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Relation Between Specific Ionization of Various Radiations and Their Relative Biological Effectiveness in Mammalian Systems

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OF VARIOUS
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FURCHNER

RELATION BETWEEN SPECIFIC IONIZATION OF VARIOUS RADIATIONS AND THEIR RELATIVE BIOLOGICAL EFFECTIVENESS IN MAMMALIAN SYSTEMS

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ABSTRACT

The relative biological effectiveness of several radiations of differing specific ionizations was determined. The radiation effect studied was impairment of bone marrow function, and the biological test system used was the depression of Fe^{59} uptake by the red blood cells of male Sprague-Dawley rats. The effectiveness of the mixed radiations in the thermal column of a homogeneous reactor was compared with 250-KVP X radiation, and the effect of the beta particles of tritium was compared with that of Co^{60} gamma rays. The effect of the alpha particles of Pu and Ra on bone marrow function was also determined.

An RBE of 1.14 was found for the neutrons of the thermal column when compared with 250-KVP X rays, and the RBE of the 4 Mev gamma radiation in the thermal column was 0.6 compared with the same radiation. The RBE of the beta particles of tritium was 1.59 when compared with the gamma radiation of Co^{60}.

It was not possible to assign a value for the RBE of the alpha particles of Pu and Ra. The inhomogeneous distribution of these elements in the body made valid comparisons with total body radiations impossible. Plutonium was roughly 20 times as effective as Ra in depressing bone marrow function, probably because Pu was deposited in the endosteum and the periosteum, whereas Ra was deposited in the apatite structure of the bone.

The RBE of the various radiations increased with specific ionization, but no numerical relation was evident.

A survey of RBE's reported in the literature for mammalian systems indicated that a maximum value of RBE may be reached when RBE's are plotted against specific ionization and that a decrease in RBE may be found associated with very high specific ionizations.

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Chapter 1

INTRODUCTION

By definition, ionizing radiations cause the formation of ions within the substance irradiated. The Wilson cloud chamber can be used to determine visually the spatial distribution of ions in gases irradiated by ionizing radiations. Ions are formed in definite paths which vary in length and density. The length and density of the ion track is a function of energy and charge of particulate radiations and of the photon energy of electromagnetic radiations. The volume of an ionization path in a cell is but a small fraction of the cell volume.

Whatever the source of the ionization, the properties of the ions formed (and of the molecules excited, but not ionized) are independent of the radiation source. The principal differences in the ion tracks of alpha, beta, and gamma or X radiation lie in the length of the track and in the density of ions formed along the track. The density of the ions per unit length of track, or path, is called the specific ionization.

Since all radiations are not equally effective per dose unit in reacting with biological materials, and since there is no difference in the agents that produce the injury (i.e., the ions), the source of the differences in the RBE (relative biological effectiveness) of various radiations is sought in the specific ionization of these radiations.

Very soon after the discovery of X rays by Roentgen in 1895 it was found that X radiation was injurious to humans. In 1896 E. H. Grubbe

of Chicago, a manufacturer of vacuum tubes, was treated for an X-ray dermatitis by Dr. J. E. Gillman. In 1901 Becquerel was burned by a small amount of radium which he carried in his vest pocket. A little later Pierre Curie intentionally produced with radium a similar lesion on the skin of his arm (Holmes and Schultz, 1950). Although the danger associated with X radiations and radiations from radium was recognized, injuries and deaths due to these radiations were reported (Brown, 1936).

In the early stages of the study of ionizing radiations much of the data collected was of necessity qualitative. Quantitative measurements had to wait until standardized units of measurement were adopted. It was not until 1929, at the Second International Congress of Radiology in Stockholm, that the presently used unit of radiation, the roentgen unit or r, was adopted and defined as follows:

"The unit of dose is that quantity of roentgen radiation which, when the secondary electrons are fully utilized and the wall effect of the chamber is avoided, produces in 1 cc. of atmospheric air at 0°C and 760 mm. mercury pressure such a degree of conductivity that one electrostatic unit of electric charge is measured under saturation conditions. This unit shall be called the roentgen and designated by 'r.'"

A similar unit had been proposed by Villard (1908) but neither the method nor the unit was accorded much attention at that time. The r was widely used prior to the time of its adoption, but other units were also used and this multiplicity of units resulted in some confusion in the literature (Quimby, 1945).

The r, which has been extended to include gamma radiation, cannot be properly applied to particulate radiations. In addition, the r is a measure of the energy dissipated in air and not necessarily equal to the energy dissipated in tissue by an equal quantity of radiation. A unit, the roentgen equivalent physical (rep), was proposed by Parker (1948) to serve as the dose unit for all tissue irradiations. It was defined as "that dose of any ionizing radiation which produces energy absorption of 83 ergs per gram of tissue." This definition assumes that the energy dissipation associated with a roentgen in air is the same as the energy dissipation associated with a roentgen in tissue. Attempts to equate the r and the rep have resulted in a higher value for the amount of energy dissipated by 1 rep in tissue. Failla (1953) defines the rep as "that quantity of any ionizing radiation, such that the energy imparted to matter by the ionizing particles present in the locus of interest is 95 ergs per gram." For lightly filtered X radiation of 200 to 250 KVP, 1 r is equivalent to 1 rep. This is the definition of rep used in the present study.

Parker (1948) introduced a unit, the roentgen equivalent mammal (rem), that embodies both radiation dose and RBE. The rem may be defined as "the quantity of any ionizing radiation such that the energy imparted to a biological system...per gram of living matter by the ionizing particles present in the locus of interest, has the same biological effectiveness as one rep of X radiation ..." (Failla, 1953). The physical magnitude of a dose in rem of any radiation may be determined

from the following:

$$\text{Dose in rem} = (\text{dose in rep})(\text{RBE})$$

$$\text{Dose in rep} = \frac{\text{dose in rem}}{\text{RBE}}$$

$$\text{RBE} = \frac{\text{dose in rem}}{\text{dose in rep}}$$

The latter expression may be used as a definition of RBE, i.e., the relative biological effectiveness of an ionizing radiation is equivalent to the radiation effect (measured in rem) produced in a specific biological system per rep of energy imparted to that system.

The difference in the penetrating qualities of "soft" or long wavelength X rays and "hard" or short wavelength X rays led to the concept of the "differential susceptibilities" of tissues to different radiations (Failla, 1924), or to the idea that various radiations were graded in biological effectiveness (Russ, 1924). Redfield and Bright (1924), as a result of their studies of the comparative effects of alpha, beta, gamma, and ultraviolet radiations on the eggs of Nereis limbata, concluded that the "ionizing power" of the various radiations was a factor in determining their effectiveness. Zirkle (1935), after exposing fern spores to alpha radiation, concluded that biological effectiveness was a function of the variable ion concentration in the path of the particle. Since that time numerous radiobiological investigations have been carried out in which two or more radiations have been compared to evaluate their relative biological effectiveness (Zirkle, 1943).

Zirkle (1935) attributed differences in RBE to ion concentrations

along the path of the ionizing particle. In 1936 he stated: "Although biological effectiveness is clearly not a linear function of ionization per unit length of path, there is, apparently, a simple mathematical relationship between the two. This can be expressed by the empirical equation

$$B = kI^{2.5}$$

where B is the biological effectiveness, k a constant, and I the ionization per unit length of path." Lea (1947) says that in biological actions in which many ionizations are required to produce an effect, densely ionizing radiations are more effective per ionization than less densely ionizing radiations. Patt (1952) states that biological effectiveness increases with linear ion density. Curtis (1951) says, "Thus we can say that the older literature indicates that the specific ionization is an important aspect of a radiation from a biological point of view, but does not allow a generalization beyond that point."

Here we find a range of views, from a definite empirical relation to an undefined importance, ascribed to the relation between specific ionization and RBE. Perhaps, because of what Failla (1953) called "differential variations," no definite relation can be established.

The results of quantitative irradiation experiments with biological material are difficult to evaluate. The normal variations found within a "homogeneous group" of organisms added to the daily "normal variations" in an individual give rise to a wide range of reactions to a carefully selected and measured stimulus. In addition to this factor there is

the great variety of cell types, tissues, and organs, each of which may respond differently or in different degree to such a stimulus. Perhaps such variety is an important factor in "differential variations." The following examples are given as an illustration of this concept.

