears in Table III. ~~(Table 12)~~. 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 to the pelvic region for whole body and lower body exposure is shown in Table V ~~(Table 16)~~. The sum over all active bone marrow yields the weighted relative stem cell survival. The calculations were extended to ~~other levels~~ of midline air exposures other than 300 R by weighting the dose to each bone portion by the ratio of the new exposure level to 300 R. multiplying The results of this procedure appear in Figure 6. Thus, for any of the given nonuniform exposures, we can determine from Figure 6 the dose of uniform

The integral absorbed dose for whole body exposure of 300R divided by the total bone marrow weights yields an marrow weighted average dose of 204 rads to the bone marrow.

RESULTS (continued)

whole body irradiation that would result in the same mortality rate. The corresponding "doses" thus 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 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 curve (D_o=95 rads) as well as the hurocal curve for human hemopoietic cells (D_o=137 rads) was utilized. It is assumed in this extention of the model that the nadir 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 Figures 7 and 8

We tested the validity of this extention of the model by comparing the predicted and measured nadir circulating fractions of white blood cells and platelets for several groups of patients. We 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 dose respectively. A small number of patients in our study received trunk and upper body exposure but not in sufficient numbers to group them for an adequate comparison with the proposed model.

DISCUSSION

Figure 4 reveals that considerable variation in dose to bone marrow subunits is expected for a given midline air exposure to Cobalt-60 radiation delivered bilaterally. In spite of this, it is interesting to note that the average lateral absorbed dose in the plane of the phantom's ziphoid 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, we feel that the calculated average lateral absorbed dose in the plane of the ziphoid provides a means of comparing patients with 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 with equal 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 abundantly clear in our phantom studies. For example, an upper body exposure of 600R 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 ~~100~~ 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

DISCUSSION - (Continued)

stem cells, whatever their distribution in the body; and (b) that the requirement for mature cells following any nonuniform exposure is the same as that following the uniform exposure equivalent to it with respect to total stem cell survival. In extending this model to the nadir peripheral blood levels, an additional assumption was made: that the nadir 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 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 [redacted]. If the value for Do or extrapolation number for man in vivo is markedly different from those used in the calculations, the model as applied to our phantom measurements would have to be altered.

TABLE I

(Slide 2)

Marrow distribution

Table II

slide 14

Integral absorbed dose

Table III

Midline dose see Cliff Table 23

Table IV

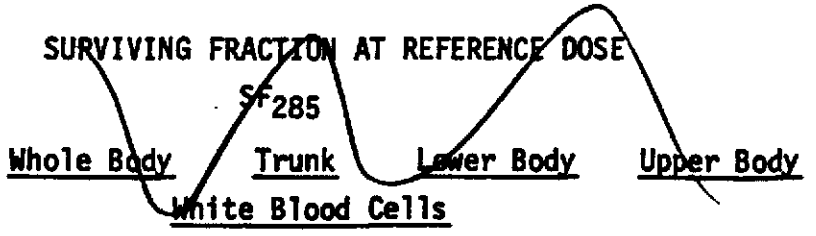
Dose to organs see Cliff Table 24

Table V

Example of calculations - slide 16.

TABLE I: MARROW DISTRIBUTION OF THE AVERAGE MALE ADULT

SITE	MARROW WEIGHT g	FRACTION RED MARROW (Age 40)	RED MARROW WEIGHT (Age 40) g	% 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



.53 ± /

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

AGE 40

SKELETAL ANATOMY	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				
2 Humerus, head and neck	6,012	5,407	485	4,789
2 Scapulae	11,705	11,573	1,384	8,686
2 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				
2 Os Coxae	55,278	1,985	53,972	54,027
2 Femoral head and neck	10,197	314	10,212	6,174
	273,531	130,918	166,755	205,019

TABLE III: AVERAGE MIDLINE DOSE FOR VARIOUS IRRADIATION PROCEDURES

300 R MIDLINE AIR EXPOSURE

	Average Dose rads
Whole Body	217.8
Partial Body	
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 rads	Partial Body (rads) Upper	Lower	Trunk
Lung	217.3	180.5	81.4	207.3
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	207.2	6.9	189.4	183.8

