ACTIVE BONE MARROW DOSE RELATED TO HEMATOLOGICAL CHANGES IN WHOLE BODY AND PARTIAL BODY ^{60}CO GAMMA RADIATION EXPOSURES[1]

James G. Kereiakes, Ph.D., William Van de Riet, Ph.D., Clifford Born, M.S., Carol Ewing, Edward Silberstein, M.D., and Eugene L. Saenger, M.D.

INTRODUCTION

It has been recognized that uniform whole-body exposure is more effective than nonuniform exposure for the production of 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 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). Their work provides a basis in the mouse for the translation of the effect of either partial-body irradiation or nonuniform irradiation into an equivalent effect of a lower dose of whole body irradiation. 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 the human for the specific uniform and the non-

[1] From the Radioisotope Laboratory, University of Cincinnati College of Medicine, Cincinnati, Ohio.

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uniform exposure procedures used in our program and to test the validity of its use to predict the nadir in peripheral blood cell levels resulting from the various exposure conditions.

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 this 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 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) who used the spleen colony technique and obtained a D_0 dose (dose required to reduce the number of cells to 37% of an initial value in the exponential portion of the curve) 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 (1,2,4). Since the shape of the curve at lower doses is not well known for man, the curve shown in Figure 1 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 (5) 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 hematopoietic cells has a D_0 of 137 rads and an extrapolation number of 1.0.

To apply this model, one has to know the distribution of bone marrow (assumed to parallel that of stem cells) and the radiation dose distributed throughout the bone marrow. Using the detailed distribution of the active bone marrow as given by Atkinson (6), the percentage of total bone marrow distribution times the cellularity factor for the principle bone groups at age 40 was calculated. Table 1 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, these data are considered to be the best 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 away with the midline of the patient at 286 cm from the source. For whole body exposures, the radiation beam size for the 60% isodose curve at the patient midline distance is a square approximately 120 cm x 120 cm. 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 a percentage depth dose table 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) and a conversion factor of 0.957 rads/Roentgen for cobalt-60 gamma radi-

ation, the midline air exposure required to give a desired midline absorbed dose in rads is calculated. The validity of this procedure was established with measurements in an Alderson Rando phantom using thermoluminescence dosimeters. Over the course of the study, the air exposure rates at the distance indicated above varied from 3R - 6R per minute. Because of the differences in lateral thicknesses for the various body sections, there is a variation in dose over the patient for a given midline exposure. For a given midline absorbed dose, Figure 2 indicates the dose extremes and the average lateral absorbed dose received in the plane of the xiphoid.

For individuals receiving partial body radiation, the teletherapy collimator is used to restrict the beam. The lateral dimension in the plane of the xiphoid is again used for calculating the desired midline dose. As for the whole body exposure, the dose is delivered bilaterally. For partial body radiation, the xiphoid is used as the boundary of the field for upper and lower body exposures (see Fig. 3).

A tissue equivalent phantom (Rando) containing a human skeleton and simulated lung cavities was used to measure the active bone marrow dose under simulated whole body and partial body cobalt-60 exposure conditions. Figure 3 shows the exposure of the Alderson phantom 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 xiphoid of about 200 rads as calculated by the procedure indicated above.

Clinical Information

Peripheral blood counts of patients receiving whole or partial body exposure to cobalt-60 radiotherapy were obtained prior to irradiation and followed until all counts had returned to normal. Prior to irradiation these patients had normal peripheral blood counts with the occasional exception of mild anemia with the hematocrit always exceeding 35%. Furthermore, the granulocyte reserves of the patient, as measured with etiocholanolone, were normal.

The patients received either prophylactic radiotherapy following local irradiation of a Ewing's Tumor or palliative wide field irradiation for metastatic carcinoma not amenable to surgical or conventional radiotherapy. All patients were functioning effectively outside the hospital and capable of self-care. Many were employed. Each patient gave his informed consent to these studies.

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 is 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 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 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 the pelvic region 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 exposures other than 300R by multiplying the dose to each bone portion by the ratio of the new exposure level to 300 R. The results of this procedure appear in Figure 4. Thus, for any of the given nonuniform exposures, the dose of uniform whole body irradiation that results in the same mortality rate can be determined. 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 was utilized (D_0 - 95 rads) as well as the survival curve for human hematopoietic cells (D_0 = 137 rads). It is assumed in this extension of the model that the nadir of the circulating fraciton 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 5.

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. The patients were grouped 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 study received trunk and upper body exposure but not in sufficient number to group them for an adequate comparison with the proposed model.