The biological effectiveness of a radiation is not a fixed value, but varies with the rate at which the radiation dose is delivered. For example, Henshaw, Riley, and Stapleton (1947) found that a given dose was only 70 per cent effective when the exposure time was increased by a factor of 10. Glasser et al. (1944) point out that the effect of prolonging the time of exposure, for a given dose, varies with different organisms. Thomson et al. (1950) report that intensities of 2,300, 896, 240, and 67 r per hour gave LD_{50}^{30} values of 817, 805, 796, and 1,006 r, respectively. Exposure times of less than 3 hours resulted in no significant difference in the LD_{50}^{30} dose, but when the exposure time was extended to 15 hours the LD_{50}^{30} dose was definitely increased.

Another factor which may effect an RBE value assigned to a radiation is the nature of the biological end-point chosen. Tissues vary in susceptibility to injury due to ionizing radiations. Siri (1949) says, "As yet no wholly satisfactory biological indicator is known since different tissues and organs as well as different species of animals exhibit marked variations in radiation resistance." This may be illustrated by an experiment (Axelrod et al., 1941) in which 200-KV X radiation was compared with a fast neutron flux. The biological indicator used was the inhibition of successful transplantation in mice of an

irradiated tumor. For three types of tumor: lymphoma, mammary carcinoma, and lymphosarcoma, the RBE's were 2.3, 2.45, and 3.0, respectively. Comparing the effects of the same radiations on weight loss in mice, Lawrence and Tennant (1937) obtained an RBE of 6 for fast neutrons compared with 200-KV X rays. Use of different tissues in the same animal may result in differing values for RBE's. Harris and Brennan (1952) obtained RBE's of 1.55 and 1.73 for spleen weight loss and thymus weight loss when comparing the effects of a thermal neutron flux with 250-KV X rays. Storer et al. (1953) and Storer (1952) obtained RBE's of 1.3 and 1.7 by comparing the effects of the same radiations on testicular atrophy and on the mitotic index of the skin of the mouse ear.

Factors other than differences in the delivery rate of radiation, in the radiosensitivity of tissues, or in biological indicators may give rise to differential variations. Temperature, age, oxygen tension, sex, etc., may all affect the value of the result in experiments such as those just cited.

If the damage caused by exposing animals to ionizing radiations of differing specific ionization delivered at a uniform rate were measured with the same biological end-point, valid values for the RBE's of these radiations could be calculated, providing the animals were a homogeneous group. Rigorously, values obtained in this manner would be applicable only to the animals and only to the biological end-point selected. Despite this limitation, such values can serve as a measure of

radiosensitivity of various tissues, organs, or animals when differing biological indicators are used to measure radiation damage. RBE values obtained in this manner may also help to define the relation between RBE and specific ionization.

The specific ionization of several radiations is given in Table 12. Unfortunately, it is difficult, perhaps impossible, to deliver these radiations at a uniform rate. Total body irradiation can be delivered from an external source of X rays, gamma rays, or neutrons. The range of alpha particles in tissue is less than 50 microns and the range of beta particles in tissue is only a few millimeters at energies of ~1 Mev. Radiations from an external alpha or beta particle source would obviously be absorbed by the superficial layers of tissue. Some beta-particle-emitting isotopes that distribute homogeneously in the mammalian body are available. Such isotopes make possible total body beta irradiation, but the time lag between injection and homogeneous distribution makes short exposures, comparable in duration with X-ray exposures, difficult to evaluate. The dose delivered over a period of several days can be calculated with considerably greater certainty. Total body irradiation from an internal source may be compared with total body irradiation from an external source, provided both radiations are delivered at the same rate.

Most alpha-particle-emitting isotopes do not distribute homogeneously in the mammalian body. Consequently, the dose to different tissues varies with the distribution. Tissues with high concentrations

of the isotope are subject to high doses of radiation whereas tissues with low concentrations receive low doses.

In the present paper the results of exposure to a thermal neutron flux and to a high-photon-energy gamma flux are compared with the results of irradiation with 250-KV X rays. The duration of these exposures was a matter of minutes. These exposures are referred to as "acute" for convenience of reference. The results of exposure to Co^{60} gamma rays were compared with the results of exposure to the beta radiation of tritium (T) and the alpha radiation of Ra^{226} and Pu^{239}. The duration of exposure to the radiations of Co^{60}, T, Ra^{226} and Pu^{239} was 5 days in each case. These exposures are referred to as "chronic" in contrast to the acute exposures.

Depression of bone marrow function, as shown by the decreased amounts of radioiron (Fe^{59}) incorporated in the red blood cells, was used in this study as the biological indicator of degree of radiation damage. Bloom and Bloom (1947) found morphologic evidence that the erythropoietic tissue of the bone marrow is extremely sensitive to ionizing radiation. Hennessy and Huff (1950) showed that the amounts of Fe^{59} appearing in the red blood cells of rats injected with Fe^{59} after exposure to radiation varied inversely with the X-ray dose. Fe^{59} introduced into whole blood <u>in vitro</u> fails to exchange with the hemoglobin of mature erythrocytes (Hahn et al., 1940). Fe^{59} administered enterally or parenterally is incorporated in the red blood cells as an integral part of the hemoglobin molecule (Hahn et al., 1939). Therefore, Hennessy and Huff (1950) concluded that depression of Fe^{59} uptake by the red

blood cells in rats was a measure of damage to bone marrow. This method of measurement of radiation damage has been used in other studies (Huff et al., 1950).

Chapter 2

MATERIALS AND METHODS

2.1 Radioiron Uptake

Hennessy and Huff (1950) found that the administration of Fe^{59} 24 hours after irradiation resulted in a maximum differentiation in Fe^{59} uptake by the red blood cells following varying doses of X radiation. In addition, when the blood sample for radioassay was taken 72 hours after the administration of Fe^{59}, the differentiation in the amount of Fe^{59} incorporated in the red blood cells was again at a maximum. These data were confirmed in a preliminary experiment.

Twenty-four hours after the acute exposures the animals were anesthetized and about 0.1 μc. of Fe^{59} was injected under direct visualization into the surgically exposed external jugular sinus. After injection the incision was closed with steel wound clips. Seventy-two hours after injection the animals were anesthetized and weighed. The animals were bled by cardiac puncture with a syringe and needle wet with heparin. One cubic centimeter of blood from each rat was placed in hematocrit tubes and centrifuged at 2,600 r.p.m. for 30 minutes. The hematocrits were recorded and an aliquot of plasma was removed for radioassay. The remainder of the blood was washed into a second vial for radioassay. The animals given chronic exposures to radiation were anesthetized 48 hours after the beginning of exposure for injection of Fe^{59} and were bled at the end of the exposure time, i.e., 72 hours after injection

of Fe^{59}. This procedure was followed in each series of exposures. At every injection, bleeding, radioassay of blood from the experimental animals, etc., a group of unirradiated control animals was subjected to exactly the same procedure.

The percentage of normal Fe^{59} uptake was calculated as follows:

$$\frac{(A)(B)-(C)(D)}{I} \times 100 = \text{percentage of } Fe^{59} \text{ uptake}$$

$$\frac{\text{Percentage of } Fe^{59} \text{ uptake (experimental)}}{\text{Percentage of } Fe^{59} \text{ uptake (control)}} \times 100 = \text{percentage of normal } Fe^{59} \text{ uptake}$$

where A = counts per minute per cubic centimeter $(\frac{c/m}{cc.})$ of whole blood

B = whole blood volume of the rat

C = $\frac{c/m}{cc.}$ of plasma

D = plasma volume of the rat

I = c/m injected.

Discussion of the methods of determination of the various factors in the above equation is given below.

(A) All Fe^{59} assays were made by counting the 1.3 and 1.1 Mev gamma photons emitted in the decay process of Fe^{59}. It was possible to count these photons by using a thallium-activated sodium iodide crystal in contact with a photomultiplier tube (RCA-5819) which had appropriate amplification and counting apparatus similar to that described by Anger (1951). The sample to be assayed was placed in a 5-ml. specimen vial. The vial was then placed in the specially shaped crystal (Fig. 1) and the gamma activity measured.

