Nuclear Weapons Effects Research No. 03.011

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Sub-task Title: The Effect of Total Body Irradiation on Immunolo
Tolerance of Bone Marrow and Homografts of Oth
Living Tissue

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The primary purpose of this investigation is to define and quantitat the effects of total body irradiation.

The fundamental problem of physical dosimetry is that a simple numerical expression of dose is inadequate to describe the distribution ntensity and quality of radiation delivered throughout the body. While striving to achieve uniformity of distribution in order to allow a meanin and reproducible statement of dose, it is recognized that any radiation exposure received under other than controlled conditions, is apt to be a partial body exposure, likely to be of unknown geometry, and certain to be of uneven distribution throughout the body.

The biologic component of irradiation dosimetry has these factors, among others:

1. The observed biologic responses are not specific for irradiation
2. Mechanisms of compensation and repair obscure the direct effect of irradiation injury
3. Such mechanisms are themselves sensitive to continued irradiation as recognized in the concept of a time-dose relationship
4. Uncertain and uneven distribution of radiation throughout the body must have uncertain and inconstant effects on repairative reserve
5. Such reserves are peculiar to the individual and influenced by ate, current state of health and prior illness or injury possibly unrecogni:

The complexities are seen more clearly with increasing knowledge but the complexity of the problem itself is not increased. Some perspec in studying the problem is gained from recognizing that irradiation can b used clinically with acceptable safety and effectiveness.

Many approaches to the problem have been undertaken, and reviewe for this report. Major studies which have been completed and reported previously are listed, and the continuing study of clinical observations or patients receiving therapeutic total body irradiation is summarized. Details of investigations carried out over the past year follow the summa

A total of 110 patients have received therapeutic total body irradiati On each patient, follow-up is continued as long as possible so that effect of irradiation may be observed and recorded. All patients were sufferin from generalized disease; because many were approaching the terminal stage at the time of treatment, long term observations were limited. In some instances, the therapeutic response was dramatic,--enlarged nodes 'sappeared, impending obstruction was relieved, and a few bedridden atients became ambulatory. While long terms control of disseminated ncer cannot be expected with any method of treatment, survivals up to 9 - 10 years following exposure demonstrate that moderate amounts of t body irradiation can be tolerated without dangerous sequelae.

At the beginning of the study, it was planned to collect two series of patients for comparison of response,--one receiving single doses o body irradiation and one receiving protracted exposures. The single series includes a larger number of patients than the protracted expos group because, for many patients, plans for protracted exposure coul not be carried out. In some cases the desired therapeutic effect was obtained with the first exposure and protracted irradiation was not indicated; in others, further irradiation was contra-indicated because of poor general condition. Among the latter group are patients who, having run the gamut of all other forms of treatment, are referred fo irradiation as a last resort.

In addition to the two series, a third group evolved during the cou of study. This is represented by patients who received protracted ex with good response but who, after periods varying from 3 to 29 month developed symptoms requiring additional total body irradiation.

Accordingly, for the present review, the patients have been divide into three categories: 1) single exposures ranging from 25r - 250r, 2) protracted exposures ranging from 25r - 400r over periods of 4 to 23 days, and 3) repeated protracted exposures ranging from 50r - 250 per course (2 - 4 courses) over periods of 5 to 42 months. The numl of patients in each category, with range of exposure and elapsed time, shown in Table 1.

Table 1

Category	Patients	Range of Exposure & Time
I.	70	25r - 250r/1 day
II.	33	21r/4 days - 400r/32 days
III.	7	50r-250r/5 mos. - 2 courses 50r-200r/3½yrs. - 4 courses

Table 2 summarizes the number of patients in Category I with the amount of irradiation given in a single exposure, and the number of patients in Category II with total amount of irradiation received in exposures protracted over periods ranging from 2 to 33 days.

Table 2.

Amount of radiation	I. Single exposures No. of Pts.	II. Protracted exposures No. of Pts.	Time
25r	6	1	(4 days)
50r	20	2	(2-5 days)
75r	5	0	
100r	8	2	(7-28 days)
125r	1	0	
150r	7	9	(3-18 days)
200r	21	4	(6-19 days)
215r	1	1	(21 days)
250r	1	6	(7-17 days)
300r	0	4	(6-33 days)
350r	0	2	(22 days)
400r	0	1	(23 days)
545r	0	1	(18 days)
Total	70	33	

Because expression of dose requires a statement of time, and patients s Category III received more than one course, the amount of irradiation el red in each course for each patient is outlined in Table 3.

Table 3.

Patients	Time Lapse	Total Time	Amount of Radiation/Course
M.M.	0		125r/62 days
	8 mos.		50r/11 days
	17 mos.	25 mos.	282r/113 days
F.M.	0		200r/1 day
	5 mos.	5 mos.	200r/1 day
I.S.	0		90r/35 days
	3 mos.		30r/16 days
	1 mo.	4 mos.	50r/63 days
E.R.	0		100r/35 days
	4 mos.		50r/14 days
	9 mos.	42 mos.	150r/1 day
	29 mos.		200r/9 days
M.B.	0		150r/1 day
	10 mos.		100r/1 day
	7 mos.	17 mos.	50r/1 day
J.B.	0		250r/58 days
	5 mos.	5 mos.	50r/1 day
J.T.	0		100r/7 days
	25 mos.	25 mos.	100r/6 days

Although systemic effects of radiation were recognized and reported as early as 1897, there is still no satisfactory explanation for the set of symptoms known in 1912 as "Rontgenkater" (roentgen-hangover), and to called "radiation sickness." Ellinger* has summarized a series of biochemical changes, noted clinically and experimentally, that account for "radiation sickness." According to his report, symptoms develop "most commonly after total body irradiation," and in partial body irradiation, the incidence and severity of symptoms depend upon the anatomical area exposed.

The present series has been investigated with relation to protraction of exposure, to amount of radiation in single exposures and, during the last year, by physiologic studies before, during and after total body irradiation. For purposes of evaluation, the severity of symptoms has been graded as follows: 0 = none, 1 = anorexia only, 2 = nausea only, 3 = nausea and vomiting one day, and 4 = nausea and vomiting more than one day. Two patients were omitted from this study; one patient, termina at time of treatment, died within 24 hours and one, an out-patient with concurrent tuberculosis, was lost to follow-up. Table 4 summarizes the severity of symptoms according to single, protracted and repeated course of exposure.

Table 4.

Categories	No. of Patients	Grades				
		0	1	2	3	4
I	68	53	4	3*	8*	0
II	33	28	2	2	1	0
III	7	6	0	0	0	1
Total	108	87	6	5	9	1

*One patient with Grade 2 and one patient with Grade 3 symptoms had nausea and vomiting prior to irradiation.

The table indicates that a total of 21 patients (19%) had symptoms varying from mild to severe. While this figure is not high, it cannot be accepted without reservations for several reasons: 1) any or all symptoms could be due to cancer and/or its complications, 2) two patients had symptoms prior to irradiation exposure and 3) no explanation is provided for the 87 patients (81%) who developed no symptoms at all.

*Ellinger, F. P. Newer concepts of radiation sickness and its treatment. Proc. Rudolf Virchow Medical Soc. 14:9-24, 1955.

In evaluating radiation sickness according to amount of irradiation, Category I is used because response to a single exposure is easily recognized and symptoms are not complicated by the cumulative effect repeated exposures. Table 5 shows the number of patients developin nptoms according to amount of irradiation following a single exposur

Table 5.

Exposure	No. of Patients	Grade 0	1	2	3	4
25r	5	5	0	0	0	0
50r	20	15	0	2	3	0
75r	5	5	0	0	0	0
100r	8	8	0	0	0	0
125r	1	1	0	0	0	0
150r	7	5	2	0	0	0
200r	20	14	2	1	3*	0
215r	1	0	0	0	1	0
250r	1	0	0	0	1*	0
	68	53	4	3	8	0

*One patient receiving 200r and one receiving 250r had nausea and vomiting prior to irradiation.

Study of Table 5 shows that, for this group, radiation sickness following single exposures up to 200r is negligible except for the puzzlin incidence following 50r. This is particularly interesting in view of the 53 patients who developed no symptoms,--48 of whom received equal or greater amounts of irradiation. For this reason, the histories of these 5 patients were reviewed.

The first patient had widespread metastases with possible involveme of gastrointestinal tract from carcinoma of breast. She was terminal at the time of treatment, requiring narcotics for pain. Nausea and vomiting occurred following irradiation but symptoms could have been caused by motion and manipulation, by medication, or by disease. The patient died 15 days following treatment.