DISCUSSION

Because of differences in lateral thicknesses of the various body sections,a variation is observed in the doses to bone marrow subunits for a given midline air exposure to cobalt-60 radiation delivered bilaterally. In spite of these differences the average lateral absorbed dose in the plane of the phantom's xiphoid calculated by the procedure outlined above 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 that the calculated average lateral absorbed dose in the plane of the xiphoid provides a means of comparing patients with the phantom studies.

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

abundantly clear in the 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 proposed by Bond and Robinson assumes that for 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 equivalent to it with respect to total stem cell survival. In extending this model to the nadir of peripheral blood levels in 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 curve to man appear to yield fair agreement between the proposed model and the average clinical findings. Our observations may be affected to some degree by the fact that these patients had cancer being treated by palliative radiation. Although their initial hemograms were within normal ranges, it is possible that the radiation effect may be different from normal to a degree as yet not well defined. Also, more work is needed on the specific dose-

effect curve for human stem cells. If the value for D_o 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.

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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

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				
Humeri, 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
Total g-rads	273,531	130,918	166,755	205,019

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

Exposure Condition	Average Dose rads
Whole Body	209
Partial Body	
Upper	194
Lower	194
Complete Trunk	203

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

	Whole Body	Partial Body (rads)		
Organ	rads	Upper	Lower	Trunk
Lung	213	177	80	198
Liver	219	39	204	214
Spleen	225	102	201	223
Kidneys	211	19	199	215
Ovaries	202	7	190	185
Uterus	198	7	186	180

TABLE V: EXAMPLE: CALCULATION WEIGHTED RELATIVE STEM CELL SURVIVAL

Body Section - Pelvic Region

Active Marrow Weight - 170.0 gram

Portion Total Active Marrow - 0.129

Dose - 198 rads

Relative Stem Cell Survival (RSCS) = 2.40 (from Fig. 1)

Weighted RSCS = Portion Total Active Marrow x RSCS

Weighted RSCS = 0.129 x 2.40 = .309

TABLE VI: DOSE EQUIVALENTS FOR VARIOUS IRRADIATION EXPOSURES

MIDLINE AIR EXPOSURE	EXPOSURE CONDITION	"DOSE EQUIVALENT"	PERCENT OF WHOLE BODY DOSE
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 %
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 VII: MEASURED AND PREDICTED NADIR OF CIRCULATING FRACTIONS OF BLOOD ELEMENTS FOR PATIENT EXPOSURE CONDITIONS

Exposure Conditions	Average Lateral Absorbed Dose rads	Number of Patients	Nadir Fraction		
			Measured Average (Range)	Predicted D_o = 95 rads	Predicted D_o = 137 rads
WHITE BLOOD CELLS					
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
PLATELETS					
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

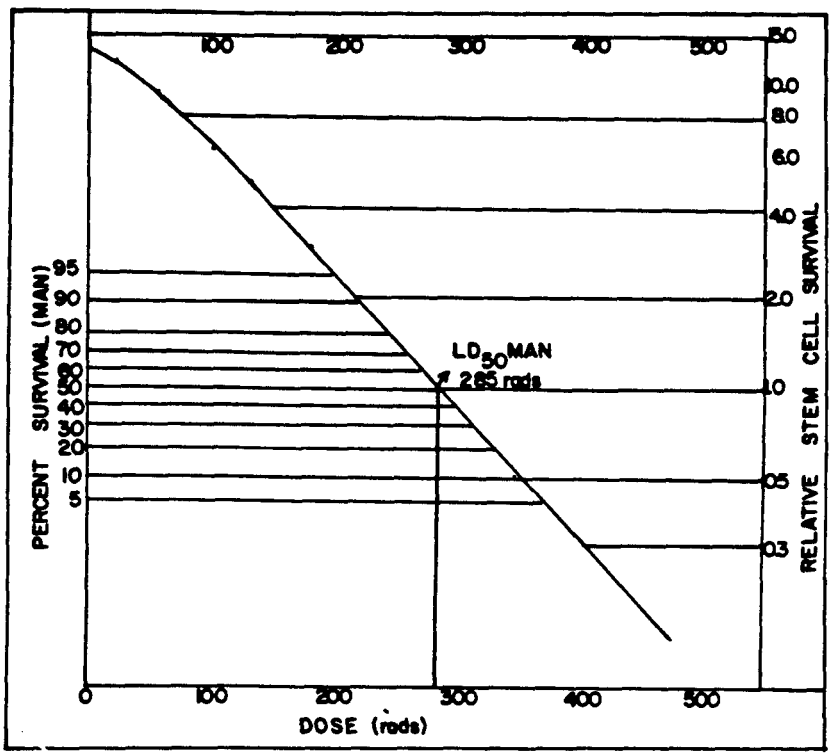


Figure 1. Proposed survival curve and relative stem cell survival curve for man exposed uniformly to whole-body radiation, adapted from Bond and Robinson (1)