(B) The whole blood volume of the rat was determined on a cc./100 gm. basis. Three anesthetized rats were injected by way of the surgically exposed external jugular sinus with 0.5 μc. of Fe^{59}. Three days after injection the rats were bled by cardiac puncture, under anesthesia. The blood was centrifuged and the plasma was removed. The remaining red blood cells were washed twice with normal saline and brought back to the original volume with normal saline. The blood was pooled and 0.5 cc. was then injected into the exposed jugular sinus of each of 21 anesthetized rats. Three minutes later 1.0 cc. of blood was removed from each rat by cardiac puncture and placed into vials for radioassay. One cubic centimeter of the pooled, donor blood was placed in a vial for radioassay. The whole blood volume was calculated as follows:

$$\frac{\text{c/m injected (donor blood)}}{\frac{\text{c/m}}{\text{cc.}}\ \text{recipient blood}} - 0.5 = \text{whole blood volume}$$

$$\frac{\text{whole blood volume}}{\text{rat wt. (gm.)}} \times 100 = \text{cc./100 gm.}$$

The value obtained in this manner was 5.89 ± 0.46 cc./100 gm. (Table 1). This value, which lies within the range found by other authors for the whole blood volume of rats [6.7 cc./100 gm. (Cartland and Koch, 1928) and 4.5 cc./100 gm. (Berlin et al., 1949)], was used in the present study. Therefore, the whole blood volume was calculated by multiplying $\frac{\text{wt. (gm.)}}{100}$ by 5.89.

(C,D) The amount of Fe^{59} in the plasma was determined by radioassay of the plasma aliquot taken from the centrifuged blood sample.

The plasma volume was calculated as follows:

(1.0 - hematocrit) x (whole blood volume) = plasma volume

(I) The c/m of Fe^{59} injected was determined by radioassay of a volume of injection solution, equal to the volume injected. In all the experiments described the volume of the injection solution of Fe^{59} was 0.3 cc. The Fe^{59} was injected as $Fe^{59}Cl_3$ diluted with normal saline at a pH of 4 to 5.

Sprague-Dawley male rats 3 to 4 months old were used in this study. It was determined by preliminary experiments that no great advantage could be obtained by the use of very young males, old males, females, or animals in which an attempt had been made to stimulate erythropoiesis by withdrawal of 2 cc. of blood by cardiac puncture immediately prior to administration of Fe^{59}. Data from these preliminary experiments are given in Table 2.

2.2 Care and Handling of Animals

Sprague-Dawley male rats obtained from commercial sources were used. The animals were 6 to 7 weeks old on arrival in Los Alamos. At the time of exposure the animals were 3 to 4 months old. The animals used in any one exposure series were selected from a single shipment of rats, thereby avoiding age differences. The animals in a shipment were weighed individually and then selected so the range of their weights was minimal. The selected animals were assigned to the various exposure groups by means of random number tables. In all cases the animals were allowed several days before exposure to become accustomed to their new

quarters. Before and after the acute exposures the animals had access to water and Purina Laboratory Chow ad libitum. Before, during, and after the chronic exposures the animals had access to water and Purina Laboratory Chow ad libitum. For each series of animals exposed, a group of control animals was maintained as nearly as possible under the same conditions as the experimental animals. In those experiments in which animals received injections of Ra, Pu, and T a series of controls were injected with equal volumes of solutions of the same pH and concentration of salts.

2.3 Exposure to X Rays

The X-ray exposures were made with a 250-KV Picker industrial type unit. The operating characteristics and exposure factors were as follows:

Peak voltage	250 KV
Inherent filtration	3 mm. Al
Added filtration	0.25 mm. Cu, 1.0 mm. Al
Filament current	15 ma.
Target to specimen distance	55 cm.
Dose rate (in air)	72.6 r/min.

Eleven groups of 12 rats each were exposed 6 at a time in a Lucite cage suspended on a plywood table 3 feet above the floor. The dose rate was measured in air with a Victoreen 100-r chamber placed at mid-animal height in the Lucite cage. The dose rate was calculated from the readings observed after a 1.0-minute exposure by making the appropriate

corrections for pressure and temperature. Two series of exposures, one with 5 dosage levels and one with 6 dosage levels, were made. The doses given, in seconds of exposure time and in r, are shown in Table 3.

2.4 Exposure to Thermal Column Radiation

The Los Alamos homogeneous reactor, known as the "water boiler," and its operating characteristics and facilities for the exposure of biological materials have been described in the literature (King, 1952; Brennan et al., 1954).

The reactor consists of a sphere containing a solution of uranyl nitrate enriched in U^{235}. The amount of solution pumped into or out of the sphere determines whether the mass present is greater or less than that amount which will sustain a chain reaction. Automatically operated control rods of cadmium and boron maintain the fission rate at levels selected for experimental purposes.

The north thermal column consists of a series of graphite stringers 4 1/4 x 4 1/4 x 48 inches running from a bismuth shield 8 1/2 inches thick. The bismuth shield attenuates the fission-gamma flux arising in the sphere, while the graphite acts as a moderator and slows the fission neutrons to thermal energies. The essential features of the thermal column are shown in Fig. 2.

In addition to the thermal neutron flux, neutron interaction with the graphite moderator of the thermal column produces a gamma flux with an energy of $\sim$4 Mev.

Figure 2 shows the arrangement for the exposure of biological

materials. The point marked "P" in the diagram is the center of the exposure cage. The exposure cavity was made by four pieces of high purity graphite shaped to form a hollow right cylinder with a hemispherical end directed toward the reactor, and an open end directed away from the reactor, into which a shield of specially purified bismuth was placed. The shield consisted of two coaxial shells 1/2 inch thick, one shaped to fit the graphite exposure cavity, the other shaped to fit the first bismuth shell. A bismuth lid was provided to cover the open end of the shell to complete the shield (Fig. 3). This bismuth shield reduced the gamma flux in the thermal column by a factor of about 0.52 (Brennan et al., 1954). The cage used to expose the rats was a right cylinder made of polyethylene and had the following dimensions:

Diameter	14.0 cm.
Axial length	10.3 cm.
Thickness	0.3 cm.

Exposure to neutrons within the thermal column is complicated by three factors:

1. The inherent gamma contaminant within the column itself. The contribution of this gamma flux to the depression of Fe^{59} uptake by the red blood cells of the exposed animals had to be determined. This was done with the use of data compiled by Brennan et al. (1954) and data compiled in a following section of this report.

2. The inter-animal gamma dose. Rats exposed to a thermal neutron flux become sources of gamma radiation due to the reaction, $H^1(n,\gamma)H^2$,

and irradiate themselves and other animals. The amount of radiation contributing to the depression of Fe^{59} uptake from this source was calculated on the basis of theoretical considerations.

3. The "sink effect" (Brennan et al., 1954) or decrease in the thermal neutron flux in the region of the exposed animals caused by neutron capture in the animals. The "sink effect" was determined empirically by placing the cage containing only an indium foil in the exposure cavity and determining the neutron flux by the activity induced in the foil. This was repeated with 1, 2, and 3 rats in the cage, respectively. The decreasing amount of activity induced in the indium foils with use of increasing numbers of rats was taken as a measure of the "effect." The thermal neutron flux inside the bismuth shells with no rats present was 1.8×10^{10} n/cm.^{2}/sec. at a power setting of 25 KW (Brennan et al., 1954).

Six groups of 12 rats each were exposed, 3 at a time, in the polyethylene cage described above. The operating power levels of the reactor were varied in order to minimize the differences in exposure time. The operating power levels, seconds of exposure at these levels, and seconds of exposure normalized to a 25-KW power level are given in Table 4.

2.5 Exposure to 4 Mev Gamma Radiation

The gamma radiation inherent in the thermal column during operation of the Los Alamos homogeneous reactor was measured by Brennan et al. (1954). These authors found that a lithium shield 3 cm. thick absorbed

virtually all the thermal neutrons incident on it. Natural Li is composed of 2 isotopes, Li^6 (92.5%) and Li^7 (7.5%). The capture cross section and reactions with thermal neutrons for these isotopes are

$Li^6(n,\alpha)H^3$ σ_c = 860 barns, no gamma emitted

$Li^7(n,\gamma)Li^8$ σ_c = 0.033 barn, 1.98 Mev gamma

σ_c, the capture cross section, can be expressed by the equation:

$$\sigma_c = \frac{N}{N_o N_t}$$

where N is the number of captures occurring in the target

N_o is number of incident particles per $cm.^2$

N_t is the number of nuclei per $cm.^2$ of target area.