Histories of the remaining 4 patients are particularly pertinent. All were occupants of the same ward at the same time. The first to receive total body irradiation had carcinoma of kidney with metastases to liver; h was receiving partial body irradiation over the abdomen at the time of tal body exposure and his condition was complicated by a gastric ulcer. here was no vomiting but he complained of nausea following treatment d this was noted and discussed by his fellow patients.

The remaining three patients received total body irradiation while undergoing a course of radiotherapy for testicular cancer; abdominal

receive total body irradiation complained of nausea and though vomiting w anticipated, it dod not occur. The last two patients (R.M. and G.M.) develc nausea and vomiting during partial body irradiation and received supportiv tre ent which controlled the symptoms. Both patients received total bo irr ation on the same day and both developed nausea and vomiting soon a t(atment. There is no question concerning the validity of symptoms in th men; both were genuinely ill and both received specific medication for con of nausea and vomiting. Both were well enough to continue partial body ir diation and their courses were completed without interruption. These circ stances indicate that in at least three patients, nausea and vomiting was an cipated and the power of suggestion may have played a significant role in their reactions.

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Of the 5 patients who developed nausea and vomiting following exposur of 200r - 250r, two had symptoms prior to irradiation, two had primary ca of the stomach and were receiving partial body irradiation to abdominal fi and one, with Hodgkin's disease, had extensive involvement of stomach and

The component features of radiation sickness,--anorexia, nausea, vom and fatigue,--are particularly susceptible to augmentation or control by el of motivation or suggestion. It is well established that a patient may have the symptoms of radiation sickness after being placed in the radiotherapy e without turning on the x-ray machine.

The difference in incidence of radiation sickness from one center to a other, whether speaking of total body or partial body irradiation, may be adequately explained on a basis of the attitude and experience of the profes personnel and personal acquaintances in contact with the patient.

On this basis it is the firm impression that at levels of total body expc below 200r in a single exposure, or in protracted exposures up to one mont there need be no incapacitation due to radiation sickness.

The problem could be eliminated by selection of stable individuals, by education and sound information, and by due attention to motivation and suggestion.

Conversely, the symptoms will be induced by panic, exertion and exhaustion when the ill-prepared and uninformed individual is exposed to the suggestion that he has been exposed and that sickness is inevitable.

Therapeutic total body irradiation is offered in cases of disseminated cancer with the intent of relieving symptoms; at the same time, other effec of irradiation may be observed. While certain types of cancers are consid radioresistant, there, among these individual cancers that may be radio- ponsive. Since these cancers cannot be identified, the practice of withholding referral or treatment may lose many opportunities to help patients a to collect information. The lymphoma group is recognized as being am the most radiosensitive cancers and analysis according to diagnosis was carried out to determine if this group represented the majority of the serie Among the 110 patients, there were 30 types of cancer; these have been div into 17 related groups and summarized in Tabl according to the number

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Diagnosis	Categories I	II	III	Total
Leukemia (chronic & acute)	7	3	4	14
Lymphosarcoma	7	12	2	21
Ca. of lung	11	1	0	12
Hodgkin's disease	3	3	0	6
Multiple myeloma	6	3	0	9
Head & Neck cancer (larynx, face, tongue, etc.	7	0	0	7
Testicular cancer	5	0	0	5
Ca. of colon & rectum	3	0	0	3
Breast cancer	2	1	0	3
Cancer of stomach	3	0	0	3
Cancer of pancreas	2	0	0	2
Gynecological cancer	2	0	0	2
Mycosis fungoides	0	2	0	2
Malignant melanoma	0	2	0	2
Carcinomatosis (primary unknown)	5	0	0	5
Ewing's sarcoma	1	1	0	2
Miscellaneous cancer (paraganglioma, ca. of liver, kidney, prostate, etc.)	6	5	1	12
	70	33	7	110

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The lymphoma group (leukemia, lymphosarcoma and Hodgkin's di is represented by 41 (37%) of the 110 patients. Of the 14 patients who received total body irradiation for leukemia, 3 were terminal at the ti of treatment and died of disease within 3 months; one patient with acti tuberculosis was lost to follow-up. The remaining 10 patients had cor siderable relief of symptoms with survivals ranging from 6 to 46 mont Two of these are still living; one (No. 91) received 250r/14 days in February 1959 and has been observed for 35 months; the second (109) received 150r in a single exposure and has done well for 9 months.

Of the 27 patients who received total body irradiation for generali lymphosarcoma and Hodgkin's disease, 16 died of disease within 3 mo Eleven patients survived from 4 months to 6 years and 5 of these are living. Of the five living patients, one is current and the other 4 have observed for periods of 14 to 41 months. The longest survivor (No. 4(died of hypertensive cardiovascular disease 6 years after treatment a age 89, with no evidence of radiation change.

Of the entire group of 110 patients, 9 were lost to follow-up, 89 ar kno n to have died and 12 r still living. Table 7 s mmarizes survi

hronic & acute)	[illegible]	[illegible]	[illegible]	
nphosarcoma	7	12	2	21
of lung	11	1	0	12
lgkin's disease	3	3	0	6
ltiple myeloma	6	3	0	9
ad . Neck cancer				
arynx, face, tongue, etc.	7	0	0	7
sticular cancer	5	0	0	5
. of colon & rectum	3	0	0	3
east cancer	2	1	0	3
ncer of stomach	3	0	0	3
ncer of pancreas	2	0	0	2
necological cancer	2	0	0	2
ycosis fungoides	0	2	0	2
alignant melanoma	0	2	0	2
arcinomatosis				
primary unknown)	5	0	0	5
wing's sarcoma	1	1	0	2
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Of the entire group of 110 patients, 9 were lost to follow-up, 89 are known to have died and 12 are still living. Table 7 summarizes survival over a period of ten years.

Table 7

Survival Time	Number of Patients		
	Died	Lost to F.U.	Living
0 - 3 mos.	44	5	1
3 - 6 mos.	30	0	0
6 - 12 mos.	9	0	2
1 - 2 yrs.	7	0	1
2 - 3 yrs.	5	0	2
3 - 4 yrs.	2	1	1
4 - 5 yrs.	0	1	1
5 - 6 yrs.	0	0	2
6 - 7 yrs.	1	0	1
7 - 8 yrs.	1	1	0
8 - 9 yrs.	0	0	1
9 - 10 yrs.	0	1	1
Total	89	9	12

Table 7 shows that 9 patients were followed from 5 to 10 years, providing long-term observations on effects of total body irradiation. Thes patients are listed in Table 8, along with amount of exposure and most recent follow-up.

Table 8

Patient	Age at T.B.I.	Irradiation Am't. & date	Follow-up
R.P.	28	25r/4 d. 6/56	Hgb. 15.8, WBC 7,550 12/62 Two children, ages 4 & 2 yrs.
R.M.	24	50r/1 d. 5/56	Hgb. 12.8, WBC 7,000 11/62 Wt. gain, now 243 lbs.
A.B.	54	50r/1 d. 8/56	Hgb. 14.0, WBC 7,150 1/63 Doing well
J.R.	83	545r/16 d. 10/54	Hgb. 13.5, WBC 9,000 11/60 Died 12/60 HCVD, age 89
I.G.	75	1004/1 d. 10/53	Hgb. 10.2, WBC 4,300 1/63 No complaints, age 85
C.W.	64	75r/1 d. 10/53	Hgb. 13.0, WBC 6,400 6/60 Doing well when lost - 1960
B.J.	27	200r/1 d. 9/53	Discharged to penitentiary Released after 5 yrs. Working every day, lost 1960
A.H.	60	50r/1 d. 7/53	Hgb. 13.2, WBC 6,400 1/63 Doing well
S.P.	70	125r/1 d. 7/53	Hgb. 10.6, WBC 8,900 6/60 Died HCVD 1960

Among these patients there was no evidence of radiation change ove periods of 5 to 10 years following exposure. Considering age and gener condition, blood counts were normal and there were no complaints, sign or symptoms that could be attributed to irradiation.

