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THE ACUTE RADIATION SYNDROME:
RELATION OF CLINICAL EFFECTS TO PROGNOSIS

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This report presents a brief account of research carried out at the Radioisotope Laboratory of the University of Cincinnati for the past nine years reflecting our concern with the diagnosis and treatment of the acute radiation syndrome. These studies are almost entirely derived from patients with cancer in whom curative attempts cannot be made. It has been our tenet that whole or partial body radiation is at least as effective as other forms of palliation.

Insofar as possible patients are selected with a normal hemogram and ability to maintain weight. Those with lymphomata are excluded from the study since the possible rapid destruction of tumor tissue would present changes not found in the more nearly normal subject.

Irradiation has been given with a single Cobalt 60 teletherapy unit at distances of 282 cm from the midline and with exposure rates of 3-6 R/min. Whole body exposure is given through two opposing lateral portals. Partial body radiation is given with a dividing point at the xiphoid although other boundaries are to be investigated in the future.

Each patient serves as his own control with a 3-5 week pre-treatment exposure period being compared to a 4-12 week post-treatment observation period. There is careful clinical observation, special psychic and psychiatric interviewing,

detailed laboratory tests and a number of special biochemical and other studies of interest.

Two aspects of this work will be presented here. The first is concerned with evaluation of clinical and routine laboratory observations and the second is related to estimates of effects of partial body irradiation to the better documented changes observed in total body exposure.

In the course of our clinical evaluation several episodes of sham irradiation are carried out and in most instances these have preceded the actual therapy. The preparations and procedures for sham are the same as for the irradiation. At no time is the patient informed as to symptoms or signs which he might experience nor is he questioned about such manifestations subsequently.

One of our specific interests has been the occurrence and frequency of prodromal symptoms in relation to prognosis. An early hypothesis was that subjects who had received previous radiation therapy would be more likely to have prodromal symptoms and that these would be more severe than in patients who had been so treated earlier. This hypothesis was rejected. No difference in prodromal findings between these two categories of patients was noted nor was there any difference in hematological findings not attributable to the underlying disease.

Insofar as a dose response relationship is concerned, prodromata were not found below 100 rad. There was a gradual increase in the frequency of nausea and vomiting between 100 and

200 rad, the probabilities being shown in Table 1. These responses vary somewhat from those reported by Lushbaugh (1) but our patients were carefully screened from inferential questioning or subjective stimuli. Also as mentioned earlier, there were no patients with lymphoma in this study. It is of considerable interest, however, that none of our subjects have ever shown nausea or vomiting from episodes of sham whether given before or after the actual exposure.

The other clinical finding of considerable interest was the lack of change in the incidence of prodromal symptoms with partial body irradiation. In this part of our study patients received irradiation to the upper or lower parts of the body, the separation point being at the xiphoid. The dosimetry of these two situations is shown in Fig. 1 and 2. Our highest dose to date has been 300 rad. The clinical response to the partial body irradiation was the same as if the patient received total body irradiation. The frequency and severity of nausea and vomiting were related to dose. It was not possible to distinguish these patients clinically from the total body group.

But in regard to their hematological changes, one is struck by the remarkable paucity of changes following 50-300 rad of this partial body exposure. No difference in response has been observed between upper and lower body irradiation. Although there may be small decreases in certain of these values it would be quite difficult to determine that such an individual had received radiation.

Even early lymphocyte depression was less marked than for comparable degrees of whole body radiation. Using the technique of profile scoring (2) as modified for previous evidence of disease shows that partial body patients fall between those receiving less than 100 rad and those receiving 100 rad. (See Table 2).

Thus one might expect less response from the PBR patients by an objective hematological measure.

An extensive battery of psychological and psychiatric studies were carried out (See Table 3). These tests have been designed primarily to demonstrate possible evidence of cognitive impairment. As yet there is no evidence of such change though this negative finding may be due to the poor intellectual quality of our patients. A major problem in this sphere is the development of suitable tests to permit adequate evaluation.