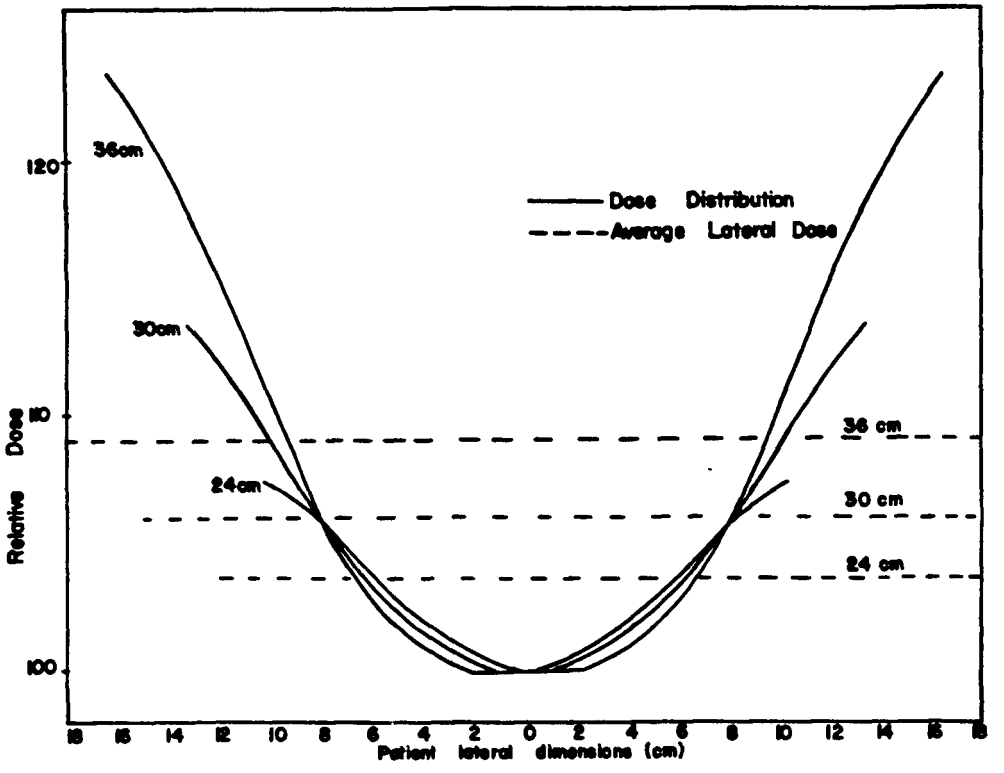
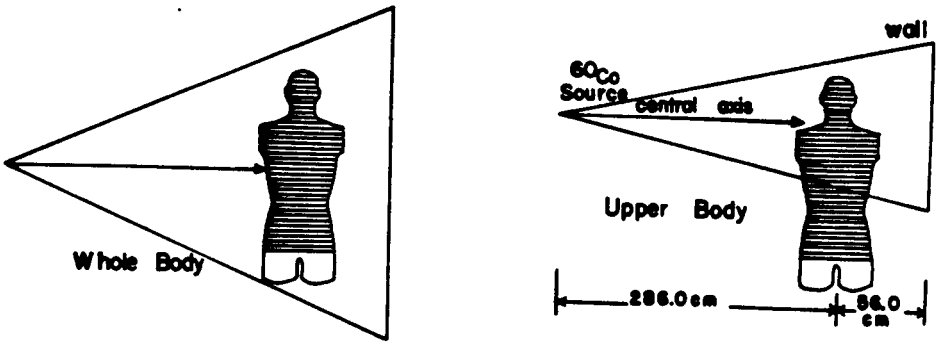


Figure 2. Dose distribution for bilateral exposure: dose distribution as a function of lateral dimension for a given midline dose.



Total midline air exposure at 286.0 cm is 300 roentgens (bilateral exposure).