Table 3

TABLE 3

ATIVE STEM CELL SURVIVAL (WEIGHTED)

300 R Midline Air Exposure

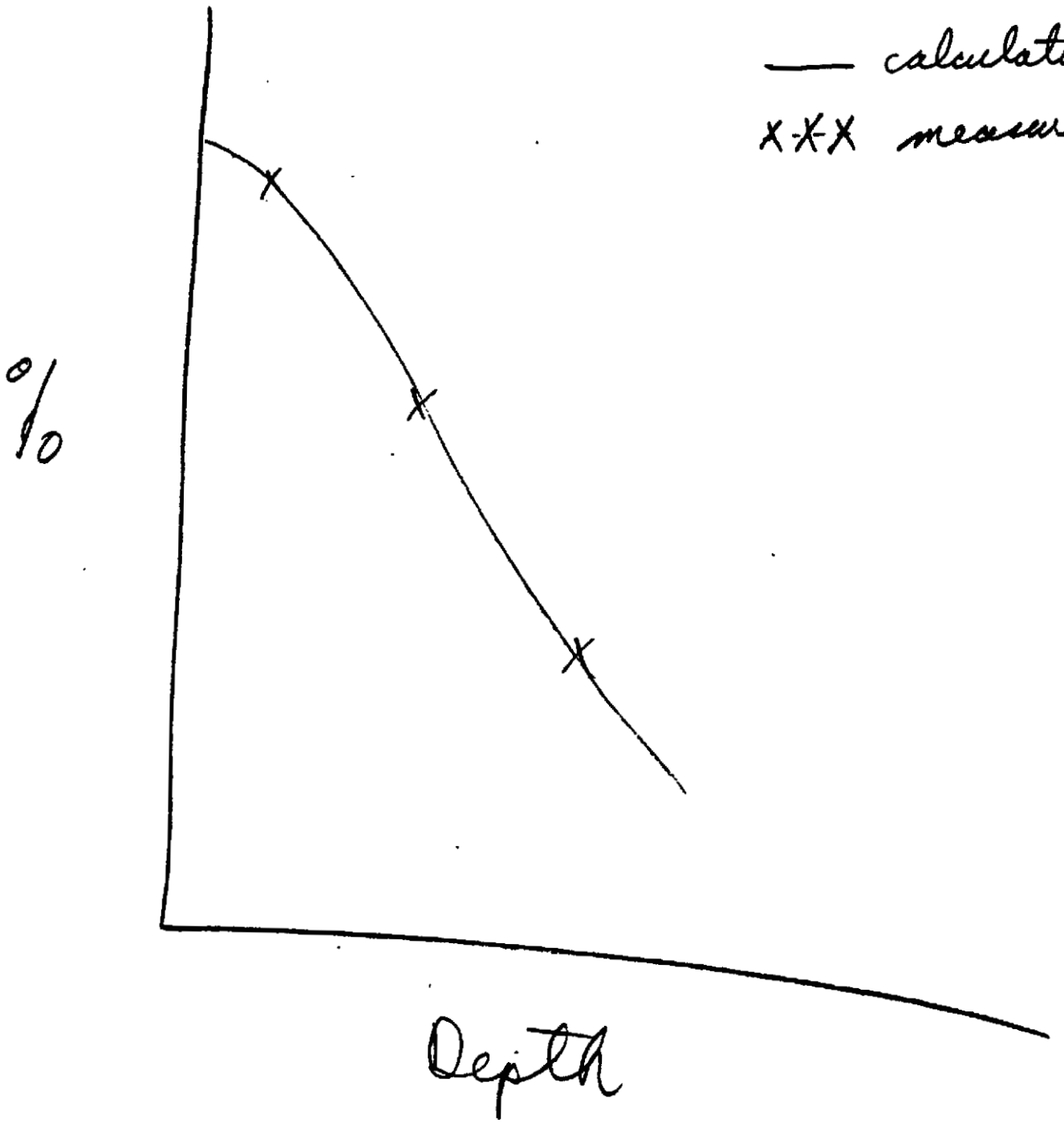
ortion otal ctive larrow	WHOLE BODY Dose rad	Relative Stem Cell Survival (RSCS)	Weighted RSCS	LOWER BODY Dose rad	Relative Stem Cell Survival (RSCS)	Weighted RSCS
.129	198	2.40	.309	190	2.60	.334
.206	203	2.30	.474	198	2.42	.499
.039	198	2.45	.096	198	2.42	.095
			.879			.928