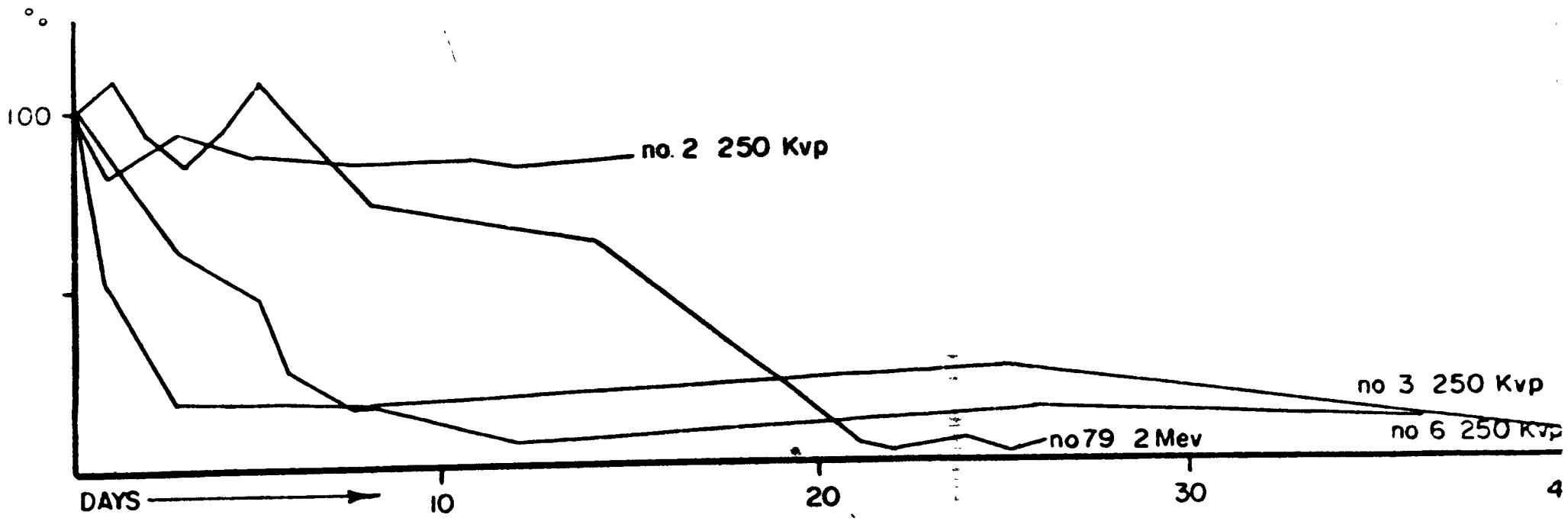
Details of response of hematopoiesis as observed in peripheral bloo counts have been reported as patients have been added to the series. Fo this report, a comparison of response of white blood cell count is made according to amount of radiation given in single exposures with energies of 250 Kvp. and 2 m.v. (see figures 1 - 5). Captions and legends make these illustrations self-explanatory. In general, the degree of depressio increases as the amount of irradiation is increased. The graphs show some indication, too, that differences in energies may produce differenc in response and this may be attributed to diversions of dose distribution that occur with 250 Kvp. However, comparable curves following compar. exposures cannot be achieved because the patients are not comparable.

The search for a suitable biologic index of radiation has led to nume investigations. Each of these has required the development of techniques often with the modification and/or design and construction of equipment; continuous studies in dosimetry have been carried out for animals and humans receiving single doses, protracted exposures, and repeated cour of irradiation. All studies are related to hematology, blood chemistry, individual tissues, cells, organs and systems, or to physiological respons The following list is not complete but provides a basis for an estimate of the problems involved.

1. Dosimetry (special studies)
   a) Integral dose
   b) Phantom studies for rotation therapy
   c) Uniformity of skin dose by film monitoring
   d) Air dose distribution in entire field with Victoreen Chamber and rate meter probe
   e) Theoretical (mathematical) check on inverse fall-off
   f) Depth dose in local irradiation fields using solid molds
   g) Total body absorption dose checked by Victoreen within the body of animals
   h) Total body absorption dose checked by film within phantom

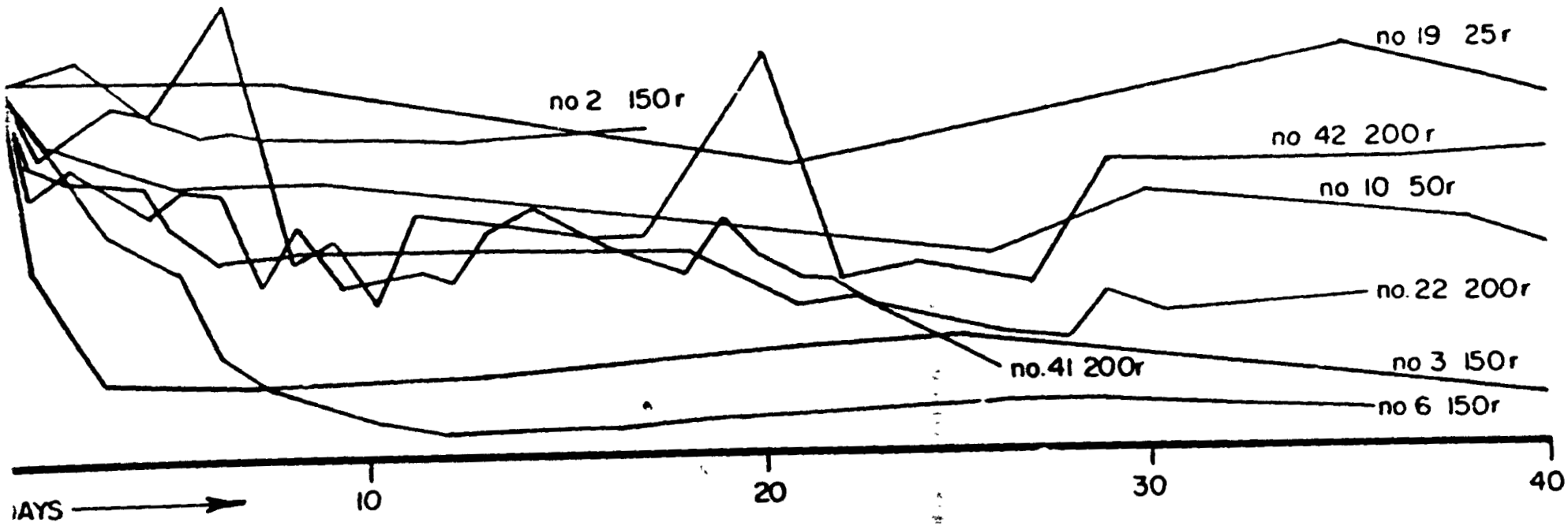
2. Red blood cells and hemoglobin
   a) Fe^{59} turnover studies
   b) Cr^{51} red cell survival studies
   c) Blood volume studies
   d) Cell indices (ratio of cell size, volume and hemoglobin concentration in red cells)
   e) Circulating cell concentration

Fig. 3. Total Body Irradiation - White Blood Cell Count (%)
Comparison of response following 150r - 250 Kvp. and 2 m.v.



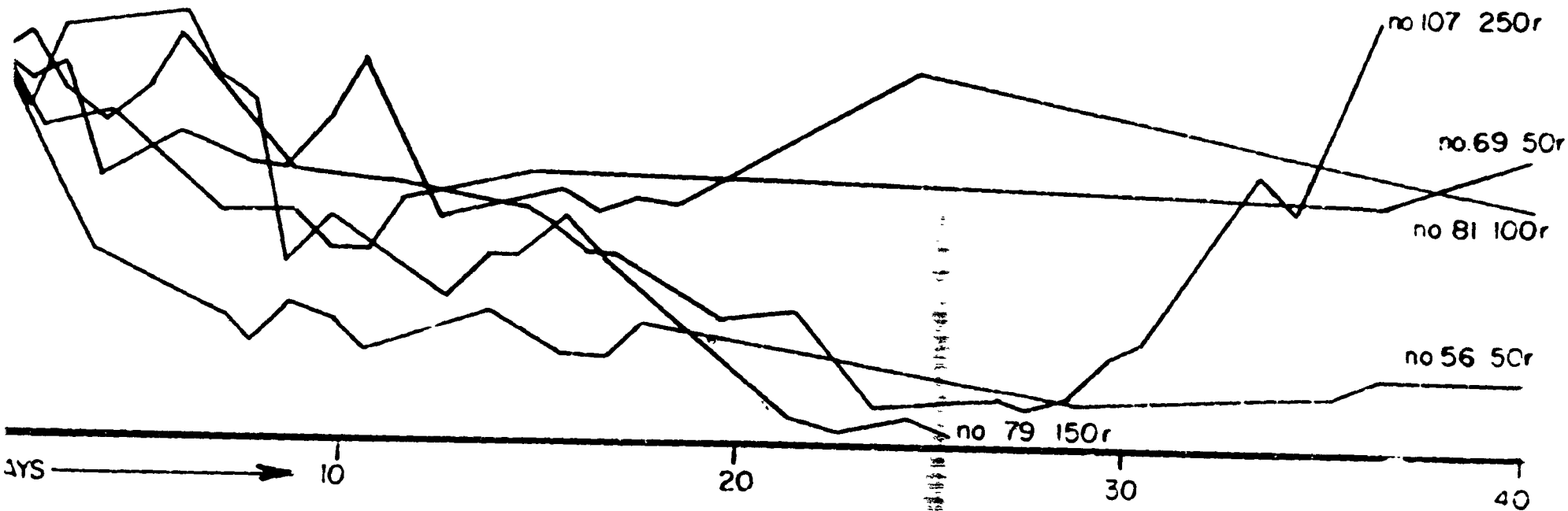
Similarity of the curves for 2 patients (Nos. 3 & 6) demonstrate the influence of comparable conditions not only in factors of irradiation but diagnosis (chronic lymphatic leukemia), age (over 60) and prior exposure (none) were the same for both patients. Identical factors of irradiation were used for patient No. 2 but there was no evidence of blood dyscrasia (diagnosis - multiple myeloma); because of his terminal state, follow-up was discontinued before depression became evident.
Rate of depression in patient No. 79 (2 m v.) followed the expected pattern but depth of depression was more severe than usual because of his terminal state.