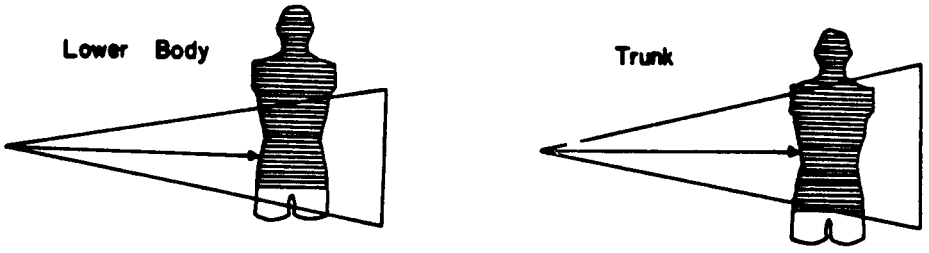


Figure 3. Irradiation technique for patients

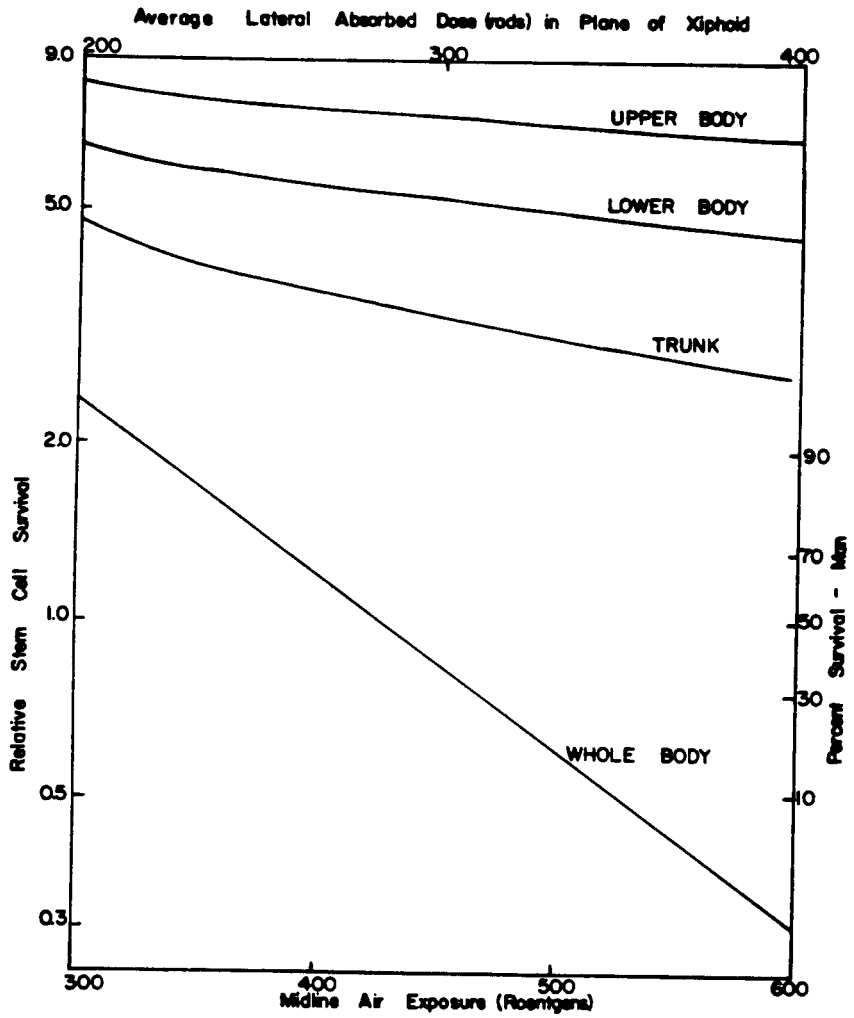


Figure 4. Proposed survival curve for the hematopoietic syndrome under conditions of bilateral uniform and nonuniform exposure (based on Do=95 rads)

