# DOSIMETRY FOR RADIOBIOLOGICAL STUDIES OF THE HUMAN HEMATOPOIETIC SYSTEM[1]

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## *INTRODUCTION*

At present, physical measurements of radiation exposure field fluxes are considerably more accurate than retrospective biologic estimates of the radiation dose in any particular exposure incident. However, wide individual variation in clinical response to radiation exposure often creates an apparent disagreement between physical and biological dose estimates. This disparity is largely caused by biologic variations in radiosensitivity and systemic repair but is also the result of individually different depth-dose distributions owing to body size differences or orientation geometry occurring during otherwise equal exposures.

Medical appraisal of the range of human biological variation in hematologic responses is needed, but has not been made because dosimetric information about the real depth doses to the bone marrow of individual patients is not available. The wide spatial distribution of bone marrow in the human skeleton makes the determination of the total averaged dose or any local bone marrow dose difficult and at present requires an empirical approach. This study was performed to devise a system for estimating individual bone marrow doses in therapeutic radiation exposures of leukemic patients. These measurements are needed to make dose-response correlations and to study the effect of dose protraction on peripheral blood cell levels. Such correlations are basic to medical management of irradiated persons since the bone marrow is one of man's most important radiosensitive tissues; lethality within 60 days of acute exposures from 200 to about 1000 R usually results from hematopoietic failure. Some studies (refs. 1 and 2) have shown that in selected patient populations the human $LD_{50/60}$ may approach a low of 250 rads average body-dose, but confidence in these estimates is poor.

During extended space explorations there may be little risk of receiving such sizeable doses acutely but there is a real chance of accumulating doses to the marrow that may be biologically significant. True correlation and variation of human hematologic responses to total-body irradiation (TBI) are sorely needed to help in establishing workable limits for these occupational exposures during missions in outer space. While the studies we have made were primarily intended for clinical uses, the data obtained is applicable to some of the dosimetric and shielding problems of space medicine.

In the Oak Ridge Associated Universities (ORAU) Medical Division program of therapeutic TBI, three irradiators with different exposure rates are in use: the ORAU low-exposure-rate total-body irradiator (LETBI) and medium-exposure-rate total-body irradiator (METBI), and the University of Tennessee-AEC Variable Dose Rate Irradiation Facility (VDRIF). Each of these irradiators was specifically designed to produce a uniform field of high-energy-gamma radiation for total-body exposures of large animals and man.

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*THE IRRADIATORS*

The LETBI facility consists of a large outer room (Fig. 1B) in which a smaller exposure room (Fig. 1A) is centrally positioned. Eight cobalt-60 sources of 16 Curies each are located in the outer room and they irradiate the treatment room from all sides. This arrangement provides a radiation field uniform to within ±10% in the living volume (16×16×8 ft) occupied by the patient. Treatments given at an average exposure rate of 1.5 R/hr have ranged from 3 to 8 days duration to provide total protracted exposures up to 250 R. During exposure the patient is free to move about the exposure room while being irradiated for 18 to 22 hr per day. This facility is described in more detail by Andrews, et al. (ref. 3).

A model of the METBI facility is shown in Fig. 2. The control room is connected by a curved hallway to the 8×8×8 foot treatment room. Eight cesium-137 sources of 500 Curies each, located in the walls, irradiate the centrally suspended treatment bed. The radiation field in the 2×2×6 foot volume occupied by the patient on the bed is uniform to within ±5% of the 1.5 R/min exposure rate in the volume center. Exposure times here range from a few minutes to a few hours for total exposures of 20 to 350 R. A complete description of this facility has been published by Brucer (ref. 4).