As a result of the lack of evidence of hematopoeitic damage in the partially irradiated patient an attempt has been made to determine the effect of these doses and to estimate at what point the partial body dose would be equivalent to total body radiation.

Bond (3) has derived a curve (Fig.3) for estimating the mortality from exposure of bone marrow with either uniform or non-uniform distribution. An LD_{50} of 285 rad is used and is set equal to a relative stem cell survival of 1.0. Kereiakes and Rogers (4) have measured the actual bone marrow dose in rad for the conditions of bilateral cobalt-60 exposure in the phantom.

Thus for the conditions of our study the actual doses may be used with Bond's curve to calculate the relative stem cell survival. This curve has been extended somewhat to explore the effect of higher partial body doses (Fig.4). In this way one can estimate that a midline dose to the lower body of 600 rad (900 R midline air exposure) would be equivalent to a whole body dose of 120 rad and would produce minimal significant hematological effect. At these dose levels, however, and at somewhat higher ones it might be possible to produce other localized effects, e.g. skin or gastro-enteric.

Further consideration should be given to the employment of human subjects who in the course of their disease receive radiation therapy and can contribute to our understanding of acute effects. Many of the findings in lower animals are not confirmed in the human being.

Our studies indicate that human data can be useful in estimating radiation effects and that patients can serve as important sources of data which cannot be obtained in any other way. Such studies need be expanded.

TABLE 1

Stimulus (prodromal symptoms[a]) at which proportion P would be expected to respond (Cincinnati data).

P	Midline dose (rads)
0.10	58
0.20	86
0.30	107
0.40	125
0.50	141
0.60	157
0.70	175
0.80	195
0.90	224
0.99	292

a. Nausea, vomiting, etc.

TABLE 2

Type of rad	No. of Pts.	Dose	Mean Rad Score
TBR	8	< 100 rad	12.6
TBR	8	100 rad	41.2
PBR	8	100-300 rad	21.3

TABLE 3

(a) Reitan Trails Test, Parts A and B.

(b) Catell's 16 PF IPAT, Form A.

(c) Gottschalk-Gleser Values Inventory

(d) Wechsler Depression Rating Scale

(e) Clinical Depression Scale of Gottschalk.

(f) Selected portions of the Wechsler-Bellevue Adult Intelligence Scale.

(g) Clinical Hope and Denial Scales.

(h) A structured questionnaire designed to pinpoint certain specific dynamics contributing to depression such as separation, guilt, shame and machochism.

(i) A five-minute tape recorded verbal sample.

Figure 1

RELATIVE DOSES FOR ^{60}Co PARTIAL BODY (LOWER) IRRADIATION AS MEASURED WITH TL-100 POWDER AT CENTER OF RANDO PHANTOM LATERAL IRRADIATION