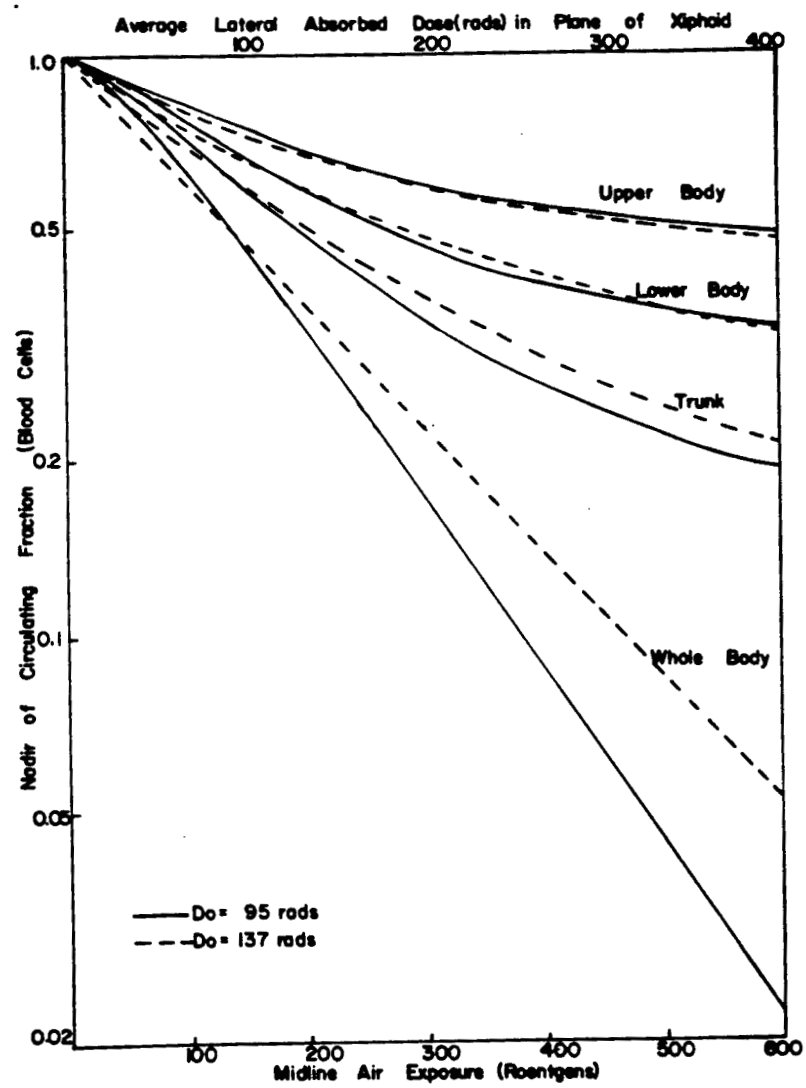
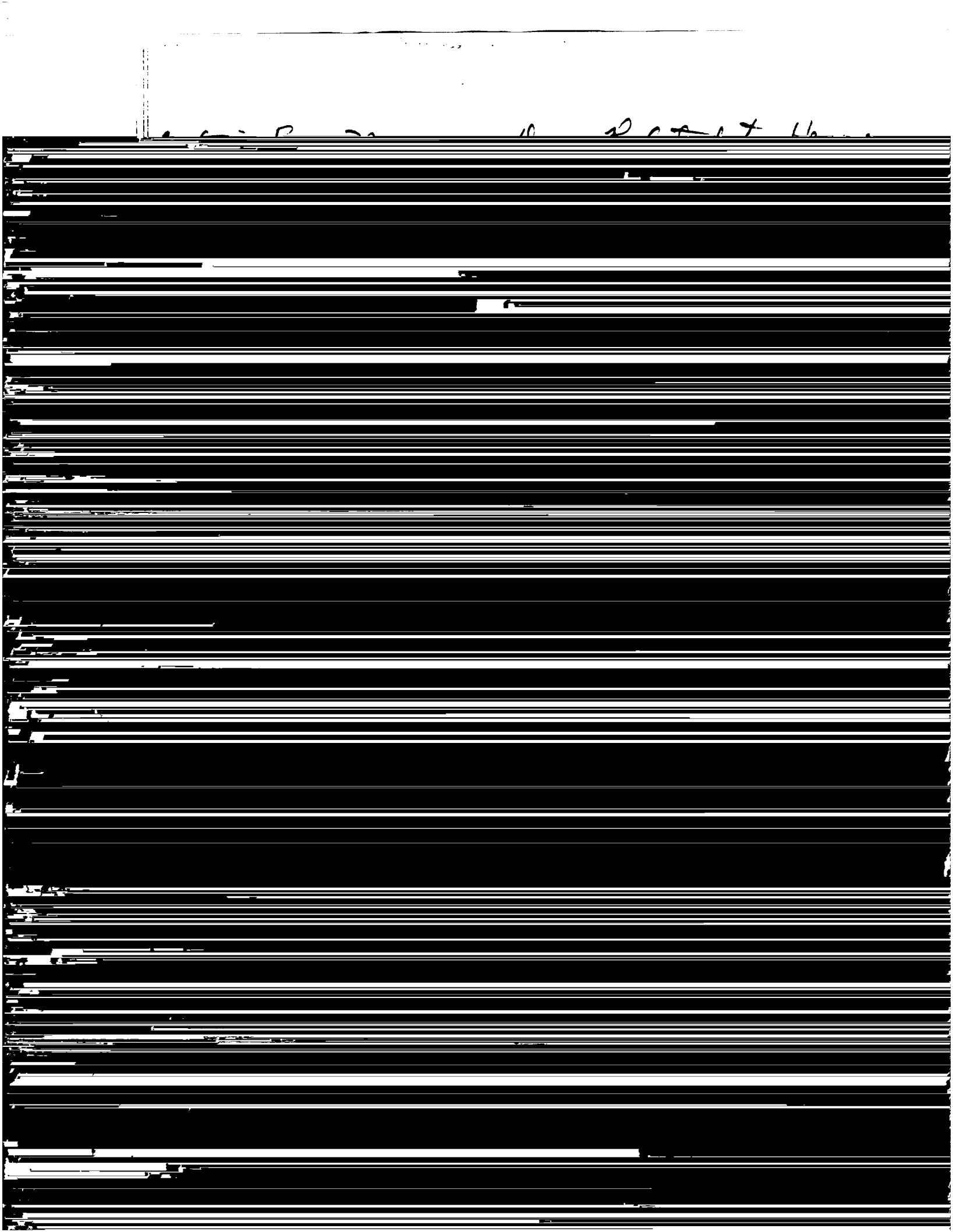