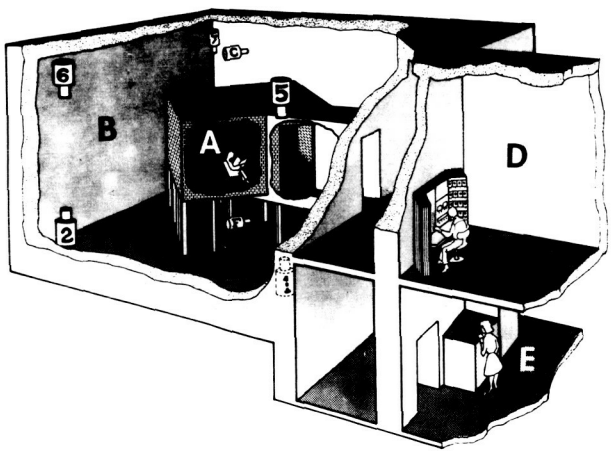


Figure 1.—Cutaway drawing of the low-exposure-rate total-body irradiation facility (LETBI) showing:
(A) Centrally positioned radiation exposure/living room.
(B) Concrete shielded radiation containment room.
(D) The remote control room for operation of the $^{60}Co$ sources (only sources No. 1,2,5,6,7, C and F are shown), radiation exposure level supervision, nursing and physiologic surveilance of the patient.
(E) The on-line and data processing room.

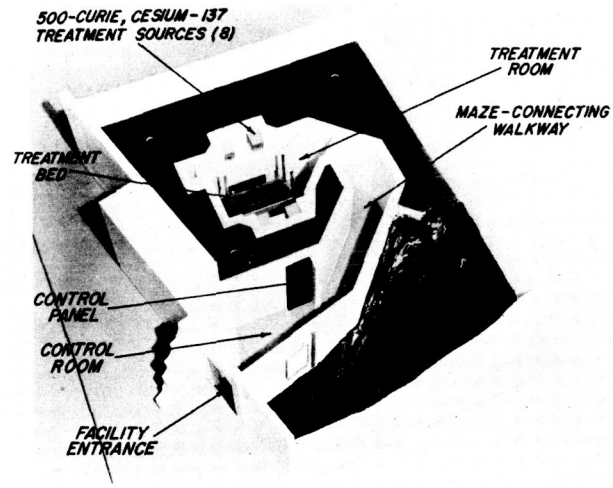


Figure 2.—Cutaway model of the medium-exposure-rate total-body irradiation facility (METBI).

The floor plan of the third irradiator (VDRIF) used in this therapy program is shown in Fig 3. Six cobalt-60 sources of 7700 Curies each are arranged in a rectangular array with 20 ft between adjacent sources. Exposures are done with the patient lying on his side on a hospital stretcher in the center of the source array. During patient therapy five sources are used to provide exposure over the stretcher at a rate of 40 R/min ±5%. To minimize the radiation hazard to hospital attendants, who might be required to aid the patient in case of equipment failure, we do not use source No. 1, which is nearest the entrance to the exposure room. A more complete description of this irradiator is given by Checka, et al. (ref. 5).

The radiation characteristics and dimensions of these irradiators are summarized in Table 1.

TABLE 1

RADIATION CHARACTERISTICS AND DIMENSIONS OF THREE TOTAL-BODY IRRADIATORS

| FACILITY | SOURCES | RADIATION (Gamma) | EXPOSURE VOLUME | EXPOSURE RATE TREATMENT VOLUME | MODE OF EXPOSURE | SOURCE TO CENTER EXPOSURE VOLUME |
|---|---|---|---|---|---|---|
| LETBI | 8 $^{60}$Co | 1.25 MeV | 16×16×8' (room) | 1.5 R/hr (±10%) | Multilateral | 19.5' |
| METBI | 8 $^{137}$Cs | 0.662 MeV | 6×2×1' (above bed) | 1.5 R/min (±5%) | Multilateral | 5.8' |
| VDRIF† | 5† $^{60}$Co | 1.25 MeV | 6×2×1' (above bed) | 40 R/min (±5%) | Bilateral | 10' (Sources 3,4) 22.5' (Sources 2,5,6) |

*This irradiator belongs to the UT-AEC Agricultural Research Laboratory.
†VDRIF has 6 sources, but only 5 are used during therapy to patients.