TABLE VI: DOSE EQUIVALENTS FOR VARIOUS IRRADIATION EXPOSURES

MIDLINE AIR EXPOSURE	EXPOSURE CONDITION	"DOSE EQUIVALENT"	PERCENT OF WHOLE BODY DOSE
300R	Whole Body	200 Rads	100 %
300R	Upper Body	73	36 %
300R	Lower Body	98	49 %
300R	Trunk	127	64 %
600R	Whole Body	400 Rads	100%
600R	Upper Body	95	24 %
600R	Lower Body	133	33%
600R	Trunk	191	48 %

Figure 2

Show calculated 7.00 & TLD measured depth dose



References

1. Bond VP, Robinson CV: Nonuniform exposure to penetrating radiations. Personal communication, 1968.

2. Bond VP, Robinson CV: Dose-effectiveness modifying factors in military and space radiation medicine. Personal communication, 1968.

3. McCulloch, E.A., [redacted], Till, J.E.: The sensitivity of cells from normal mouse bone marrow to gamma radiation in vitro and in vivo, Rad. Res. ~~16 (1962) 332-32,~~ 16: 532-537, 1962

4. Bond, V. P., and Robinson, C. V. A Mortality Determinant in Non-uniform exposure of the Mammal. Rad. Res. Suppl. 7: 265-275, 1967.

5. Bond, V. P., and Robinson, C. V: Bone-marrow Stem-cell Survival in the Non-uniformly Exposed Mammal, in Monograph "Effects of Ionizing Radiations on the Hematopoietic Tissue", Proceedings of a Panel held in Vienna, 17-20 May 1966, International Atomic Energy Agency, Vienna, 1967.

6. Robinson, C. V: Relationship between Animal and Stem Cell Dose-Survival Curves. Rad. Res. 35: 318-344, 1968.

7. Senn, J.S., McCulloch, E.A.: Radiation sensitivity of human bone marrow cells measured by cell culture method. Blood 35 (~~1970~~): 56-60, 1970
8. Atkinson, H.R.: Bone marrow distribution as a factor in estimating radiation to the blood-forming organs: A survey of present knowledge. J. Coll. Radiol. Aust. 6: (~~1962~~) 149- , 1962

(1)

ROUGH DRAFT

We have a program at the University of Cincinnati College of Medicine for total body exposure and for partial body exposure (either upper ~~half~~ or lower ~~half~~) of patients for treatment of cancer. The radiation is delivered by cobalt-60 teletherapy units under the following exposure conditions. The radiation beam is directed horizontally at a wall 338 centimeters away with the patient midline at 282 centimeters from the source. SLIDE 1 The beam area for the 50% isodose curve at the patient midline distance is a square approximately 70 centimeters x 70 centimeters ~~(slide)~~. 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.~~ SLIDE 2 Preliminary measurements were made in a masonite phantom using ~~thermoluminescence dosimeters~~ small chambers placed on lateral surfaces and at the midline of the head, ~~front~~ trunk and knee portions of the phantom. ~~These results are shown on the next slide~~. It is seen that if midline doses to the trunk, head and knees are compared, the maximum variation in these doses is about 16%. The exposure to the patient is determined as follows. Percentage depth dose at different depths for 400 square centimeter field area in a source skin distance of 80 centimeters is corrected for the source skin distance used for the patient. Using the corrected depth dose at patient midline (1/2 lateral dimension of the trunk) and a conversion factor of .97 rads/roentgen for cobalt gamma radiation, the

surface dose and midline air exposure required to give a desired midline absorbed dose in rads is calculated. A direct comparison between calculated and measured (phantom) doses was made for one patient who had the same lateral trunk dimensions as the phantom. ~~The doses indicated by crosses and the measurements by the straight line and it is seen that there is a~~ Band good agreement were found. good comparison with the calculated doses. The combined dose of the two radiation fields is also given in ~~this figure~~ this SLIDE 3 It shows a good homogeneous dose distribution through the patient. Maximum variation in lateral dose distribution was plus or minus 3% for one patient having a lateral trunk dimension of 36 centimeters. Air exposures rates varied from 6R per minute down to 3.5R per minute as ^{60}Co source decayed.