The barn, 10^{-24} $cm.^2$, is the cross section unit. This unit is obtained by dividing σ_c by 10^{-24}.

Because of the large capture cross section of the rarer isotope, only about one capture in 2,000 occurs in the more abundant isotope, and very little additional gamma radiation results from use of lithium as a neutron shield. The 4 Mev gamma radiation is very little attenuated by the thickness of lithium used (3 cm.). Eight centimeters of lithium reduce the gamma flux by 7 per cent. The lithium, however, acts as a neutron "sink" and the effective neutron flux activating the graphite adjacent to the lithium shield is reduced, thereby reducing the gamma flux within the shield. Measurements by Brennan et al. (1954), from whom the above data were taken, show that at an operating power level of 25 KW the gamma flux within the lithium shield was 27.2 r/min. Six groups of 12 rats each were exposed 3 at a time inside the lithium

shield in the polyethylene exposure cages used for the exposure to thermal column radiation. The exposure times used in the experiments are given in Table 5.

2.6 Exposure to Tritium Beta Radiation

Tritium is a pure beta emitter (no gamma radiation is associated with its decay (see Seaborg and Perlman, 1948)) and tritium oxide (HTO) is distributed homogeneously in the animal body, since it reaches equilibrium with the body water very rapidly (Pinson and Anderson, 1951). Urinary excretion and loss of water vapor in respiration decrease the initial equilibrium concentration resulting from a given dose. However, the original concentration may be maintained if additional tritium to replace the loss is supplied in the drinking water. It has been shown that 30 per cent of the water intake of mice (Pinson, 1952) comes from water of metabolism and from water absorbed from the air. It may be assumed that the value is also true for rats. By giving drinking water containing 1.4 times the tritium concentration measured in the body water, it is possible to balance the tritium intake and excretion.

In a series of preliminary experiments it was found that dosage levels, measured in rep but comparable to those delivered in the acute X-ray exposures, were ineffective in depressing bone marrow function. The dose delivered by tritium beta particles over a period of 5 days was not equivalent to the same dose delivered by X ray in a few minutes. Therefore, higher dosage levels as shown in Table 6 were given.

Six groups of 12 rats each were injected intraperitoneally with sufficient HTO to obtain concentrations of 254, 293, 342, 368, 413, and 514 μc./ml. of body water. After injection the animals were placed in individual metabolism cages and given Purina Laboratory Chow and water containing appropriate concentrations of tritium ad libitum for 5 days. Urine samples were collected daily and assayed for tritium concentration by the method described by Pinson (1952). The value obtained for tritium concentration in the urine was used as the value for tritium concentration in the body fluids. The average tritium concentration over the 5-day period was used to calculate the total dose of beta radiation delivered to the rats.

The dose in rep delivered in 5 days was calculated as follows:

$$\frac{(A)(D)(E)(T)(C)}{R} = \text{dose in rep}$$

where A = activity in c./ml. in body fluids obtained from radioassay of urine

D = disintegrations/sec./μc. (3.7×10^4)

E = average energy of the tritium beta particles in electron volts (6.0×10^3) (Jenks et al., 1949)

T = seconds in 5 days (4.32×10^5)

C = ml. of water per gram of tissue (0.75) (Pinson, 1952)

R = electron volts/rep (1 rep = 93 ergs/gm. = 5.8×10^{13} ev/gm.)

The doses calculated were 314, 362, 423, 455, 511, and 636 rep, respectively, for each of the experimental groups. The amounts of tritium injected, the expected tritium concentrations in body water, the

tritium concentrations in the drinking water, the tritium concentrations found in the urine, and the doses calculated in rep are shown in Table 6.

2.7 Exposure to Co^{60} Gamma Radiation

It was not possible to use the X-ray exposure facilities to deliver a standard chronic exposure dose continuously over a period of 5 days. Instead, the 1.2 Mev gamma radiation of Co^{60} was used as the standard of comparison.

The source used was a 5-curie pellet of Co^{60} enclosed in a lucite cylinder 3 cm. long, 1 cm. in diameter, with a wall thickness of 0.75 mm. Exposure cages shaped to fit arcs of circles of appropriate radii were fixed at 91, 101, 109, 119, 131, and 142 cm. from the source (Fig. 4). The cages were so constructed that the long axis of the rats necessarily remained tangent to the source of radiation, and shielding of one rat by another was negligible. Ten rats were placed in each cage.

Dosage determinations were made with Victoreen 100-r thimble chambers exposed in air before, during, and after exposure of the animals. The average values found after four 16-hour exposures of the thimble chambers were used as a basis for dosage calculations. The total doses received by the rats were calculated to be 302, 354, 404, 468, 579, and 632 r. These doses were delivered over a 5-day time interval. Throughout the exposure period the animals had free access to Purina Laboratory Chow and water. Cage-source distances and the calculated doses are given in Table 7.

2.8 Exposure to Plutonium

Since Pu is not distributed homogeneously in the animal body, differing radiation doses are delivered to organs or parts of organs depending on the local concentrations of Pu. As a result of uneven distribution, only rough comparisons with total body irradiation may be made. But the relative significance of the difference in the pattern of deposition of Pu and Ra in producing bone marrow damage can be determined in part using uptake of Fe^{59} by the red blood cells.

Six groups of 12 rats each were injected with appropriate volumes of PuO_2Cl_2 buffered with a citrate solution to a pH of 3. The Pu was injected into the external jugular sinus in the same way as was the Fe^{59}. Immediately after injection the animals were placed in individual metabolism cages where they had free access to Purina Laboratory Chow and water. Urine and feces were collected daily for assay of Pu. After 5 days the animals were sacrificed.

The daily urine samples were placed in 200-ml. beakers and a few drops of concentrated nitric acid were added. The beaker contents were allowed to evaporate in a drying oven at 110°C. When the samples were dry they were heated in a muffle furnace at 500°C until only a white ash remained. The white ash was dissolved in 2 N nitric acid and washed into a volumetric flask which was then brought to volume. A carefully measured aliquot was then evenly spread and dried on a 2-inch stainless steel disk. The alpha activity was determined by the use of a proportional alpha counter.

The daily feces samples were dried in a drying oven at 110°C and then scraped into porcelain crucibles. The crucibles were placed in a muffle furnace at 650°C for 24 hours. The resultant ash was dissolved in 2 N nitric acid and washed into a volumetric flask which was then brought to volume. Radioassay of a carefully measured aliquot was made in the manner described for the daily urine samples.

After sacrifice the animals were placed in porcelain crucibles and dried at 110°C for 48 hours. They were then dry-ashed at 650°C in the muffle furnace until no carbon residue was visible. The crucible contents were then placed on a fine mesh screen (No. 20) and the skeletal ash was separated from the soft-tissue ash with forceps. The skeletal ash was dissolved in 2 N nitric acid in a volumetric flask which was then brought to volume. The remains and the washings from the crucible were placed in another volumetric flask which was also brought to volume. These solutions were assayed in the same manner as were the daily urine and feces samples. One hundred microliters of the injection solution was diluted to 100 cc. in a volumetric flask. One hundred microliters of this solution was then plated on a stainless steel disk for assay of the injection solution.

The doses in μgm./gm. of bone and in rep delivered to bone are given in Table 8.

The doses were calculated as follows:

$$\frac{\mu\text{gm. in bone}}{\text{body weight} \times 0.1} = \mu\text{gm./gm. bone}$$

based on the assumption that 10 per cent of the body weight is bone (Donaldson and Conrow, 1919). The rep delivered to the bone was calculated by the following expression:

$$\frac{(A)(D)(T)(E)}{R} = \text{rep to bone}$$

where A = μgm./gm. of bone

D = disintegrations/sec./μgm. (2.3×10^3) (Seaborg and Perlman, 1948)

T = seconds in 5 days (4.32×10^5)

E = energy of the alpha particle in ev (5.15×10^6) (Seaborg and Perlman, 1948)

R = ev/rep (5.8×10^{13})

2.9 Exposure to Radium

The procedure for exposing rats to Ra was the same as that used for Pu. The Ra was injected as $RaBr_2$ in a water solution at a pH of 3.9. Six groups of 12 animals each were injected with appropriate volumes to give dose levels calculated to range from 0.5 μgm./gm. of bone to 2.5 μgm./gm. of bone. After injection the animals were placed in individual metabolism cages. Urine and feces were collected daily.