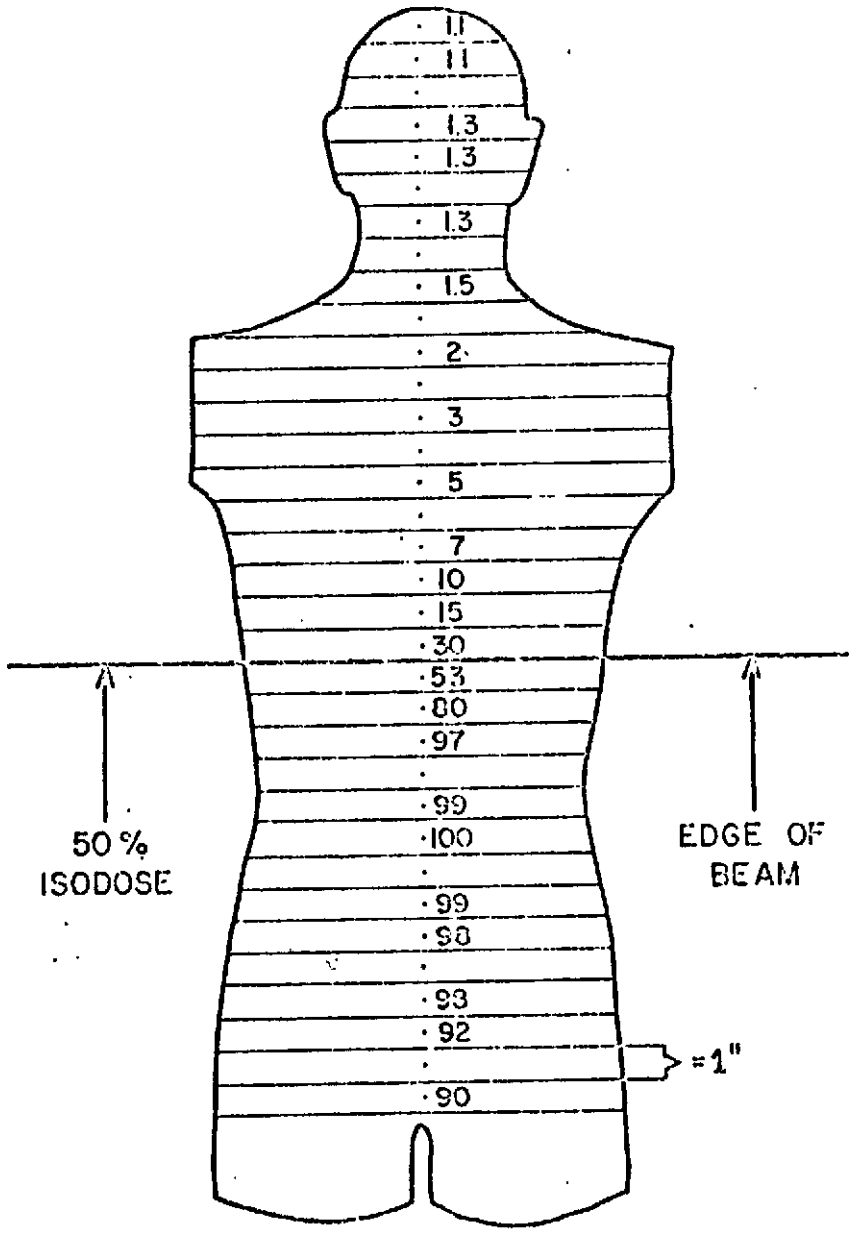


Figure 2

RELATIVE DOSES FOR ^{60}Co PARTIAL BODY (UPPER) IRRADIATION AS MEASURED WITH TL-100 POWDER AT CENTER OF RANDO PHANTOM LATERAL IRRADIATION