For the individuals receiving partial body radiation, the teletherapy collimator is used to restrict the beam. The ~~special~~ spatial dose distribution for this latter case is shown in the next slide. SLIDE 4 SLIDE 5 The relative dose distribution for upper body radiation is shown in the next slide; SLIDE 6 that for the lower body in the following slide. SLIDE 7 The phantom measurements were measured with thermoluminescent dosimeters. For partial body radiation, the xiphoid was used as the boundary of the field.

start

We are then confronted with some approach to allow comparison between the socalled uniform (whole body) and the nonuniform (partial body) exposures used in our specific study. Although it is easily seen that a nonuniform exposure to penetrating radiation requires a higher dose of radiation to at least some portion of the body to produce a similar or equal degree of a given effect, than ~~it~~ is necessary with uniform whole body exposure, the full quantitative characterization of dose and dose effect relationships are necessarily more complex for nonuniform than for uniform doses. For uniform whole body exposure, all tissues receive essentially the same dose, and thus the dose delivered to any

tissue is satisfactory in characterizing the dose received by the animal. Absorbed dose at the midline, is commonly used for convenience, with no implication that a particularly sensitive organ or region lies in that location. With nonuniform exposure, however, it has been shown clearly that, for death from the bone marrow syndrome, neither the entrance dose, the absorbed dose at the midline of the animal, the exit dose, the integral dose nor the average dose will normalize and allow dose effect predictions for the full spectrum of different dose distributions. Thus additional factors must be taken into account and a weighted, dose averaging procedure, must be used to predict dose effect relationships. An approach by Vic Bond and the group at Brookhaven National Laboratory has provided a basis for dealing with nonuniform exposure. The approach is particularly helpful in dealing with the bone marrow syndrome. In this approach, one has to know the dose distribution and also the distribution of bone marrow (assumed to parallel that of stem cells) and the dose distribution to bone marrow.

~~that better data on the active bone marrow distribution in man is urgently needed.~~

We were then interested in obtaining dose distribution data for simulated human ^{60}Co exposures, namely, whole body versus upper ~~half~~ and ~~lower half~~ body exposure

~~To obtain the dose~~ distribution data ~~the following procedure~~ was used. The ~~purpose is to determine experimentally~~ the active ~~bone marrow~~ dose under ~~simulated whole body and~~ partial ~~body~~ cobalt-60 exposure conditions ~~for humans~~. A tissue equivalent phantom (Rando) containing a human skeleton and simulated lung cavities was used. SLIDE #7 Capsules filled with lithium fluoride were judiciously 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 ~~mentioned above~~ by Ellis. 8 ~~Next series of slides indicates to some extent the place~~ SLIDE 9

~~bone marrow distribution for standard man is given in the next slide.~~ SLIDE 9 This ~~is the~~ data of Ellis was obtained from the original work of Mechanik but corrected for percentage cellularity factors as provided by Custer. These are essentially corrections for the cranium, mandible, vertebral column, and pelvis by cellularity factor values obtained by Custer for the vertebrae. Further work by Atkinson also allows an assessment of the bone marrow distribution with age as a parameter. In the absence of any large scale study of the distribution of active marrow in man, the ~~above~~ data on this slide are considered to be the best data ~~that can be obtained~~ available at present. In terms of being better able to discuss the bone marrow syndrome, it appears that better data on the active bone marrow distribution in man is urgently needed. no