The Ra assays were made with a scintillation counter in much the same manner as the Fe^{59} assays were made. The gamma-emitting daughter products of Ra, rather than Ra, were assayed.

In order to assay the Ra by means of its gamma-emitting daughter products it is necessary to seal the sample to be assayed for a period

of a month to allow an equilibrium to be reached (Rutherford, Chadwick, and Ellis, 1913). For this reason, all samples that were used for Ra determinations were flame-sealed in soft glass ampoules and allowed to stand for 30 days before radioassays were made.

The daily urine samples were collected in graduated centrifuge cones. The volumes were recorded and a carefully measured aliquot of each was put into a soft glass ampoule which was then sealed. Thirty days after sealing the ampoules were placed in the scintillation counter for radioassay.

The feces were dried and ashed in the same manner as were the feces of the animals treated with Pu. The ashes were dissolved in 2 N nitric acid and placed in volumetric flasks which were brought up to volume. A carefully measured aliquot from each sample was placed in an ampoule which was sealed. After 30 days the amount of Ra in the ampoule was determined as above.

The sacrificed animals were treated in the same manner as were those injected with Pu, up to and including dissolving the ashed skeleton and remains in 2 N nitric acid and bringing the volumetric flasks up to volume. The measured aliquots were placed in ampoules and sealed. The contents were assayed for Ra after 30 days.

The injection solution was assayed for Ra content by diluting 100 µl. of injection solution to 100 cc. and putting a 2-cc. aliquot of this solution into an ampoule which was sealed. After an appropriate interval a Ra determination was made as above.

All the Ra determinations were compared with Ra standards obtained from the National Bureau of Standards.

In calculating the dose in rep delivered by Pu, only the energy of the alpha particle emitted by Pu was considered. The daughter product of Pu^{239} is U^{235}, which has a half-life of 7.07×10^8 years; therefore, very little energy is contributed to the rep dose of Pu by its daughter product. The situation with radium is quite different. The daughter products of Ra are short-lived and emit high energy radiations. These radiations contribute to the radiation dose delivered by Ra. The relatively small contribution of the beta and gamma radiations may be ignored (Boyd and Fink, 1950). Another factor that must be considered is the metabolism of radon, the first daughter product of Ra. Boyd and Fink estimated that 85 per cent of the radon formed in the body was lost in respiration. Hoecker and Roofe (1949) measured the growth curve of the daughter products of Rn in rats injected with Ra and hermetically sealed in metal containers immediately after sacrifice. They calculated that 91.5 per cent of the Rn formed in the rat was exhaled. This value was used to calculate the dose in rep delivered by Ra. The calculations were made as follows:

$$\frac{(A)(D)(T)(E + 0.085\ C)}{R} = \text{rep to bone}$$

where A = μgm./gm. of bone

D = disintegrations/sec./μgm. (3.7×10^4)

T = seconds in 5 days (4.32×10^5)

E = energy of the Ra alpha particle in ev (4.7×10^6)

C = sum of the alpha particle energy of the daughter products of Ra in ev (29.96×10^6)

0.085 = fraction of Rn not exhaled

R = ev/rep (5.8×10^{13})

The μgm. injected/gm. body wt., μgm./gm. bone, and the calculated rep to bone are given in Table 9.

Chapter 3

RESULTS

3.1 Results of Exposure to X Radiation

In the two series of exposures to X radiation, the first was made at dosage levels of 50, 100, 150, 200, and 250 r. It was observed that the uptake of Fe^{59} by the red blood cells varied inversely with the dose. Table 3 shows the percentage of normal Fe^{59} uptake with the corresponding dose. When these data are plotted on semi-log paper, using a logarithmic abscissa to record the dosage in r or in seconds of exposure time, and an arithmetic ordinate to plot the percentage of normal Fe^{59} uptake, a straight line is obtained.

The best line of fit to the experimental data may be calculated by the method of least squares. Such a line may be defined by an equation of the type

$$Y = a + bX$$

where Y = percentage of normal Fe^{59} uptake

a = the intercept constant

b = the slope constant

X = the logarithm of the dose

Because the response seemed to be a function of the logarithm of the dose, a second series of exposures was made with the dose levels spaced equally on a logarithmic scale. This procedure was followed in all subsequent exposures in the present study. The dosage levels selected were 50, 69, 95, 131, 181, and 250 r. The equation of the line best fitting the combined data of these two series of exposures,

calculated by the method of least squares, was

$$Y = 239.3 - 93.4X$$

where Y = percentage of normal Fe^{59} uptake and X = logarithm of the dose in r.

The dose may also be expressed in seconds of exposure time for purposes of comparison with other radiations. When this was done the equation for the line of best fit became

$$Y = 231.6 - 93.4X$$

where Y has the same meaning as before, and X is the logarithm of the dose in seconds of exposure. These data are plotted in Fig. 5.

3.2 Results of Exposure to Thermal Column Radiation

Exposures in which the exposure cage contained an indium foil only, and an indium foil plus rats, showed that the thermal neutron flux was reduced 5, 10, and 22.5 per cent with 1, 2, and 3 animals in the cage, respectively. The 22.5 per cent "sink effect" corresponding to three rats exposed simultaneously reduced the thermal neutron flux of 1.8×10^{10} n/cm.^{2}/sec. to 1.39×10^{10} n/cm.^{2}/sec.

The depression of Fe^{59} uptake by the red blood cells of rats exposed to thermal neutron flux plus the inherent contaminating radiation was qualitatively the same as that measured in rats exposed to X radiation, i.e., with increasing exposure doses the amount of Fe^{59} incorporated in the red blood cells was decreased. The percentages of normal Fe^{59} uptake corresponding to the various exposure times are shown in Table 4 and the data are plotted in Fig. 5. The line of regression,

calculated by the method of least squares, was

$$Y = 212.9 - 86.6X$$

where Y = percentage of normal Fe^{59} uptake and X = logarithm of the dose in seconds of exposure. This equation represents the effects of the mixed radiations inherent in exposure to thermal neutrons in the thermal column of the Los Alamos homogeneous reactor. The 4 Mev gamma radiation resulting from neutron interaction with the graphite moderator and the inter-animal radiation caused by the $H^1(n, \gamma)H^2$ reaction in the animals are factors that must be evaluated before the above data can be interpreted in terms of thermal neutron effect alone.

3.3 Results of Exposure to 4 Mev Gamma Radiation

The rats exposed to 4 Mev gamma radiation within the lithium shielded exposure cavity were affected in a manner qualitatively similar to those exposed to X radiation and to thermal neutrons plus accompanying radiation. The exposure time and the percentage of normal Fe^{59} uptake corresponding to each dosage level are given in Table 5. These data are plotted in Fig. 5. The line of regression, calculated by the method of least squares, was

$$Y = 243.8 - 74.7X$$

where Y has the same meaning as before, and X is the logarithm of the dose in seconds of exposure.

Inspection by eye of Fig. 5 where the lines of regression are drawn after calculation of the data gathered following X radiation, 4 Mev gamma radiation, and a thermal neutron flux suggests that the slopes of

these lines are not significantly different. "t" Tests of the differences in the slope gave the following P values:

X rays, thermal column	0.5
X rays, 4 Mev gamma rays	0.3
4 Mev gamma rays, thermal column	0.4

that is, the probabilities that such differences in slope would occur by chance alone were 50 per cent, 30 per cent, and 40 per cent, respectively.

Since the significance of the differences in slopes of the lines of regression was relatively small, the slopes were adjusted to be equal by weighting each slope constant by the inverse of its variance and finding the mean (T. White, 1952). This value was then substituted for the slope constants in these equations and new values for the intercept constants were calculated. The equations for the lines of regression became:

X ray	$Y = 218.1 - 86.6X$
Thermal column radiation	$Y = 213.2 - 86.7X$
4 Mev gamma rays	$Y = 273.6 - 86.6X$

where Y = percentage of normal Fe^{59} uptake, and X = logarithm of the dose expressed in seconds of exposure (Fig. 5).