Figure 5. Proposed dose response curve for the nadir of the circulating fraction of blood cells under conditions of bilateral uniform and nonuniform exposure.



exposures. The phantom received 300 R midline air exposure for each exposure condition. A summary of the integral active bone marrow doses are shown in Table 2. The doses for each section were averaged and multiplied by total grams of active bone marrow in that section. The active bone marrow integral dose for upper body, lower body, and complete trunk are 48%, 61% and 75%, respectively, of that determined for whole body exposure.

Using the radiation dose distribution to active bone marrow, we then proceeded to calculate the weighted stem cell survival (following the approach of Bond and Robinson) for the various exposure conditions. For ~~irradiation~~ exposures in the $LD_{50(30)}$ range, the normalized stem cell survival curve shown in Figure 1 was used. This curve is based on the data of McCulloch and Till (4). An example of the procedure as applied to the pelvic region for whole body and lower body exposure is shown in Table 3. The sum over all active bone marrow yields the weighted relative stem cell survival. The calculations, also extended to other midline air exposures, are shown in Figure 2. ~~For any~~ Thus, for any of the given non-uniform exposures, one can determine the dose of uniform whole body irradiation that would produce the same ~~mortality~~ rate. The

corresponding "dose" thus derived for uniform whole body exposures can be thought of as being "dose equivalent".

Insert A

Extended this approach to the circulating fractions of the peripheral blood elements at the nadir point, the un-normalized bone marrow stem cell survival curve (D_o = 95 rads) was utilized as well as the survival curve for human hematopoietic cells (D_o = 137 rads). It is assumed in this extension of the approach 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 validity of this extension was tested by comparing the predicted and measured nadir circulating fractions of white blood cells and platelets for several groups of patients. Peripheral blood counts of the patients were obtained prior to irradiation and were followed for as long as practical following exposure. The data reported here were obtained from patients elected to have normal blood counts prior to exposure. The patients were grouped as to type of exposure and the nadir dose recorded. Table 4 shows the comparison for three groups of patients who received whole body exposures to achieve 100, 150 and 200 rads nadir absorbed dose, respectively; and two groups

of patients who received lower body exposure to achieve 200 and 300 rads midline absorbed doses, respectively. ~~A number of parameters~~ The assumptions given above as to the application of the mouse stem survival curve to man appear to yield fair agreement between the proposed model and the average clinical findings. Because of the wide range observed in the 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 were markedly different from those used in the calculation, the model as applied to our phantom measurements would have to be altered. In addition, patient data presently being obtained on lower body vs complete trunk exposures will allow extension of the model to modes of non-uniform exposure. Senn and Till-Culloch (5) have recently shown that the sensitivity of human bone marrow (by colony-forming ability in culture techniques) 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 hematopoietic cells has a D_0 of 137 rads and an extrapolation number of 1.0.

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curve

Figure 1. Dose-survival for man exposed uniformly to penetrating x- or gamma radiation and relative survival rate of bone marrow stem cells; the survival rate of stem cells is normalized to the number surviving at the LD_{50} dose for man, uniform total-body exposure.

Fig 2. Weighted relative stem cell survival (and associated percent survival for man) and dose expressed either as midline air exposure in Roentgens or as average lateral absorbed dose in rads in the plane of the zygoma.