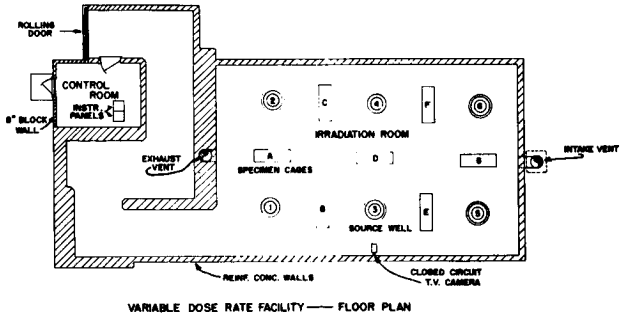


Figure 3.—Floor plan of the University of Tennessee-Atomic Energy Commission (UT-AEC) Agricultural Research Laboratory Variable Dose Rate Irradiation Facility (VDRIF). Source positions are indicated by No. 1-6.

## *THE PHANTOM*

An Alderson Rando phantom (ref. 6) was used as a patient analogue. This standard-man-sized phantom is constructed of isocyanate rubber, equivalent to tissue in interactions with ionizing radiation. A human skeleton and density-adjusted lungs are contained within the otherwise solid phantom. The phantom is sliced into transverse sections 2.5 cm thick with holes of 5 mm diameter arranged in a 3×3-cm grid to provide positions for thermoluminescent dosimeters (TLD). When not in use as dosimeter sites, the holes are filled with removable plugs of tissue-equivalent material.

Each of the 137 dosimeter sites located within the bone-marrow loci, identified from radiographs of the 34 transverse sections of the phantom, contained an individually calibrated TLD during periods of irradiation similar to the exposure of the patients.

## *DOSIMETERS*

Extruded lithium fluoride dosimeters[2] (1.4×1.4×7 mm) were used to make all measurements within the phantom. These dosimeters are well suited for this application because of their small size, energy independence, approximately tissue equivalence, sensitivity, reusability, and ease of handling. They have a linear response from $10^{-2}$ to $10^{3}$ rads and a slightly supralinear response from $10^{3}$ to about $5\times10^{5}$ rads when radiation damage becomes a limiting factor. In our laboratory we found the response of freshly calibrated dosimeters to be reproducible with a standard deviation of the order of 1-2% when exposed under calibration conditions. Repeated measurements in the same position in the phantom rarely disagree by more than 5%. We have previously reported details for calibrating, annealing (processing for reuse), and analyzing these dosimeters (ref. 7).

## *MARROW DOSE CALCULATIONS*

Since the active marrow is not uniformly distributed within the body in a simple, well-defined volume, it was necessary to know the spatial distribution of the marrow to determine average marrow dose. The distribution of active marrow for normal adults as estimated by Ellis (ref. 8) is expressed as the percent of the total amount located in a particular anatomical marrow compartment, e.g., the ribs or skull. The distribution of the dosimeters in the marrow compartments defined by Ellis was not proportionate to the amount of marrow therein. For example, 19% of the 137 dosimeters were located in ribs which contained only about 8% of the total active marrow. Therefore, average total dose to marrow had to be calculated by first determining the average dose for a specific compartment and then using its percentage of total marrow as a weighting factor. Table 2 lists the average compartment dose and its range per 100 R of exposure from each of the three irradiators. Table 3 summarizes the average marrow dose calculations.

TABLE 2

MARROW COMPARTMENT AVERAGE DOSE IN RADS/100 R

| | IRRADIATORS | | | | | |
|---|---|---|---|---|---|---|
| | LETBI | | METBI | | VDRIF | |
| Marrow Compartment | Average Dose | Range | Average Dose | Range | Average Dose | Range |
| Head | 82 | 73-89 | 78 | 71-85 | 68 | 61-74 |
| Upper Limb Girdle | 69 | 58-75 | 66 | 58-73 | 78 | 70-82 |
| Sternum | 75 | 73-77 | 69 | 65-71 | 77 | 74-77 |
| Ribs | 63 | 46-76 | 68 | 62-72 | 75 | 70-84 |
| Vertebrae | 58 | 47-75 | 65 | 59-80 | 70 | 63-78 |
| Sacrum | 45 | 41-46 | 54 | 50-56 | 75 | 67-83 |
| Lower Limb Girdle | 52 | 44-62 | 59 | 52-71 | 72 | 63-77 |