Comparison of response following exposures of 25r - 250r
250 Kvp.



In general, the lowest point of depression occurs between the 20th and 35th day post-irradiation, except in patients with leukemia (Nos. 3 & 6) or other blood dyscrasias. For the remaining patients, rate of depression is roughly similar, and there appears to be some correlation between depth of depression and amount of exposure.

Fig. 5. Total Body Irradiation - White Blood Cell Count (%)
Comparison of response following exposures of 50r - 250r
2 m.v.



Here again, there may be similarity in rate of depression but it is difficult to identify correlation between degree of depression and amount of irradiation because of differences in clinical material (patient No. 79 was terminal, patient No. 56 had received considerable treatment prior to total body exposure). For the remaining patients, response followed patterns expected from the amount of exposure each received.

1) absolute change
2) per cent change & central tendency (weighted means)

b) Differential cell count
1) absolute change per cell type
2) per cent change & central tendency (weighted means) per cell type
3) absolute total circulating cell type

4. Platelets
a) Absolute change
b) Per cent change

5. Lipoprotein - ratio of changes in molecular weight to changes in protein moiety

6. RISA absorption

7. Antibody response
a) Rebuck test
b) Radiation altered serum gamma globulin (Dr. Luzzio)

8. Extracorporeal irradiation of blood

9. Bone marrow shielding

10. Pre- and postirradiation studies of bone marrow changes

11. Bone marrow bank
(aspiration, processing, storage, and re-infusion)

12. Determination of degree of protection using B.S.A. (Dr. Knox)

13. Determination of inhibition of tumor growth with single exposures of total body irradiation (Dr. Wesley Starbuck)

14. Evaluation of response when factors known to influence effect of radiation are comparable (age, integral dose, prior injury, amount of exposure, general condition, etc.)

15. Survey of literature with a view to compiling bibliography on radiation effects.

16. Current comprehensive protocol for patients receiving total body irradiation (hematology, blood chemistry, uring tests, psychology, liver function, muscular, body composition, cardiodynamic, etc.) with all tests recorded for data processing (see progress report for period ending Jan. 31, 1962).

[illegible] recently acquired equipment [illegible] additional personnel (radiophysics and radiochemistry) have permitted extension of the entire program. New studies in dosimetry have been initiated and studies in physiologic response to total body irradiation a being extended.

Dosimetry Studies

The standard method of reporting the exposure of total body irrad. is the amount of irradiation measured in air at the point to which the patient is centered in fixed beam therapy or the axis of rotation if the patient is rotated.

The use of any single numerical value such as skin dose or mid li dose does not imply uniformity throughout the patient or improve the certainty that the dose can be duplicated from one patient to another. I reasonable uniformity of dose distribution throughout the body could be obtained, then a simplified statement of dose would be meaningful and l comparable exposures, comparable biologic response might be expecte or discrepancies sought for on some other basis.

It has been thought that a 4 π irradiation source of appropriate qua of sufficiently large diameter might accomplish this result and other c have developed the "4-poster" technique using a specially designed roo and eight Cobalt-60 sources. A comparable technique has been develop using the 2 m.v. Van de Graaff to simulate a 4 ii source of 8 meters diameter. The patient is placed on a low litter with the beam at an ang of 28° and a target axis distance of 4 meters with a dose rate of 3.1r/n air at the axis. The litter is rotated in the beam with the patient first supine and then prone.

Phantom studies indicate a variation of 3% throughout the trunk. Studies are in progress to determine the variation in head and extremi Under these conditions a simple expression of dose becomes possible a meaningful; e.g., an individual of average diameter of 28 cm. for torso receives a dose of 70% ± 3% of the exposure measured in air at the axis To deliver 100r/gm. of bone marrow requires 140r measured in air at the axis.

An individual of 20 cm. average diameter of torso receives a dose of 80% ± 3% of the exposure measured in air at the axis. To deliver 100r/gm. of bone marrow (or any other tissue) requires 125r measured in air at the axis.

While further investigation is required, the method of delivering uniform dose throughout the body may result in a method of directly relating biologic response, particularly hematologic response, to dose delivered. The method may have further application in tissue and organ transplant studies when, presumably, uniform dose throughout the body desirable for [illegible]

Body Composition Studies

The elements measured or calculated are:

1. Total body water
2. Extracellular water
3. Intracellular water
4. Total body fat
5. Total body lean weight
6. Mineral mass
7. Cellular solids
8. Cellular mass

These are correlated with work efficiency as measured by O_2 c sumption and heart rate. Most of the work has been done on well in duals with attention to physical fitness, sex differences, dietary and obseity studies, growth studies and aging.

This is an area of study where radiation effects appear not to h been explored. Considering the effect on growth, the life shortening aging effects that are ascribed to radiation, body composition studie an appropriate approach to recognizing and appraising radiation effe

Physiograph Studies

The vital functions recorded at this time are:

1. Electro-encephalogram
2. Electrocardiogram
3. Blood pressure
4. Respiration rate and depth
5. Cardiotach (amplitude of defection is index of heart rate)

Animal Studies (Dose rate 350r/min. at 40 cm.)

Heart Irradiation - Dose range 12,000r - 50,000r

- 25,000r - dog survived 9 days
- Earliest change between 5000r & 6000r - slight skip of S T s
- Inversion of T wave at 24 - 72 hours
- Marked tachycardia and Q wave changes
- Terminal - tamponade with serosanguineous effusion

Brain Irradiation - Dose range 15,000r - 25,000r

- 25,000r - animal survived 2 weeks
- No changes in first 24 hours, then gradual increasing weakne unsteadiness
- Day 5 - Partial paralysis beginning
- Day 7 - EEG changes, spiking tachycardia & loss of sinus ar
- Day 9 - 10 Weeping encrustation of skin
- Day 11-14 Conscious and responsive
- Day 14 - died

No clear change in function noted in patients in doses used.
Humans Possible exception: Disappearance of sinus arrythmia preceding nau

Partial body irradiation - Dose rate 87r/min at 81.7 cm.

Abdomen: 3000r/28 days (Lymphoma)

After 900r in first week

1) Sinus arrythmia disappeared
2) S T segment became isoelectric (heart not in treatment field)

After 2300r in 3 weeks

1) Sinus arrythmia returned
2) EKG abnormality persisted (no explanation)

Brain: 1500r in 18 days (Medulloblastoma)

No change detected in any of the vital functions measured (This was re-treatment for recurrence of increase 1-C pressure Previously, patient had received 2500r in 71 days to entire brain and spinal subarachnoid space)

Patient remains paraplegic but is living and well 9 mos. after irra

Total Body Irradiation - Humans

M.R. 48 year old male. Diagnosis: seminoma, left testis

Following orchiectomy, the patient was referred to radiotherapy for treatment of metastases. There was a 3 cm. mass in left supraclavicular region, an ill-defined abdominal mass, mediastinal involvement, and lymphangiography demonstrated enlarged iliac and para-aortic nodes. Th s moderate anemia and the patient complained of weight loss, anorexia, and occasional nausea and vomiting. After bone marrow aspiration (280 c radiotherapy was started to involved areas and the patient was admitted to the Texas Institute for Rehabilitation and Research for wor-up according to the comprehensive protocol adopted last year.