When the slopes of the lines of regression are parallel, at all dosage levels the relative effects of the agents in question are constant. Therefore, the relative effectiveness of the various radiations may be calculated from the equation

$$\log E = \frac{a_1 - a_2}{b}$$

where a_1 and a_2 are the intercept constants from the equations for the lines of regression, b is the common slope constant, and E is the relative effectiveness (Finney, 1952).

Substitution in and solution of the above equation gives a relative effectiveness on the basis of seconds of exposure of 1.14 for the mixed radiation of the thermal column and 0.229 for the 4 Mev gamma radiation when comparing each with X radiation.

The X rays were delivered at the rate of 72.6 r/min., or 1.21 r/sec. Therefore, the mixed radiation of the thermal column within the bismuth shield delivered 1.38 rem/sec. (1.14 x 1.21). The 4 Mev gamma radiation within the lithium shield delivered 0.277 rem/sec. (0.229 x 1.21).

Brennan et al. (1954) gave the value 0.453 r/sec. for the gamma flux measured inside the lithium shield. Assuming equivalence of r and rep, the RBE of the 4 Mev gamma radiation can be calculated from

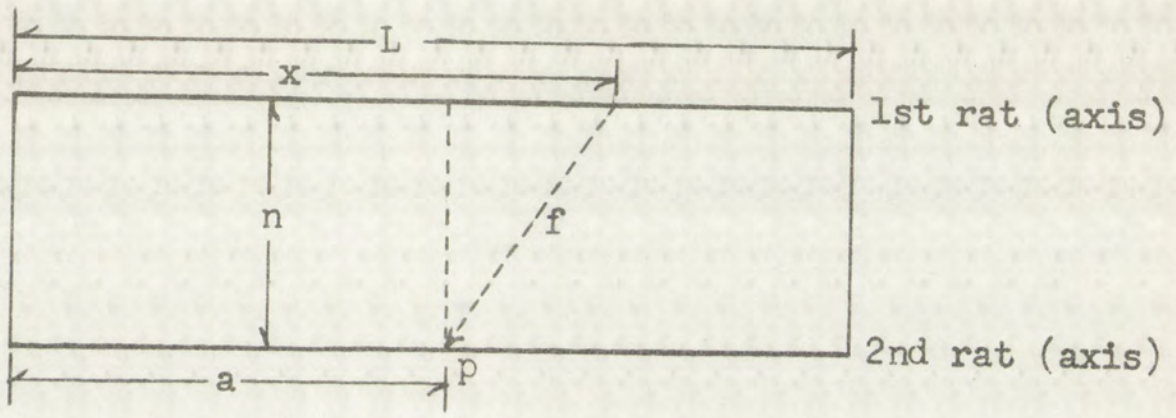
$$\text{RBE} = \frac{\text{dose in rem}}{\text{dose in rep}} = \frac{0.277}{0.453} = 0.61$$

The gamma flux in the bismuth shield, as measured by Brennan et al. (1954), was 0.405 r/sec. This value, multiplied by the RBE of 0.61, gives a value of 0.247 rem/sec. as the contribution of the inherent gamma radiation.

3.4 The Contribution of the Inter-Animal Radiation

The contribution of the inter-animal gamma radiation was calculated on a theoretical basis.

If it is assumed that the activity induced in a rat by a thermal neutron flux is concentrated in an axial line through the center of a rat, and that a second rat at some distance from, and parallel to, the first rat absorbs this radiation along a similar line, it is possible to calculate the dose to the second rat.



The intensity distribution along the first rat is $I\Delta x$, so that $\int I\Delta x\, dx$ = the total intensity. If we consider the dose at p, a point in the second rat at distance f from a source element, $I\Delta x$, in the first rat, the intensity at point p is

$$dI_p = \frac{I\Delta x}{4\pi f^2} \tag{1}$$

Substitution of $f^2 = (x-a)^2 + n^2$ in the above expression gives

$$dI_p = \frac{I\Delta x}{4\pi}\left[\frac{1}{(x-a)^2 + n^2}\right] \tag{2}$$

The total intensity, I_p, at point p from rat 1 is given by

$$I_p = \frac{I\Delta x}{4\pi}\int_0^L \frac{dx}{n^2 + (x-a)^2} \tag{3}$$

where L is the length of the rat.

If we let $x - a = u$, then $dx = du$; when $x = 0$, $u = -a$; and when $x = L$, $u = L - a$. Substituting these values in equation (3), and integrating between limits, gives

$$I_p = \frac{I\Delta x}{4\pi n}\left(\tan^{-1}\frac{L-a}{n} - \tan^{-1}\frac{-a}{n}\right) \qquad (4)$$

The dose to various points along the second axis will vary as the position p varies, e.g.,

At $a = 0$, $I_p = \frac{I\Delta x}{4\pi n}\left(\tan^{-1}\frac{L}{n}\right)$, a minimum

At $a = L$, $I_p = \frac{I\Delta x}{4\pi n}\left(-\tan^{-1}\frac{L}{n}\right) = \frac{I\Delta x}{4\pi n}\left(\tan^{-1}\frac{L}{n}\right)$, also a minimum

At $a = L/2$, the midpoint,

$$I_p = \frac{I\Delta x}{4\pi n}\left(\tan^{-1}\frac{L}{2n} - \tan^{-1}\frac{L}{2n}\right) = \frac{I\Delta x}{2\pi n}\left(\tan^{-1}\frac{L}{2n}\right)$$

a maximum

The plot of I_p against a is a continuous curve between $a = 0$ and $a = L$ with symmetry about a maximum at $a = L/2$. The average dose to the rat can be determined by

$$I_p(\text{av.}) = \frac{2\int_0^{L/2} I_p\, da}{\int_0^{L} da} = \frac{2}{L}\int_0^{L/2} I_p\, da \qquad (5)$$

If we substitute the value for I_p from Eq. (4), we get

$$I_p(\text{av.}) = \int_0^{L/2} I_p\, da = \frac{I\Delta x}{4\pi n}\int_0^{L/2}\left(\tan^{-1}\frac{L-a}{n} - \tan^{-1}\frac{-a}{n}\right)da \qquad (6)$$

Letting $(L-a)/n = v$, $da/n = -dv$; when $a = 0$, $v = L/n$; and when $a = L/2$, $v = L/2n$. If we also let $-a/n = w$, then $-da/n = dw$; when $a = 0$, $w = 0$; and when $a = L/2$, $w = -L/2n$.

Substitution of these values in Eq. (6) gives

$$I_p(av.) = \frac{I\Delta x}{4\pi}\left[\int_{L/n}^{L/2n} \tan^{-1}(v)\, dv + \int_{0}^{-L/2n} \tan^{-1}(w)\, dw\right] \qquad (7)$$

Integration of Eq. (7) between limits gives

$$I_p(av.) = \frac{I\Delta x}{2\pi L}\left[\frac{L}{n}\tan^{-1}\frac{L}{n} - 1/2\ \ln\left(1 + \frac{L^2}{n^2}\right)\right]$$

The average body length of the rat was about 10 cm. (L), and the animals were an average of about 5 cm. apart (n) when in the cage.

Substituting the appropriate values in and solving the above equation, we have

$$I_p(av.) = 0.02254\ I\Delta x.$$

According to Mayneord (1950), the gamma flux emanating from an animal can be calculated from

$$\text{gamma flux} = Nn^H\sigma_H$$

where N = the neutron flux in $cm.^2/sec.$ (1.81×10^{10})

n^H = number of H atoms/gm. of tissue (6.02×10^{22}) (Mayneord, 1950)

σ_H = H capture cross section for thermal neutrons $(0.32 \times 10^{-24}$ cm.) (Mayneord, 1950).

Substitution in and solution of the above equation showed that the gamma photon flux = 3.49×10^8 photons/sec./gm.

A 200-gm. rat, 10 cm. long, weighs about 20 gm./cm. If these values are applied to the conditions assumed, $I\Delta x = (20 \times 3.49 \times 10^8) = 6.98 \times 10^9$ photons/sec./cm., and the average dose to the rat becomes $(6.98 \times 10^9)\ (0.02254) = 1.57 \times 10^8$ photons/cm./sec. Each photon has an energy of 2.2 Mev and the absorption coefficient for 2.2 Mev gamma radiation in tissue is 0.022 (Mayneord, 1950).