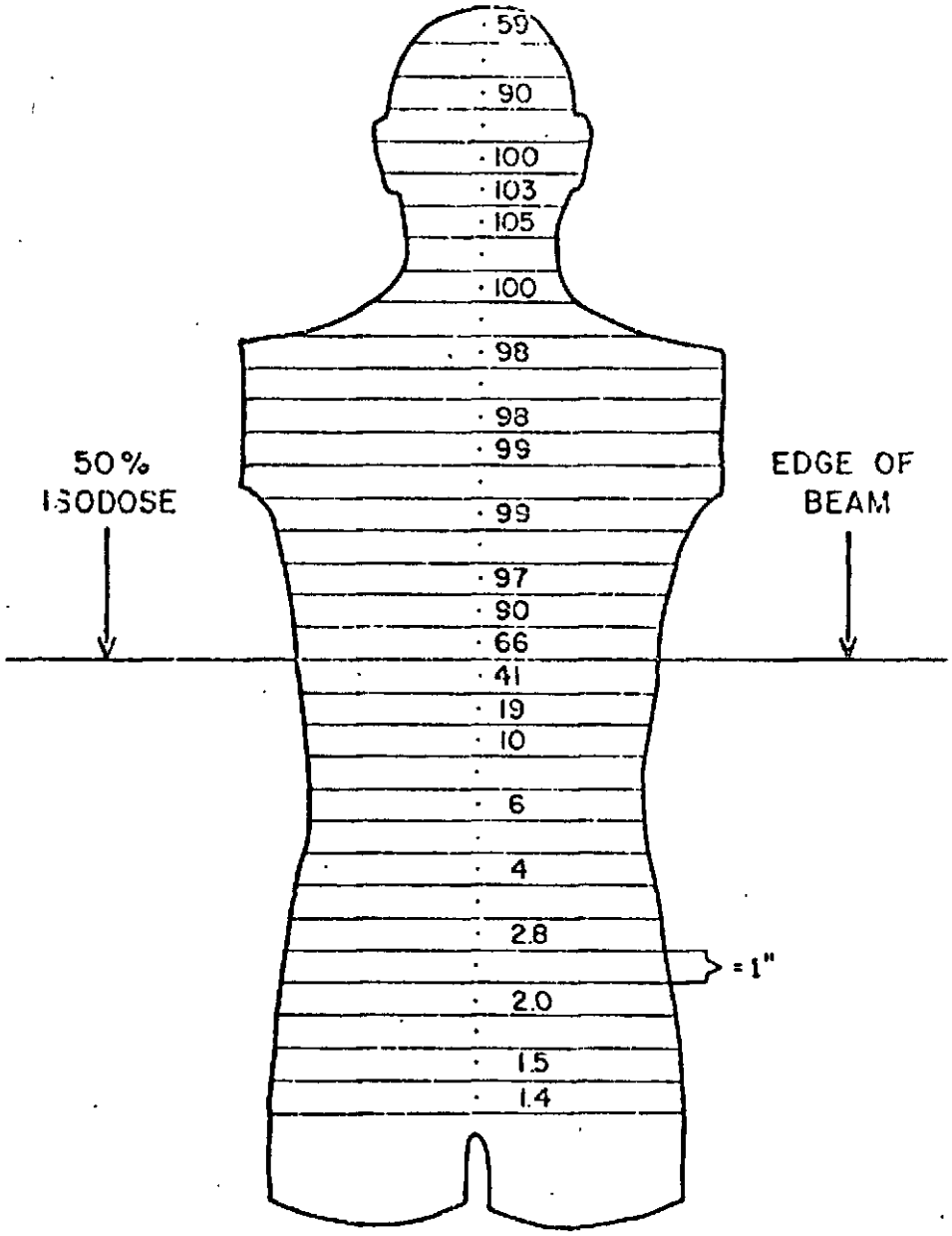


Figure 3