Day 0	Prior to exposure, Hgb. 8.4 gms.;WBC 5,000; Plts. 297,000. Total body irradiation 250r/1 day, 2 m.v., rotation Nausea and vomiting prior to exposure - unchanged
Day 8	Hgb. 10.3 : WBC 2,240: Plts. 316,000 Transfusion 1000 cc. whole blood
Day 13	Partial body irradiation resumed Hgb. 12.2; WBC 2,500; Plts. 184,000
Day 25	Lowest point of depression; patient isolated Hgb. 11.7; WBC 376; Plts. 62,000
Day 31	One half stored marrow re-infused
Day 44	Hgb. 10.1: WBC 5,950; Plts. 488,000
Day 86	Masses reduced in size 50 - 90%, discharged
Day 109	Exacerbation of symptoms - radiotherapy - downhill course
Day 124	Expired

Physiological tracings per-irradiation revealed a heart rate within normal limits but there was an absence of fluctuations of the heart rate du

to respiration. Immediately after exposure, [illegible] of deceleration that coincided with nausea or vomiting.

A passive tilt test -re-irradiation was within normal limits. Five [illegible] later, the passive tilt test showed a slight drop in the systolic blood pre[illegible] with a marked reduction in pulse pressure and a marked increase in hea[illegible] ate. This was even more manifest on the passive tilt test that was obta[illegible] 39 days post-irradiation.

Gross body composition studies showed an increase in extracellular water and a decrease in intracellular water two weeks after irradiation. During this time the patient had lost weight (10 lbs.) with changes in lean body weight and fat content. These studies are summarized in Table 9. It is felt that change in extracellular and intracellular water may be due [illegible] irradiation, or to progressive disease, since loss of weight alone does n[illegible] alter this ratio.

Table 9

Gross Body Composition Before Irradiation (M.R.)

Measurement		Value Found	% of W	% of Theoretical W	Normal (% of W)
Total body water	(L.)	30.2	58.3	45.1	58.6 ± 3.50
Extracellular	"	22.6	43.6	33.7	21.0 ±
Intracellular	"	7.6	14.7	11.3	32.0 ±
Plasma volume	"	3.6	6.9	5.4	4.5 ±
Blood volume	"	4.9	9.5	7.3	7.7 ±
Lean body weight	(Kg.)	41.9	80.9	62.5	80.0 ± 4.53
Fat content	"	9.9	19.1	14.8	19.8 ± 4.51
Mineral mass	"	2.9	5.6	4.3	5.6 ± 0.31
Cellular solids	"	8.8	17.0	13.1	16.1 ± 0.95
Cellular mass	"	16.4	31.7	24.5	46.0
Post-irradiation					
Total body water	(L.)	33.2	70.3	49.3	58.6 ± 3.50
Extracellular	"	27.9	59.1	41.5	21.0 ±
Intracellular	"	5.3	11.2	7.9	32.0 ±
Plasma volume	"	2.5	5.3	3.7	4.5 ±
Lean body weight	(Kg.)	45.5	96.4	67.6	80.0 ± 4.53
Fat content	"	1.7	3.6	2.5	19.8 ± 4.51
Mineral mass	"	3.2	6.8	4.8	5.6 ± 0.31
Cellular solids	"	9.1	19.3	13.5	16.1 ± 0.95
Cellular mass	"	14.4	24.2	21.4	46.0 ±

Effect of irradiation on peripheral blood count is shown in Table 10. Transfusion on Day 8 sustained the hemoglobin and red blood cell count but depression of other elements continued to the lowest point on Day 25 Beginning recovery was noted on Day 30 and bone marrow was returned on Day 31. The contribution of bone marrow to recovery is not certain; marrow samples taken at the time of re-infusion indicate that re-popula[illegible] had started spontaneously and this is in agreement with the expected production of cells calculated in the granulocyte proliferation study.

Table 10

Response of Peripheral Blood count Following 250r Total Body Irradi
(M. R.)

		Day 0*	Day 3	Day 8	Day 18	Day 25	Day 30	D
Hgb.		8.4	8.2	10.3	12.4	11.7	11.4	
RBC**		3.7		2.99	4.0	2.6	3.49	
WBC***		5.0	4.8	2.24	1.82	0.87	0.6	
Segs.	%	81	89	81	76	44	15	
Bands	"	0	2	1	4	3	4	
Mye.	"	0	0	0	0	0	1	
Lymphs.	"	17	6	4	19	48	65	
Monos.	"	0	1	1	1	0	0	
Eos.	"	1	0	0	0	0	0	
Baso.	"	1	0	0	0	0	0	
Plts.***		297.6	330.0	316.0	68.0	62.0	82.0	4

*Prior to total body irradiation
**Millions
*** Thousands

Multiple blood chemistry studies were carried out before and afte total body irradiation. Those which showed change are listed in Table

Table 11

Changes in Blood Chemistry Following 250r Total Body Irradiation (M

	Day 0*	Day 1	Day 2	Day 3	Day 4
Urea nitrogen	14	15	14	20	18
Glucose (fasting)	87	88	102	108	102
Amylase	24	52	33	25	6
Lipase	2.39		0.19	2.36	0.51

*Prior to total body irradiation

While these changes appear to be within normal limits, they provo many questions. Are changes of more than 10 per cent significant? C the increase in urea nitrogen be an effect of radiation and is this relat to the change in cellular solids shown in the body composition studies? the rise in glucose normal for this patient? Is glucose greatly elevate heavy exposures and is this a contributory factor to the development o infection? The answers to these, and other similar questions, will reo that similar studies be carried out on many additional patients.

In this patient, the effect of total body irradiation was obscured by presence of anemia, by symptoms of nausea and vomiting prior to tota body irradiation, and by prior partial body irradiation; evaluation of th

results must be tempered with these factors and with the patient's po general condition. The degree of bone marrow depression was not u pected and his recovery period was not unduly prolonged; at the time death, 124 days post-total body irradiation, there was no evidence of radiation change.

For the remaining patients added to the series in this report per brief histories with response of peripheral blood counts are reported Details of the comprehensive work-up, i.e., blood chemistry, body co position, physiograph tracings, etc., are omitted except when the cha are significant or might be used for comparison.

S.S. 53 year old male. Diagnosis: Hodgkin's disease.

This patient had undergone surgical excision of enlarged nodes, t courses of chemotherapy, and radiotherapy to several areas of involv over a period of 8 months. When symptoms recurred, chemotherapy withheld because of mild congestive heart failure and the patient was referred for additional radiotherapy. He was digitalized and prior to irradiation, a thoracentesis yielded 600 cc. of pleural fluid.

Day 0 Prior to exposure, Hgb. 9.8; RBC 2,580,000; WBC 13,000; Pl
Bone marrow aspiration - 350 cc. stored
Total body irradiation, 100r, 2 m.v., rotation
No untoward reaction

Day 14 Re-accumulation of fluid in chest
Hgb. 10.1; WBC 18,950; Plts. 306,000
Thoracentesis with installation of HN_2

Day 31 High fever, cultures negative
Hgb. 5.5: WBC 1,910; Plts. 30,000
Lowest point of WBC depression - 17 days after chemothera
Patient very ill

Day 39 Developed obstruction of porta hepatica
Hgb. 7.2; WBC 2,620; Plts. 22,000
Died of disease

Because of the patient's poor general condition, it was felt that tl first exposure should be limited to 100r total body irradiation and thi could be repeated if indicated. Following chemotherapy and subseque bone marrow depression, this plan was abandoned. The patient had a vigorous work-up prior to total body irradiation but because of his do hill course, the post-irradiation series could not be undertaken. Dea was due to widespread disease with involvement of lungs, mediastinu and liver. Studies on response of bone marrow by means of the gran proliferation scheme showed beginning recovery on Day 36, three day prior to death, (see figures 6 and 7).

W.B.(No. 109) 49 year old male. Diagnosis: Chronic lymphocytic leuk

Diagnosis was established in 1957 and a year later the patient de congestive heart failure. From 1958 to 1962 he received chemothera Leukeran - 5 courses, Cytoxan - 2 courses, Prednisone - maintenanc daily dose, and numerous drugs for hypertensive cardiovascular dise When referred for radiotherapy, there was massive, widespread lym pathy with enlarged liver and spleen. Lymphangiogram showed multi nodes in pelvis and para-aortic area. Radiotherapy was directed to a giving rise to most severe symptoms with remarkable relief and prob prevention of obstruction. The patient was admitted to Texas Institute Rehabilitation and Research for complete investigation prior to total b irradiation.