TABLE VII

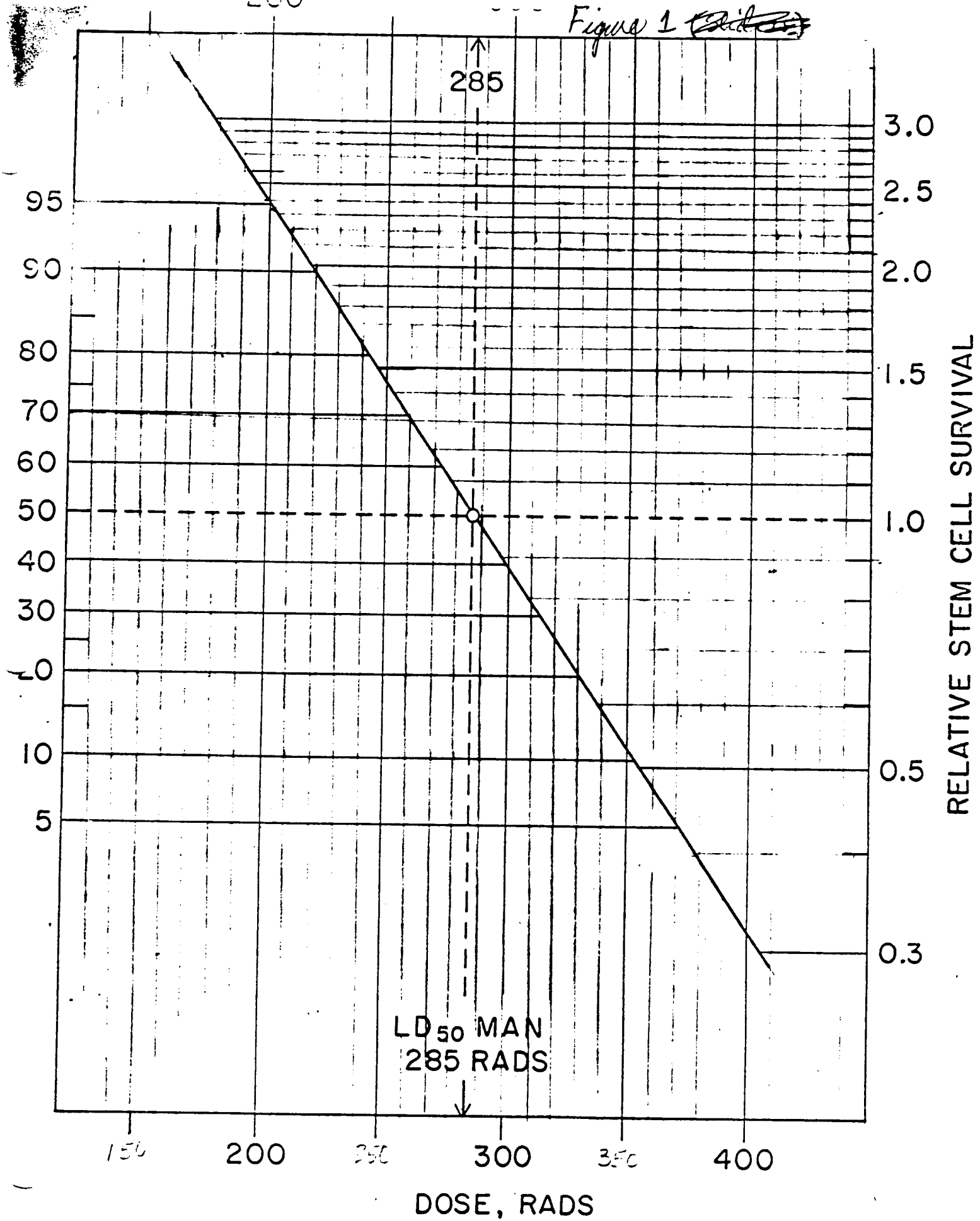
MEASURED AND PREDICTED NADIR CIRCULATING FRACTIONS OF BLOOD ELEMENTS FOR VARIOUS PATIENT EXPOSURE CONDITIONS