The dose delivered to the animal may now be calculated as

$$\frac{1.57 \times 10^8 \times 2.2 \times 10^6 \times 0.022}{5.8 \times 10^{13}} = 0.131 \text{ rep/sec.}$$

Since there were 3 rats in the cage, each rat was irradiated by 2 other rats, and 0.262 rep/sec. is the estimated inter-animal dose. Since the neutron flux was reduced by 22.5 per cent, the dose becomes 0.203 rep/sec. under the conditions of the experiment. Finally, if the RBE of the 2.2 Mev gamma is 0.8 (Brennan et al., 1954), the biologically effective dose becomes 0.162 rem/sec.

The total mixed radiation in the exposure cavity was 1.38 rem/sec. The contribution of the 4 Mev gamma was 0.247 rem/sec., and the inter-animal radiation contributed 0.162 rem/sec. Adding the contributions of the contaminants and subtracting this sum from the total of the mixed radiations leaves a remainder of 0.971 rem/sec. due to thermal neutrons alone.

To calculate the RBE of the thermal neutrons it was necessary to have a value for the rep delivered. The principal reactions responsible for radiation effects in a thermal neutron flux are those involving

hydrogen, nitrogen, and boron (Brennan et al., 1954). Less than 1 per cent of the radiation effects can be attributed to all other radiations (Curtis and Teresi, 1946). The values for the number of hydrogen, nitrogen, and boron atoms per cubic centimeter of tissue were taken from Brennan et al. (1954), who used these values in calculating the dose in rep to mice. It was assumed that the values for rat tissues were not significantly different.

The reactions of importance are: $H^1(n,\gamma)H^2$, $N^{14}(n,p)C^{14}$, and $B^{10}(n,\alpha)Li^7$.

The rep delivered per second may be calculated by means of the following equation (Conger and Giles, 1950).

$$\text{rep/sec.} = \frac{(N)(Ne)(\sigma_c)(E)(A)}{R}$$

where N = the thermal neutron flux in $n/cm.^2/sec.$ (1.395×10^{10})

Ne = the number of atoms of the element/gm. (assuming 1 gm. = 1 cc.)

σ_c = capture cross section for thermal neutrons of the element in question

E = energy in ev of the radiation emitted after capture

A = fraction of the energy absorbed by the animal

R = ev/gm./rep.

The values used for the various factors in the above expression are as follows:

	Hydrogen	Nitrogen	Boron
Ne	6.02×10^{22}	1.29×10^{21}	5.6×10^{16}
σ_c	0.32×10^{-24}	1.7×10^{-24}	7.20×10^{-24}
E	2.2×10^{6}	0.62×10^{6}	2.4×10^{6}
A	$(1 - e^{-\mu t g})L$	1.0	1.0

Since the ranges of the proton in the $N^{14}(n,p)C^{14}$ reaction and of the alpha particle in the $B^{10}(n,\alpha)Li^{7}$ reaction are very short, only a minute fraction can escape. The 2.2 Mev gamma resulting from neutron capture by hydrogen is penetrating, and the per cent absorbed must be calculated from the equation $A = (1 - e^{-\mu t g})L$, in which

e = base of natural logarithms

μ = absorption coefficient for 2.2 Mev gamma radiation (0.022)

t = radius of the rat, considering the rat to be a sphere (3.4 cm.)

g = an escape path factor for a sphere (0.75)

L = an elongation factor, since the rat is not spherical (0.87)

(Brennan et al., 1954).

Substitution in and solution of this equation gave a value of A for hydrogen of 0.0496; that is, only about 5 per cent of the hydrogen gamma is absorbed.

Substitution of this value and the other values given above in the equation for the rep/sec. delivered by neutron interaction with the various elements in a thermal neutron flux gave the following values:

Hydrogen	0.505 rep/sec.
Nitrogen	0.327 rep/sec.
Boron	0.023 rep/sec.
Total	0.855 rep/sec.

Since RBE = rem/rep, the RBE of thermal neutrons compared with X rays = 0.971/0.855 = 1.14. If 0.971 rem/sec. was delivered by 1.39×10^{10} n/cm.^{2}/sec., then 1 rem is delivered by 1.44×10^{10} n/cm.^{2}/sec.

3.5 Results of Exposure to Tritium Beta Radiation

Increasingly greater doses of tritium beta radiation resulted in increasingly greater depression of Fe^{59} uptake by the red blood cells. The percentages of normal Fe^{59} uptake and the corresponding dosage values in μc./gm. body weight and in rep are given in Table 6. The line of regression, calculated by the method of least squares, is shown in Fig. 6. The equation of this line is

$$Y = 336.9 - 119.5X$$

where Y = percentage of normal Fe^{59} uptake and X = logarithm of the dose in rep.

3.6 Results of Exposure to Co^{60} Gamma Radiation

The results of exposure to the gamma radiation from Co^{60} were qualitatively similar to those obtained from exposure to tritium beta rays. The percentage of normal Fe^{59} uptake with the corresponding radiation doses in r are given in Table 7. The equation for the line of regression, calculated by the method of least squares, is

$$Y = 333.3 - 109.4X$$

where Y has the same meaning as before and X is the logarithm of the gamma radiation dose expressed in r. The results are shown graphically in Fig. 6.

Statistical determination of the significance of the difference in the slopes of the lines of regression calculated from the data gathered after exposure of rats to tritium beta and Co^{60} gamma radiations showed that there was a 50 per cent probability that the difference was due to chance alone. Since the slopes were not significantly different, they were adjusted to be equal by weighting each by the inverse of its variance and taking the average. From this new value, the intercept constants were recalculated, and the following equations for the lines of regression were obtained:

Co^{60} gamma radiation $Y = 346.2 - 114.3X$

Tritium beta radiation $Y = 323.1 - 114.3X$

Having adjusted the slopes of the lines of regression to be parallel (Fig. 6), it was possible to determine the relative effect of Co^{60} gamma and tritium beta radiation by the substitution in the same equation used earlier for the determination of the relative effectiveness of X rays, thermal neutrons, and 4 Mev gamma radiations, namely,

$$\log E = \frac{a_1 - a_2}{b}$$

where a_1 and a_2 are the intercept constants for Co^{60} gamma radiation and tritium beta radiation, respectively, and b is the common slope constant. Substitution in and solution of the above equation gave an RBE of 1.59 ± 0.11 for tritium beta radiation compared with Co^{60} gamma rays.

3.7 Results of Exposure to Plutonium and Radium

The percentage of the injected doses of Ra and Pu found in the skeleton, in the soft tissues, and excreted in urine and feces, differed. Sixty-seven per cent of the injected dose of Pu was found in the bone, as compared to 60 per cent of Ra. The percentages found in the soft tissues were 14 and 2 for Pu and Ra, respectively. These data, as well as the percentage of the injected dose excreted daily in the urine and feces, are given in Table 10.

The alpha particle radiations of both Pu and Ra were effective in decreasing Fe^{59} uptake by the red blood cells. Percentage of normal Fe^{59} uptake and the corresponding dosages in μgm./gm. bone are given in Tables 8 and 9 for Pu and Ra respectively. The equations for the lines of regression calculated by the method of least squares were

$$Pu,\ Y = 227.8 - 79.2X$$

$$Ra,\ Y = 164.4 - 32.1X$$

where Y has the same meaning as before and X is the logarithm of the dose expressed in rep.

"t" Tests of the significance of the difference in the slope constants show the slopes are significantly different ($P = 0.01$). The same test applied to each of the above equations and to that for Co^{60} give "P" values of 0.05 and 0.001 for Pu and Ra, respectively, showing that the differences in slopes of all three regression lines are significant. The lines of regression for Pu and Ra data are shown in Fig. 7. The line of regression from Co^{60} data is also plotted in this figure for comparison.