Day 0	Prior to total body irradiation, Hgb. 13.2; WBC 17,700; Plts.14
	Total body irradiation - 150r, 1 m.v.
	No untoward reaction
Day 7	Liver slightly reduced in size, nodes less matted
	Hgb. 12.6; WBC 6,450; Plts. 154,000
	Discharged
Day 19	Re-admitted for follow-up studies
	Hgb. 9.4; WBC 5,250; Plts. 34,000
Day 23	Lowest depression of platelet count - 8,000; patient in isolatio
Day 34	Lowest depression of WBC - 3,700
Day 103	All nodes and masses somewhat reduced in size, condition goo
	Hgb. 13.8; WBC 14,950; Plts. 130,000

Physiograph tracings revealed fluctuations of heart rate associate with respiratory movement of fairly large amplitude after irradiation, contrast to the small amplitude prior to irradiation. There were seve episodes of deceleration which did not coincide with the subjective feel of nausea. Numerous extrasystoles were detected in the first 24 hour post-irradiation.

Body composition studies, carried out prior to irradiation, on Day and on Day 21, showed no significant changes.

Blood chemistry studies showed increase in cholesterol from 15[illegible] to 267 mg.% on Day 16; serum amylase increased from 28 to 137 on [illegible]

This patient is still under observation 9 months post total body irradiation. He has gained weight and feels improved; enlarged right cervical nodes will soon require treatment. Present blood count (Day 278) - Hgb. 12.6; WBC 21,000; Plts. adequate. There are no [illegible] or symptoms that could be attributed to total body irradiation.

C. W. 62 year old male. Diagnosis - Reticulum cell sarcoma

On admission, this patient complained of bilateral neck swellin fever, diarrhea, cough and weight loss for 2 months. On examinati there was generalized lymphadenopathy with massive enlargement neck nodes. Following biopsy, radiotherapy (2000r/2 weeks) was gi to supraclavicular and cervical areas with marked reduction in siz masses; untreated lymphadenopathy progressed and fever continued Protracted total body irradiation was planned with an initial exposu of 100r/1 day. Preparation included aspiration and storage of bone marrow (190 cc), bilateral lymphangiogram, intravenous pyelogram upper G.I. series, and the patient was admitted to the Texas I stitut for Rehabilitation and Research for completion of work-up accordin to the all-inclusive protocol.

Day 0	Prior to irradiation: Hgb. 10.0; WBC 20,450; Plts. 530,000 Total body irradiation - 100r, 2 m v (rotation) No untoward reaction, no nausea or vomiting
Day 3	Progress satisfactory Hgb. 9.3; WBC 13,600; Plts. 238,000
Day 15	Dyspnea due to mediastinal and respiratory involvement Patient very ill, repeat total body irradiation postponed Hgb. 10.0; WBC 11,450; Plts. 162,000
Day 26	Lowest point of depression Hgb. 8.3; WBC 5,900; Plts. 56,000 Patient losing ground
Day 27	Hgb. 10.2; WBC 7,050; Plts. 50,000 Re-infusion of bone marrow scheduled for Day 28
Day 28	Died of disease

The duration of this patient's complaints, i.e., two months, with massive lymphadenopathy at the time of admission provide some ind of the rapid growth rate of this lesion. Although previous partial bo irradiation demonstrated radiosensitivity, disease progressed so ra that the scheduled course of total body irradiation could not be carri out. Comprehensive work-up was done prior to total body irradiation many tests were repeated after exposure but because of progressive inanition, post-irradiation tests were not considered entirely reliabl and proper comparison could not be made.

Despite the patient's poor condition, total body irradiation w tolerated; bone marrow depression was mild and did not exceed that might be expected in the terminal stage as such widespread

[illegible] but treatment has been too recent for proper evaluation at this time. The diagnosis is retic cell lymphosarcoma with widespread dermal involvement manifested multiple nodules and swelling; the patient also has liver involvement and invasion of retro-bulbar area with erosion of bone and proptosis. Chemotherapy has been used without significant benefit. He withstood the total body irradiation procedure well, his response has been exce and post-irradiation investigation is now in progress. Special bone marrow studies are planned for this patient and a detailed report will included in the next progress report.

Response of peripheral blood counts of the patients receiving the peutic total body irradiation in this report period has been included in the histories. Further details on hematopoiesis of three patients (Nos. 107, 108, and 109), are given in the granulocyte proliferation stu

Evaluation of the effect of total body irradiation would be most satisfactory if all conditions were comparable, or if the clinical mate could be graded and divided according to the factors known to influenc response, i.e., age, general condition, prior partial body irradiation o other treatment, amount of total body exposure, etc. Under these cir- cumstances, it would be expected that, following a given amount of irradiation, patients in Grade A physical condition would show less depression and more rapid recovery than patients in Grade B physical condition and this could be illustrated by comparing depression and re curves. This type of analysis is not possible at present but there are for future studies to include this information. For patients treated ov the past year, details of clinical status and course are recorded for da processing and an increase in the number of patients in this study will provide material for impartial analysis by computer methods in the future.

Bone Marrow Bank

Three essential questions in connection with the clinical use of m are still to be answered:

1. Are cells that have been frozen and stored viable?
2. Do they proliferate on infusion?
3. Do they contribute to the recovery of hematopoiesis?

Even though the number of marrow banks in clinical use is [illegible] experience is limited, it might seem that these fundamental questions should have been answered by this time. The problem is that recognit of viability is uncertain and the determination of percentage viability is tenuous. Proliferation of re-infused marrow and the contribution to recovery is not readily distinguished from recovery due to stem cells surviving in situ. Before offering radiation exposure that would [illegible] survival only by means of return of stored viable autologous [illegible]

method is in the individuals who suffered exposures adequate to wipe out bone marrow. This circumstance can only occur by accident and the occasion will be rare. In the meantime, more conservative testing measures are being studied.

Sixty-two patients have had marrow aspirated and stored at sub-freezing temperatures (-80° C); this work was preceded by aspiration and storage of marrow of 37 animals. Marrow has been returned to 25 patients. In the course of this experience, the technique of withdrawal, processing, storing, and thawing has been refined and is now a routine procedure for patients receiving extensive partial body irradiation or intensive chemotherapy as well as total body irradiation.

Studies on viability of stored cells are being carried out. Trypan blue vital staining techniques have been used. We are using triated thymidine to label DNA in dividing cells, and grain counts as seen in autoradiographs before and after storage may be a useful index of viability. Present studies indicate 80 - 90 per cent viability of cells stored in the past year.

The possibility of recognizing stored cells, labelled in vitro, after they have been returned to the individuals is being explored.

Animal Experiments

The study of bone marrow shielding in animals receiving up to 1400 total body irradiation has been reported previously. The LD-100 for these animals was 700r but total body irradiation could be increased to 1200r by the use of a lead shield over the iliac marrow. Frequent blood counts were done and studies indicated that, in the unshielded animals, fall in peripheral blood count corresponded with the failure to produce new cells, i.e., as mature cells completed their life cycles and were lost no new cells appeared and life could not be sustained. In the shielded animals, mature circulating cells completed their life spans but new cells appearing in circulation were greatly reduced; following lethal exposures, new cells, granulocytes, could come only from the area of protected marrow.

Among animals receiving lethal doses without marrow shields, the absolute granulocyte count fell to 0 - 10 on the 12th day while in those protected with iliac shields, the absolute granulocyte count was 2[illegible] 3000 on the 12th day (a decrease of 60 - 70%).

All animals receiving up to 1200r with iliac marrow shielded [illegible] survived from 2 - 2½ years while all control animals (unshielded [illegible] from 5 to 17 days post-irradiation. Blood counts are done [illegible] on all surviving animals and, except for immediate depre[illegible]

that received 1000r (shielded) has been bred and bore a litter of tou healthy pups; one died of unknown cause without evidence that irrad of the mother contributed in any way to death. The remaining anim are normal and it is proposed to breed these litter mates to obser possible transmissible mutation.

Animal experiments have been designed: 1) to investigate gran proliferation in normal and aplastic marrow and 2) to determine th viability of marrow cells following aspiration, processing, storage re-infusion. Both these studies utilize tritiated thymidine to label in dividing cells, and results from the two animals used so far indi that these studies will provide helpful information.