Next series of slides indicate placement SLIDES 9,10,11,12,13 ~~10,11,12,13,14~~ ~~14,15,16,17~~ of these ~~thermoluminescent~~ capsules in the phantom. The slides include the following: radiograph of head section; line drawing of the same section with outline of bone structure and placement of capsules; dosimeter placement in the ribs; dosimeter placement in the vertebra; and dosimeter placement in the pelvis and femoral heads and necks. The next series of slides indicate exposure in Alderson phantom to the cobalt beams to simulate SLIDE 14,15,16 ~~[redacted]~~ 15,16,17 the actual whole body and upper half and lower half exposure to humans. The air exposure in all cases is 300 R corresponding to 189 rads at trunk midline. From the average rad dose and the active bone marrow weight, the integral dose to active bone marrow was calculated. We see in the next slide, SLIDE ~~#~~ 17 that integral radiation doses to active bone marrow ~~integral doses~~ for lower ~~half~~ body and upper ~~half~~ body under the simulated human exposure conditions ~~[redacted]~~ are 68.9% and 37% respectively, of that determined for whole body exposure under the radiation exposure conditions ~~given above~~ in our laboratory. We have ~~It has been~~ calculated that ~~upper~~ lower half body irradiation results in exposure of ~~[redacted]~~ 56% of the active bone marrow of the body whereas ~~upper half~~ body exposure represents exposure to ~~[redacted]~~ 44% of the body active marrow. These percentages correspond very closely to the actual portions of the body irradiated for the upper ~~[redacted]~~ and lower ~~[redacted]~~ exposures. We then proceeded to determine that for a given ~~nonuniform~~ partial body dose distribution, the dose of uniform whole body irradiation would result in the same mortality rate, as determined by using the ~~mortality~~ relative stem cell survival data shown in the next slide SLIDE 18 ~~19~~.

This is the data of Till & McCullough

~~of the dose increment to destroy the stem cells.~~ The dose survival curve for bone marrow stem cells is known most accurately for the mouse. A model presented by Bond to handle nonuniform exposure has been shown to apply to the rat and the dog as well as the mouse, using the same curve for stem cells. It was thus assumed by Bond and also assumed in this paper that this curve applies to man. The model also assumes the following: ~~that the number of mature cells is proportional to the total number of surviving stem cells whatever their distribution in the body;~~ that the requirement for mature cells following any nonuniform exposure is the same as that following the uniform exposure equivalent to it with respect to total stem cell survival. It also assumes a moderate degree of nonuniformity-extremes of local dose to any part of the body not exceeding a value of approximately 1000 to 1200 rads. The reason for this is that the higher doses may cause local blood vessel damage to become a significant factor leading to increased requirements for both neutrophils and platelets. In addition, high doses locally to the bowel can produce death in the absence of significant marrow damage.

~~exposure.~~ ~~Each subunit of bone marrow appears to act indepently of the other subunits, as regard to their response to radiation of the stem cells in that subunit.~~ Given the dose to a number of subunits in marrow and percent of bone marrow stem cells in that subunit, one can determine the relative number of surviving stem cells for each subunit ~~using the approach by Bond which is based primarily on survival of stem cells given by~~ [illegible] and [illegible] for mice. Summing over the entire marrow yields the total relative number of stem cells in the body that would survive the exposure. The mortality level to be expected from this stem cell survival can then be obtained from the plot showing relative stem cell survival as a function of a dose. Thus for any given nonuniform dose distribution, a dose of uniform whole body radiation that will result in the same cell mortality rate can then be determined. ~~To~~

The corresponding "doses" thus 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 of the dose increment to destroy the stem cells.

~~165R averaging dose~~

SLIDE ~~20~~ 19 ~~17~~

~~Further studies will explore trunk irradiation only, head + extremities only, so that correlated with the phantom dose measurements and perhaps some 5Fe measurements in patient we may be able for radiation effects to accomplish some rule (similar to the so-called rule of 9's for burns). Our interest is to predict some relative degree of injury by knowledge of parts of body exposed.~~ (over) back of page

The dosimetry approach presented here for "active" bone marrow doses allows us discuss ~~the~~ some ~~relative~~ degree of hematopoietic injury for partial body irradiation relative to whole body irradiation.

FORM CSH-78 200M 11-68

CINCINNATI GENERAL HOSPITAL

WHOLE BODY AND PARTIAL BODY EXPOSURE -

WARD:

PRINT NAME:

NUMBER:

		Body Weight Irradiated	Active Bone Marrow Irradiated	Total Active Bone Marrow Dose	Relative Stem Cell Survival x Portion of Total Active Marrow
Upper Body / Whole Body	=	.47	.44	.37	.31
Lower Body / Whole Body	=	.58	.56	.69	.56
Upper Body / Lower Body	=	.77	.78	.54	.55