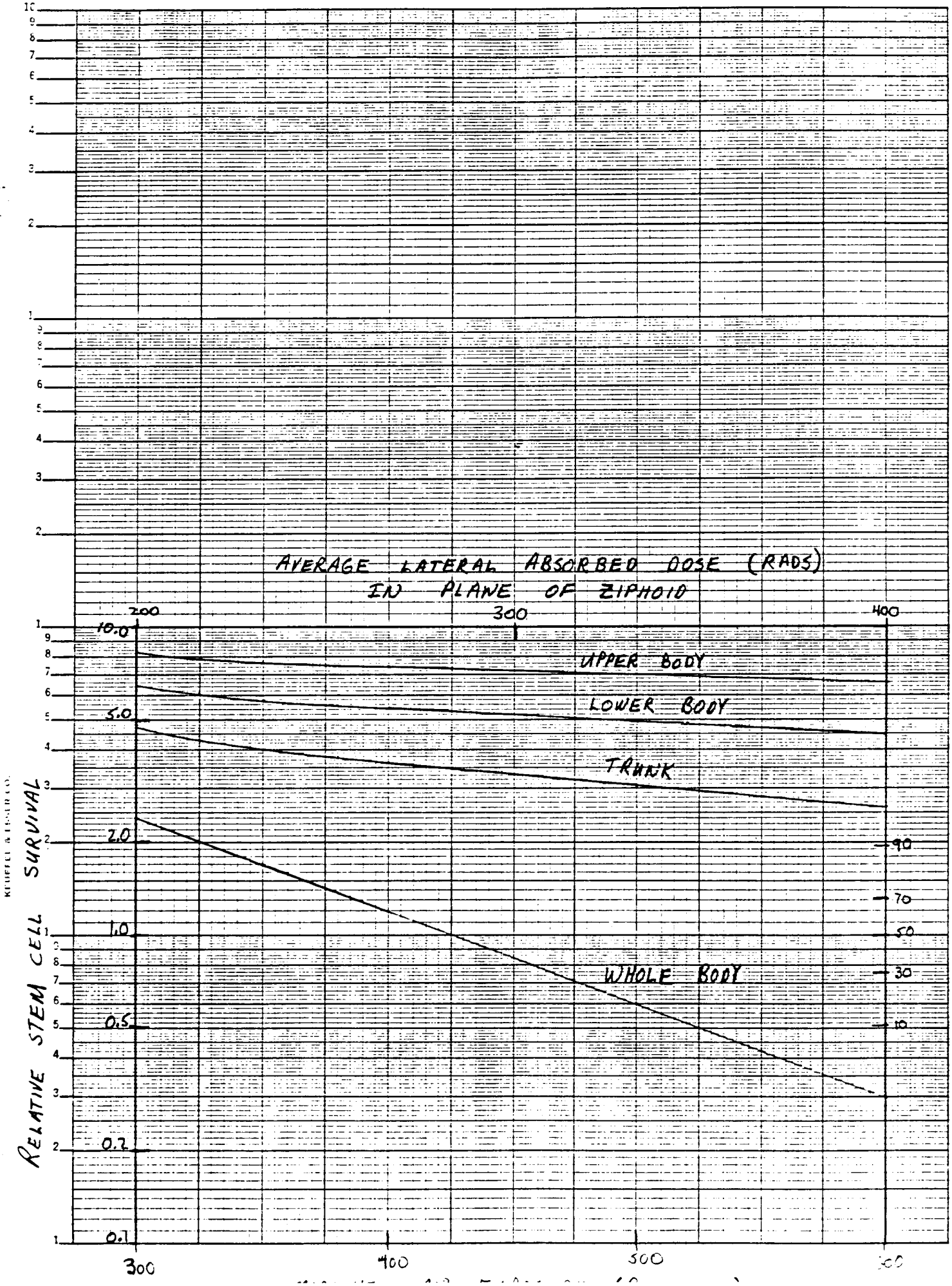
Exposure condition	Average Lateral absorbed dose (Rads)	Number of Patients	Blood Element	Nadir Fraction Measured Average	Measured Range	Predicted D_o = 95 rads	Predicted D_o = 137 rads
WHITE BLOOD CELLS							
Whole Body	107	6	White Blood Cells	.30	(.14-.514)	.43	.45
"	160	4	"	.14	(.07-.19)	.26	.30
"	214	4	"	.17	(.06-.24)	.15	.21
Lower Body	210	5	"	.58	(.47-.64)	.45	.47
"	321	4	"	.60	(.46-.95)	.37	.38
~~PLATELETS~~							
Whole Body	107	6	Platelet	.47	(.13-.74)	.43	.45
"	160	3	"	.14	(.06-.29)	.26	.30
"	214	4	"	.18	(.15-.22)	.15	.21
Lower Body	210	5	"	.78	(.44-1.0)	.45	.47
	321	4	"	.78	(.49-1.0)	.37	.38

WHITE BLOOD CELLS

PLATELETS

Figure 1


285
95
90
80
70
60
50
40
30
20
10
5
3.0
2.5
2.0
1.5
1.0
0.5
0.3
RELATIVE STEM CELL SURVIVAL
LD50 MAN
285 RADS
150
200
250
300
350
400
DOSE, RADS


AVERAGE LATERAL ABSORBED DOSE (RADS) IN PLANE OF ZIPHOID
200
300
400
10.0
5.0
2.0
1.0
0.5
0.2
0.1
UPPER BODY
LOWER BODY
TRUNK
WHOLE BODY
RELATIVE STEM CELL SURVIVAL
PERCENT SURVIVAL - MAIN
90
70
50
30
10
300
400
500
600
SEMI LOGARITHMIC
46 6010