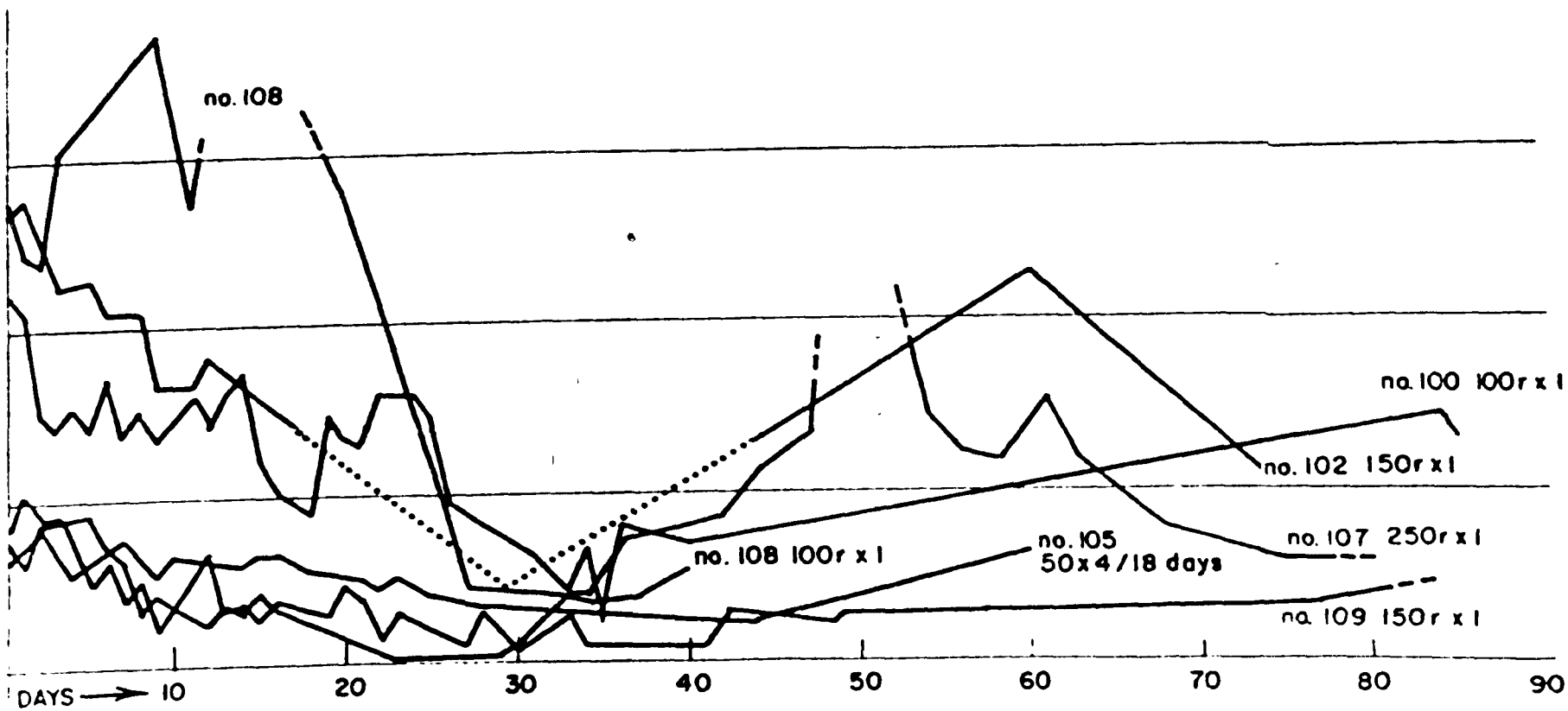
Granulocyte Proliferation Studies

The peripheral blood count has been considered the best index radiation change and among all the elements of peripheral blood, th cytes are the first to show decrease following exposure. The life s lymphocytes in circulation has been studied by several authorities (with estimates ranging from a few hours to more than two months. cells are highly undifferentiated and there is some evidence that the two or three sub-types, each having different life spans. Those with shortest life span may well be the first to be lost following radiatior exposure but since they cannot be distinguished from other types, ar since lymphocyte counts in peripheral blood cannot be based on the number in circulation (many are found in lymph channels and organs calculations on their rate of disappearance are unsatisfactory.

Granulocytes originate in bone marrow and, in man, require an estimated 4 to 5 days for proliferation through the various myeloid partments before appearing in circulation where, in our studies, the cycle is completed in 4.5 days; their circulating life span has been to be from 3 to 13 days by other investigators (5, 6). In contrast to life span of red blood cells (120 days), granulocytes would be the fir reflect radiation change in marrow and subsequent change in periphe blood. Normally, granulocytic cells constitute 50 - 80 per cent of to white blood cells while lymphocytes and other elements make up the remaining 20 - 50 per cent. Following therapeutic total body irradia granulocytes may decrease to 15 per cent or lower while other elem are decreased (see Table 10, page 15). Since these values are per c rather than absolute, the apparent increase in lymphocytes overshad the loss of granulocytes.

Figure 6 shows the changes in circulating granulocytes in five p following total body exposures of 100r to 250r in one day, and in one patient following 200r/18 days. The dotted line of the curve for patie No. 102 (150r/1 day) is projected from the rate of depression to the

Fig. 6. Total Body Irradiation - Total Circulating Granulocytes
Single exposures 100r-250r (5), protracted exposure 200r/18 days (1) 2 m.v.



similarity in the gradual depression of granulocytes to the 4th and 5th week and this is followed by beginning recovery. A second depression occurring about 2 months post-irradiation has been noted in many patie and in animals. The explanation for this is not known at this time.

Assuming that there is a primitive stem cell which is the precurso of the myelocytic series of marrow cells, and that the time involved for proliferation through the various compartments and extrusion into circulation is correct, a quantitative analysis of the number of stem cells destroyed by irradiation can be determined by the 14th day. When the number of destroyed stem cells is plotted against increasing rad dose (estimated), and roentgen dose, a sigmoid curve is drawn which closely resembles the L D values determined for dogs and postulated for human (see figure 7). The first two curves represent our observations on hum they show destruction of stem cells ranging from insignificant following 50r total body irradiation to 66 per cent following 250r. Extension of th two curves beyond 66 per cent destruction at 250r is obtained by extrap from rate of change. These curves are compared with the second two w show Cronkite's L D for dogs and his estimated L D for humans (1). Studies on marrow shielding in dogs indicate that re-population of deple marrow can be accomplished if as little as 6 per cent of the stem cells survive. The L D curve for humans should approach 100 per cent as the L D curve of stem cells approaches 94 per cent.