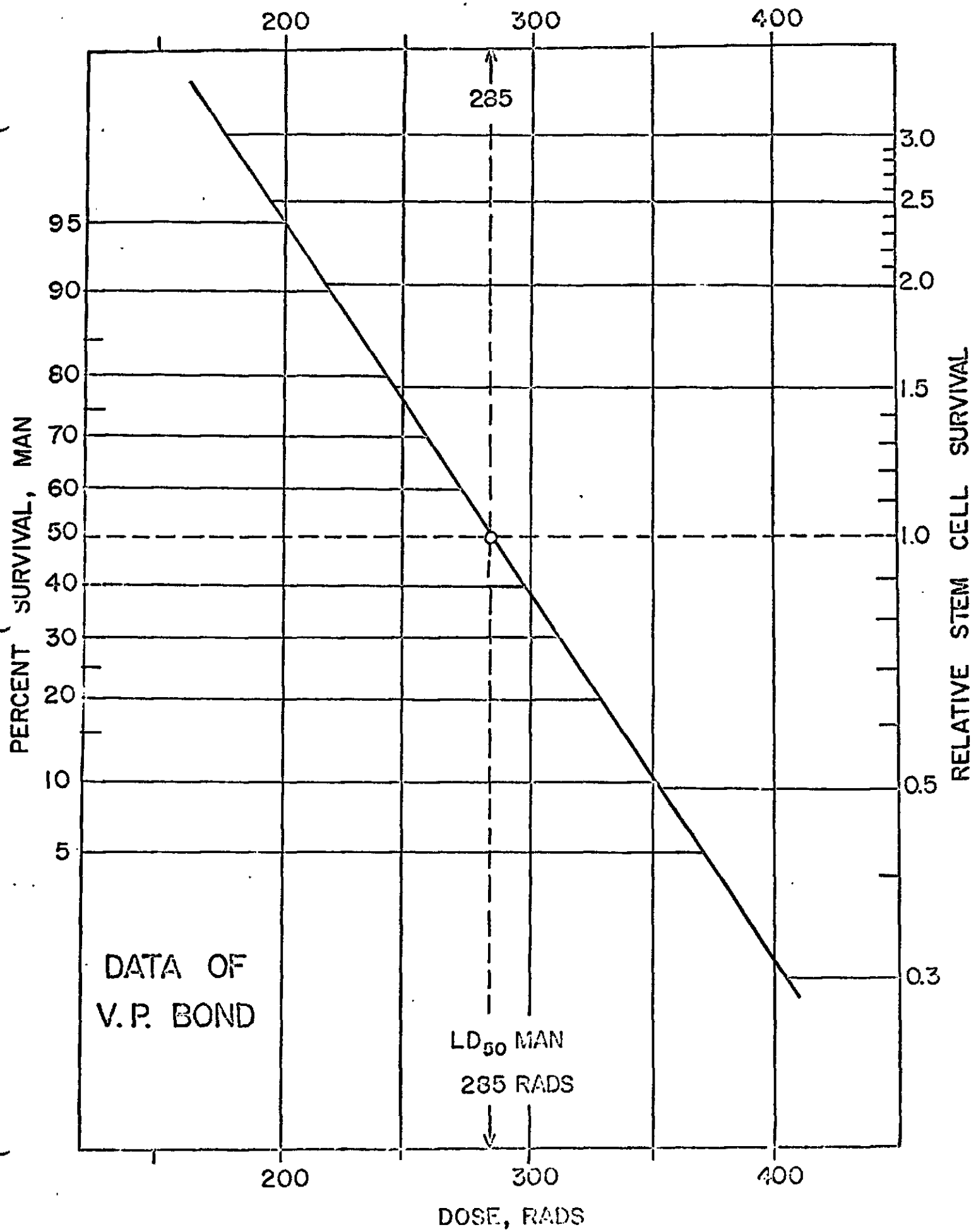
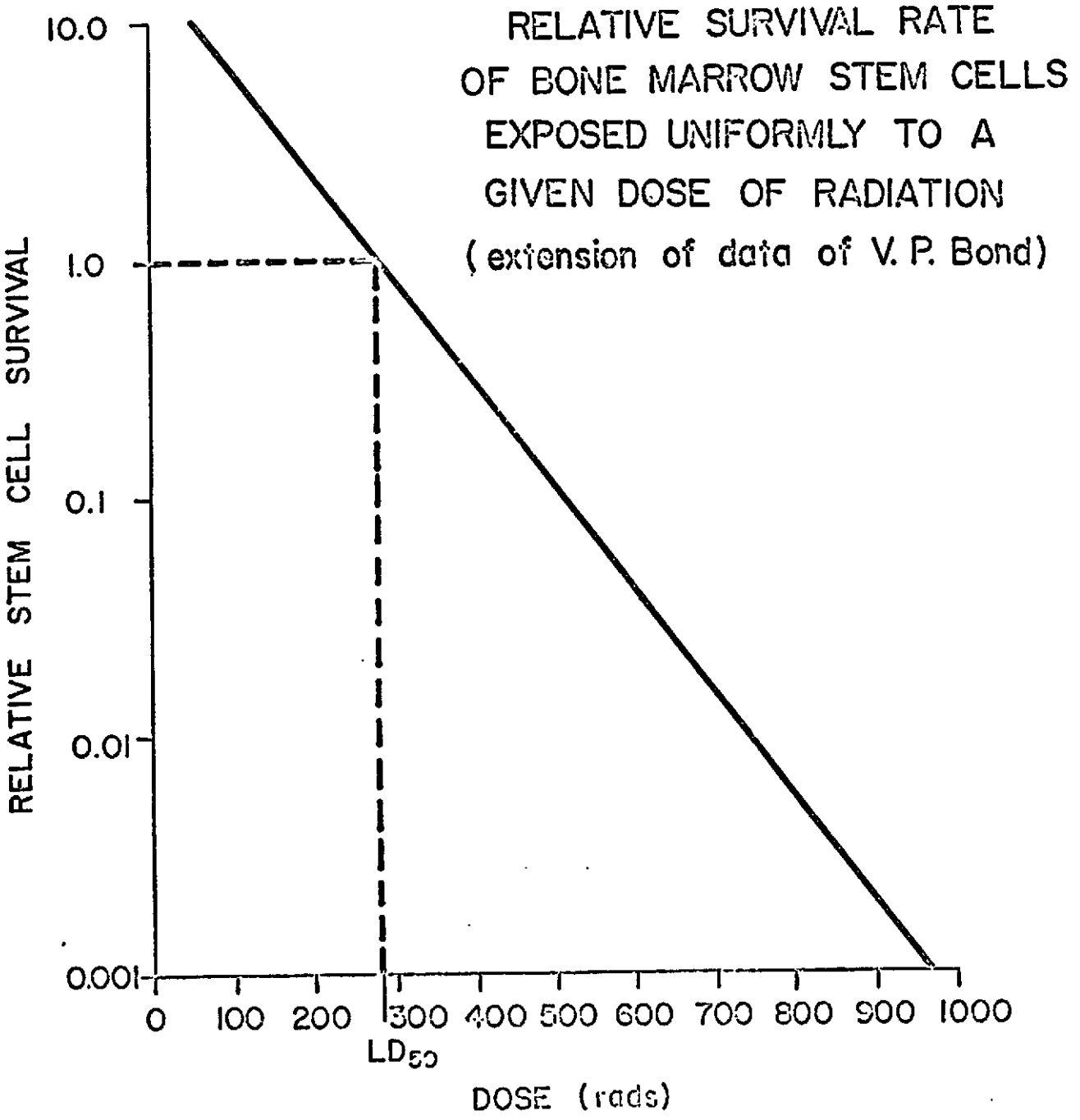