TABLE 3

CALCULATIONS OF AVERAGE BONE-MARROW DOSE IN RADS/100 R

| | | LETBI | | METBI | | VDRIF | |
|---|---|---|---|---|---|---|---|
| Bone Marrow Compartment | Percent Active Bone Marrow | Average Dose | Weighted* Factor | Average Dose | Weighted* Factor | Average Dose | Weighted* Factor |
| Head | 13.1 | 82 | 1074 | 78 | 1022 | 68 | 891 |
| Upper Limb Girdle | 6.4 | 69 | 442 | 66 | 422 | 78 | 499 |
| Sternum | 2.3 | 75 | 173 | 69 | 159 | 77 | 177 |
| Ribs | 7.9 | 63 | 498 | 68 | 537 | 75 | 593 |
| Vertebrae | 28.4 | 58 | 1647 | 65 | 1846 | 70 | 1988 |
| Sacrum | 13.9 | 45 | 626 | 54 | 751 | 75 | 1043 |
| Lower Limb Girdle | 26.1 | 52 | 1357 | 59 | 1570 | 72 | 1879 |
| Totals | 98.1† | | 5820 | | 6277 | | 7070 |
| Average Weighted Dose‡ | | 59 | | 64 | | 72 | |

* Weighted factor = average dose × percent bone marrow.
† Average weighted dose = Σ weighted factors ÷ total percent active bone marrow.
‡ Total percent is 98.1 because 1.9% of the marrow is located in the heads of the humeri where no measurements could be made.

[2]Dosimeter available from Harshaw Chemical Company, Cleveland, Ohio.

The compartment dose estimates in Table 2 indicate that the marrow dose distribution is different in each of these irradiators. The most unexpected result is that the LETBI $^{60}Co$ gamma irradiator produces a smaller marrow dose than the METBI $^{137}Cs$ gamma irradiator. The other irradiator (VDRIF) produces the largest marrow dose as would be expected on the basis of relative penetrability of the gamma rays involved. This apparent paradox between the LETBI and METBI doses can be explained only on the basis of the distance the radiation travels in the body to the deep-seated marrow sites. In the VDRIF about 80% of the radiation is incident at 90° to the long axis of the body and passes through the body's least thickness, the anterior-posterior diameter. This geometry provides the minimum radiation-path length to all marrow sites and therefore the largest average depth dose.

In the METBI facility the $^{137}Cs$ gamma rays are incident on the body's long axis at angles from 78-90° and they penetrate the body at an angle of approximately 30° to its larger lateral (side to side) diameter. The average length of radiation path in this geometry, somewhat greater than in the VDRIF, and the lower energy radiation explain the smaller marrow dose from the METBI exposures. However, other depth dose studies (refs. 9 and 10) have shown a less than 5% difference in average marrow dose from $^{137}Cs$ and $^{60}Co$ gamma rays under equal exposure geometries.

In the LETBI the exposure geometry is complicated by the patient's freedom to move about the large exposure room. We have calculated the angle of incidence for two typical positions of the patient; when he is standing near the room center, the average angle of incidence is about 70°; lying on the bed, the average angle of incidence is only about 25°. If we make the assumption that the average angle of incidence is the average for these two positions, or about 45°, then by simple geometry the length of the radiation path is 40% greater in this geometry than it would be for radiation incident at 90°. Because of this geometry, the LETBI average marrow dose is the lowest of the three irradiators studied.

The large dependence of average marrow dose on the angle of incidence of radiation is shown also by the study of Clifford (ref. 11), who measured this average dose in a rotating phantom first exposed at 90° and then at several angles down to 15° with the long axis of the body. Radiation energies of 60, 100, 212, and 660 keV were used. His results indicate that average dose to the marrow is reduced by a factor of two for exposures at 15° compared with 90° for all radiation energies. In addition, he also shows that marrow dose for 90° exposures varies by only about ±10% over the energy range from 60 to 660 keV and is maximum at about 100 keV.