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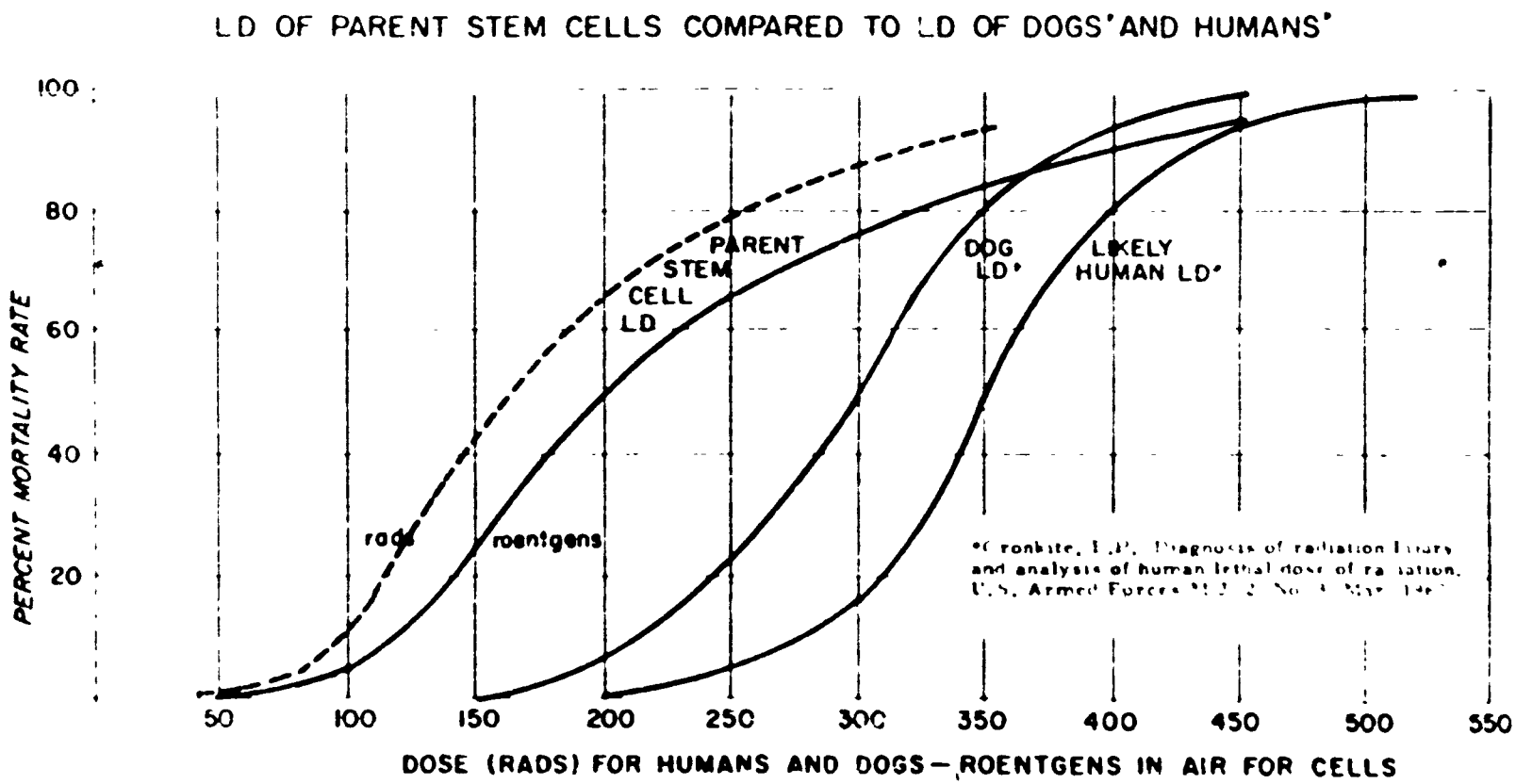
Fig. 7.


LD OF PARENT STEM CELLS COMPARED TO LD OF DOGS* AND HUMANS*
PERCENT MORTALITY RATE
100
80
60
40
20
rads
roentgens
PARENT STEM CELL LD
DOG LD*
LIKELY HUMAN LD*
50
100
150
200
250
300
350
400
450
500
550
DOSE (RADS) FOR HUMANS AND DOGS—ROENTGENS IN AIR FOR CELLS

This study has many implications. When animal experiments with marrow shielding were first undertaken, it was hoped that, if the animals survived lethal exposures, shielding would offer similar protection to humans. However, following a nuclear explosion, the amount of lead required for protection against the whole spectrum from thermal to high energy gamma radiation made this impractical. But if calculations are correct, some information is provided concerning: 1) the amount of marrow that must be protected, 2) the amount of marrow that must be transfused, and 3) the time when transfusion would be most beneficial. If, in the occupation of a radioactive area, the amount of radiation was within the range used in these experiments, then the application of these measures should be useful. In cases of accidental exposure, it seems possible that the amount of exposure could be determined or estimated from the rate of early depression and life-saving measures would be instituted before depression became critical.

All aspects of this study will be continued with 1) observations on patients receiving therapeutic total body irradiation, 2) studies in dosimetry, 3) bone marrow banking and viability, 4) granulocyte proliferation studies and 5) animal experiments. Emphasis will be placed on analysis of patients receiving protracted exposures and determining effect on hematopoiesis by means of the granulocyte proliferation study; this will provide information with which to determine effect of bone marrow transfusions and the intervals during protracted exposures when such transfusions would be most beneficial.

The essential problem posed by the possibility of massive irradiat of the human is to predict the lethal dose,--the dose at which immediat but temporary incapacity will occur, and the dose at which delayed but significant injury will occur. The possible answers proliferate as probable qualifying factors are introduced, e.g.,

1. Unless there is a uniform concept of dose and dosimetric procedure gross discrepancies in estimates of dose-effect are to be expected.
2. The effects of irradiation are not specific and are apt to be confuse with other types of injury,--mental, physical or biochemical.
3. The effect of the accidental or catastrophic irradiation exposure wil vary with the geographic, geometric and anatomic relations that ma be unsuspected or, at least, difficult to reconstruct.
4. Age, general health and competing disease will modify the response of the individual. Prediction of dose-effect is possible for individua or for uniform groups of individuals but a very wide range of dose-effects is to be expected in the general population.
5. Prediction of dose-effect in humans must be based upon the controll circumstances of clinical use of radiotherapy where uniformity of radiation throughout the body may be sought although this is unlikel ever to be achieved in accidental or catastrophic exposure.
6. Morbidity and mortality will clearly depend upon medical assistanc whether this be merely supportive or actually specific.

Nevertheless, some simple expression of the hazard of radiation i necessary and a prediction can be offered if an allowance of ± 3 d B is granted.

The following predictions are based on a hypothetical group of adul males between 30 and 50 years of age, with training or education to per a basic understanding of radiation and biology, physically and mentally conditioned to work in the field of radiation hazards and free of any previous physical or chemical trauma likely to impair tolerance to radiation. The dose is expressed as the amount of radiation measured in air at the site where the individual is exposed. The geometry of exposure and quality of irradiation is assumed to be such as to produce a uniform distribution through the entire body.

"Acute incapacity" means uncertain ability to carry out crucia' mental or physical tasks.

"Partial disability" means ability to carry out mental tasks and sedenta work but vulnerable to stress, e.g., severe physical exertion, infection or further irradiation.

The problems of single brief exposure and of protracted exposures are dealth with separately.

Predicted Effect

of

Single Exposures of Total Body Irradiation

Amount of Irradiation	Acute Incapacitation	Partial Disability	Blood Counts (% of normal)	Tim Reco
50r	0	0		
100r	0	0	75%	60 d
200r	0	0	50%	60 d
300r	1 - 6 hrs. (minor)	0	25%	60 d
500r (no deaths anticipated below this level)	1 - 12 hrs.	2 - 3 mos.	5%	90 d
700r (LD-50 range)	1 - 72 hrs.	6 mos.	1%	120 d
900r (LD-100 range)	2 mos.	12 mos. (if any survivors)	<1%	1 y (if any su

The prediction of the effects of protracted total body irradiation is less readily described in simple numerical values for dose and time.

The rule to be anticipate is that, taking values for single exposures of the order of one hour as a standard, the effect of protraction will be (A) to obscure the time of onset of signs or symptoms due to delayed and insidious development , and (B) to prolong the recovery period due to: 1) increased time required for accumulation of an effective amount of irradiation, 2) inhibition of the repairative response, 3) vulnerability to infection and other forms of stress during the period when repairative response is impaired.

It is evident that at some low level of protracted exposure, no detectable effect will occur and at some high level of protraction falling short of lethality, the above description will be clearly applicable. Intermediate exposures will be difficult to define with precision.

Table 13

Predicted Effect
of
Protracted Total Body Irradiation

Amount of Radiation and Duration of Exposure		Symptoms		Blood Co	
		Acute Incapacitation	Partial Disability	% of normal	Re
100r	in 1 wk.	0	0	90%	
	in 1 mo.	0	0	90%	
	in 1 yr.	0	0	0	
200r	in 1 wk.	0	0	75%	
	in 1 mo.	0	0	50%	
	in 1 yr.	0	0	0	
300r	in 1 wk.	0	Day 15-50	50%	
	in 1 mo.	0	Day 30-90	25%	
	in 1 yr.	0	0	0	
500r	in 1 wk.	Day 7-10	Day 10-90	20%	
(MLD range)	in 1 mo.	Day 25-35	Day 35-150	1%	
	in 1 yr.	0	Mos. 10-24	50%	
700r	in 1 wk.	Day 5-30	Day 30-150	1%	
(LD-50 range)	in 1 mo.	Day 15-50	Day 50-200	<1%	1.
	in 1 yr.	0	Mos. 10-24	25%	
900r	in 1 wk.	Day 4-30	Mos. 1-6	1%	
(LD-90 range)	in 1 mo.	Day 10-50	Mos. 2-12	<1%	
	in 1 yr.	0	Mos. 8-24	10%	

The above values are predictions, not conclusions.

They are offered as "best answers" to current conjecture base total experience in clinical radiotherapy.

The values below 300r are firm estimates.

The values below 500r are safe estimates.

The reason for continued clinical investigation is to accumulat further observations and develop more reliable tests to confirm or alter the impressions in high dose ranges.