200
300
400
285
95
90
80
70
60
50
40
30
20
10
5
PERCENT SURVIVAL, MAN
3.0
2.5
2.0
1.5
1.0
0.5
0.3
RELATIVE STEM CELL SURVIVAL
DATA OF
V.P. BOND
LD50 MAN
285 RADS
200
300
400
DOSE, RADS

Figure 4


RELATIVE SURVIVAL RATE
OF BONE MARROW STEM CELLS
EXPOSED UNIFORMLY TO A
GIVEN DOSE OF RADIATION
(extension of data of V. P. Bond)
RELATIVE STEM CELL SURVIVAL
10.0
1.0
0.1
0.01
0.001
0
100
200
300
400
500
600
700
800
900
1000
LD50
DOSE (rads)

REFERENCES

1. In Langham, W.H. (Ed.) Radiobiological Factors in Manned Space Flight, Chapter 5, p. 59-133 Part II, Radiation Effects in Man:Early Effects.

2. Metabolic Changes in Humans Following Total Body Irradiation. DASA-1422, Report for November 1, 1961 through April 30, 1963. DASA Contract No. DA-49-146-XZ-029, Defense Atomic Support Agency, Washington, D.C.

   Metabolic Changes in Humans Following Total Body Irradiation. DASA-1844, Report for February 1960 through April 30, 1966. DASA Contract No. DA-49-146-XZ-315, Defense Atomic Support Agency, Washington, D.C.

3. Bond, V.P. Personal Communication.

4. Kereiakes, J.G. and Rogers, J.W. Personal Communication.