Since the LETBI and METBI facilities produce essentially omnidirectional fields, we can compare the marrow dose estimates in LETBI of 0.59 and METBI of 0.64 rads/R with that predicted from Clifford's measurements (integrated over the angular region of 0° to 90°) of 0.62 rads/R. This agreement is surprisingly good considering that his estimates were based on measurements in only eight positions in his phantom and were primarily intended for evaluation of potential hazards of radiations from atomic weapons for civil defence planning.

The International Commission on Radiological Protection (ICRP) (ref. 12) has defined the active marrow dose as the appropriate radiation criterion for relating not only short-term hematopoietic effects but also certain late somatic biological effects to radiation exposures. To simplify its calculations to estimate marrow dose, the ICRP determined that the active marrow is located at an average depth of 5 cm. To test the validity of this simplification, we determined the average 5-cm dose to the phantom in each of the three irradiators.

The circumferential 5-cm depth line was defined in each of the 34 phantom sections and divided by radii at every 30°. The depth dose at the intercepts of the radii and the 5-cm depth line was determined by interpolation of the depth-dose data obtained from dosimeters located in surrounding grid positions. These were averaged for each section and then weighted by the mass of the section to obtain the overall average 5-cm depth dose. The comparisons of these dose estimates with the average marrow doses are shown in Table 4.

TABLE 4

COMPARISON OF ESTIMATED DOSE TO BONE MARROW WITH AVERAGE BODY DOSE AT 5-cm DEPTH

| | Average Active Bone-Marrow Dose (in rads/100 R) | Average 5-cm Depth Dose (in rads/100 R) | Ratio $\frac{\text{5-cm Depth Dose}}{\text{Marrow Dose}}$ |
|---|---|---|---|
| LETBI | 59 | 68 | 1.15 |
| METBI | 64 | 66 | 1.03 |
| VDRIF | 72 | 73 | 1.01 |

These data indicate that the 5-cm dose approximates the average marrow dose quite closely in the $^{137}Cs$ gamma-ray field (METBI) and the high-flux $^{60}Co$ gamma-ray field (VDRIF) where the incident radiation is principally at right angles to the stationary body. The agreement, while adequate, is not as good for the low-exposure-rate cobalt irradiator (LETBI) where the incident radiation is from both above and below a standing patient and where the angles change as the patient sits down, reclines, or walks about, changing his geometric relationship to each source.

These results also suggest that a dosimeter, capable of indicating simultaneously dose rate and total accumulated dose, located in the center of a 5-cm radius sphere of tissue-equivalent material could be used to approximate the astronaut's average marrow dose received during space flight. The dose-rate signal from this dosimeter could also be used to indicate when maximum shielding from unidirectional exposures, such as solar flares, is needed and to indicate what vehicle orientation provides the maximum shielding.

This study also shows clearly that average dose to the marrow is strongly dependent on the length of the radiation path in the body. It is therefore obvious that for equal exposure conditions, a very large person will receive a relatively smaller dose to the marrow than a very small person. To determine how large this variation due to body size will be, we are extending these studies to determine body self-shielding factors for a particular individual rather than the idealized 70-kg man. The exposure rate from a small radioactive source is first measured in air and then at the center point of phantoms of different sizes by a high-sensitivity whole-body counter containing an array of eight 5×4-in. sodium iodide crystals. The ratio of the counts from within the phantom to the counts in air can be used to indicate the body's self-shielding factor. The results of this study are still incomplete but the feasibility studies indicate that this experimental approach has merit. From these studies we should obtain correction curves relating average marrow dose to self-shielding factor for each of our irradiator geometries and type of source. The self-shielding factor for each individual or patient could then be obtained by having him swallow a less than 1.0-microcurie radioactive source, then counting him in the whole-body counter when the source is located at the center of the patient's body.

Accurate dosimetric information relevant to the biological effects under study are essential for improving the reliability of established human dose-response relations. This is particularly true when the effects considered are the changes in peripheral

blood-cell levels. These studies are limited to medical exposures because changes in the blood-cell levels are related to the preirradiation levels. For these reasons, we are seeking to obtain truly adequate dosimetry information from which we can deduce dose-response relations which will aid in space mission planning, management of radiation accident victims, and will improve the usefulness of TBI therapy of disseminated diseases.

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