Chapter 4

DISCUSSION

4.1 Relative Biological Effectiveness of Thermal Neutrons

The RBE of 1.14 for thermal neutrons is somewhat lower than the values determined by other investigators using the Los Alamos homogeneous reactor (Table 11). It should be noted that the test animals used in previous studies were mice and that mice are more nearly a thin foil than are rats. In a thin foil exposed to a thermal neutron flux, the density of neutrons is everywhere equal and the distribution of dose is also equal. Although these conditions are probably true in mice, there is some question concerning the uniformity of neutron density in rats exposed to a thermal neutron flux. Curtis (1951) gives data from an unpublished experiment by Curtis and Checka in which rats were killed and indium foils were placed in various parts of the body so that differences in the neutron density could be measured. They found that the side of the animal nearest the pile received a dose larger than the dose measured in air, and that the side away from the pile received a dose smaller than that measured in air. The average dose was very nearly equal to the air dose. It seems likely, therefore, that the assumption that the rat is a thin foil is not a source of large error.

The value for the dose contributed by inter-animal radiation is a possible source of error. Brennan et al. (1954) found that each of 15 mice exposed simultaneously to thermal neutrons (1.8×10^{10} n/cm.^{2}/sec.)

was exposed to a dose rate of 0.12 rem/sec. from inter-animal radiation. This value, the contribution of 14 mice weighing a total of ~350 gm., compares reasonably with the value 0.16 rem/sec. for the contribution of two 200-gm. rats. Although the distribution of the rats and mice was necessarily different, the value calculated for rats does not seem to be unreasonable when compared with the value measured in mice.

Brennan et al. (1954) measured the "sink-effect" of 15 mice and reported a 21 per cent reduction in neutron flux. This value does not differ greatly from the value of 22.5 per cent for 3 rats measured in the present study.

The exposure cage used by Brennan et al. (1954) was constructed of high-purity graphite, whereas the exposure cage used in the present study was constructed of polyethylene plastic. Neutron capture by the hydrogen in polyethylene plastic would increase the contribution of the contaminating radiations and so lower the RBE value. The neutron flux would be decreased, thus decreasing the rep values and increasing the RBE value. No estimate of this source of error was made as it was not considered large.

It is possible that the end point used, depression of bone marrow function, contains an inherent error for the measurement of damage by thermal neutrons. The marrow is surrounded by bone which is lower in hydrogen and nitrogen content than the marrow itself. The marrow may be surrounded by a region in which there is a lesser density of the radiations associated with tissue interaction with thermal neutrons.

If this is true the dose to bone marrow would be somewhat smaller than the dose received by soft tissue or marrow if it were not surrounded by bone.

The value of 1.14 for the RBE of thermal neutrons is not necessarily applicable to any biological effect other than depression of bone marrow function in rats. However, this value does fall within three standard errors of the mean value calculated from the data given in Table 11 if the value obtained for production of lens opacities is omitted. It is safe to say that the value for the RBE of thermal neutrons for rats and mice is more than 1 and less than 2, omitting incidence of lens opacities [this value for the RBE is probably due to some mechanism differing from that which operates on the total body (Storer and Harris, 1952)].

The value 0.61 for the RBE of the 4 Mev gamma rays shows fair agreement with that measured by other investigators (Table 11) and is not unexpected.

4.2 Relative Biological Effectiveness of Tritium Beta Radiation

The value 1.59 for the RBE of tritium beta radiation compared with that of Co^{60} gamma rays is in fair agreement with previously reported data in indicating that the RBE was slightly greater than 1 (Jennings and Brues, 1951); it also correlates with data from this laboratory (Worman, 1954) which indicate an RBE of 1.36 from comparison of the effects of the gamma radiations of Ra with the beta radiation of tritium using decrease in spleen and thymus weight in mice as the biological indicator. It is interesting to note that this order of agreement was

found even though the biological test systems were different and both rats and mice were used as experimental animals.

The RBE of Co^{60} gamma radiation compared with 250-KV X rays is 1 (Harris, 1952) when weight loss of the spleen and thymus of mice, after acute exposure, is used as the biological indicator. If this ratio holds true for chronic exposures, then the value for the RBE of tritium compared with X rays is also 1.59.

4.3 Effects of Plutonium and Radium

It is not possible to derive an RBE for the alpha particles of Pu and Ra from the results obtained in this study because the slopes of the regression lines for depression of Fe^{59} uptake as a function of dose differ significantly (Fig. 7). In addition, the only radiation from Pu is the 5.15 Mev alpha particle, whereas the daughter products of Ra contributed to the radiation damage caused by the 4.71 Mev alpha particle of Ra. Even if 91.5 per cent of the Rn daughter products is lost, the average energy dissipated per disintegration of Ra is 4.71 + (0.085 x 29.96) = 7.26 Mev. On an energy basis alone, when equal curie amounts of Ra and Pu are deposited in the rat, one would expect Ra to be about 1.4 times as effective as Pu. The results, however, show that it takes 20 times as many rep from Ra, on the basis of total weight of skeleton, to produce a 50 per cent depression of the Fe^{59} uptake by the red blood cells, as it does to produce the same depression with Pu (176 rep for Pu, vs 3,675 rep for Ra). This ratio varies with different degrees of depression of bone marrow function. In a study of the comparative toxicities of Ra and Pu, Boyd and Fink (1950) found that the toxicity of Pu

relative to Ra was not constant when the 50 per cent lethal dose at 20, 40, 60, 80, and 100 days after administration was used as the biological indicator. When they expressed their results in terms of relative toxicity of Pu to Ra the following values were obtained:

Period, days	Relative Toxicity (Pu/Ra)
20	25
40	21
60	16
80	12
100	9

Undoubtedly this difference in toxicity, on the basis of rep delivered, can be accounted for by differences in the distribution of Pu and Ra in the body. Radium is deposited in bone in two ways. First, there is a diffuse uniform deposit in cortical and trabecular bone, and second, there are highly localized concentrations where bone growth was in progress or had recently taken place. Some concentrations appear about the central canals of the Haversian systems.

This type of deposition was found in the femur of a dog 24 hours after injection of Ra (Arnold, 1951). In the same paper the deposition of Pu was described as being restricted to endosteal, periosteal, perivascular, and epiphyseal concentrations, with no diffuse distribution. Boyd and Fink (1950) say of Pu that "instead of being distributed in the apatite structure like radium, the plutonium is concentrated in the endosteal and periosteal layers where it can presumably subject nearby

bone marrow cells to intensive alpha-ray bombardment."

The difference in slopes of the lines of regression found for Pu and Ra makes possible only the above qualitative comparison of their relative effectiveness. The difference in their modes of deposition in bone provides a very logical explanation of the difference in their effectiveness in producing lethality as well as Fe^{59} uptake by the red blood cells. In fact the present results may provide the first actual estimation of the relative effectiveness of the two modes of deposition with respect to bone marrow damage.

Since the specific ionization of Ra and Pu alpha particles is about the same, the difference in effectiveness must be due to a factor or factors other than the energetics of the ionizing particles. The difference in deposition of Ra and Pu in soft tissues (2 per cent and 14 per cent of the injected dose, respectively) may be a contributing factor to the observed difference in effectiveness, since damage to tissues and organs other than bone marrow may effect Fe^{59} uptake by the red blood cells. It is also possible (apart from radioactivity) that a differential biochemical toxicity may contribute to the difference in the relative effectiveness of Ra and Pu in depressing bone marrow function. Evans (1943) says that Ra is not a toxic substance in the biochemical sense. If this is true, and if Pu is a toxic substance, then an additional factor is introduced in the calculation of the relative effectiveness of the two elements. However, it should be pointed out that in studies of acute Pu poisoning the symptoms observed resemble the

symptoms of the acute radiation syndrome (Langham and Carter, 1951).

Because of the lack of parallelism between the regression lines for effect of Ra, Pu, and Co^{60} gamma radiation, again only a qualitative comparison can be made. General inspection of Fig. 7 shows that Pu was about twice as effective as Co^{60} gamma radiation in decreasing Fe^{59} uptake by the red blood cells. Radium was only about 0.1 as effective as Co^{60} gamma radiation.

The values as indicated above cannot be considered as estimations of the RBE of Pu and Ra alpha particles, not only because of the statistically unacceptable procedure used to obtain them, but also because of the differences in distribution of the various radiations. The Co^{60} gamma radiation is a total body radiation, whereas Pu and Ra alpha particle radiations are localized and vary from organ to organ, and even within organs. The dosages calculated for Pu and Ra alpha particles were based on the assumption that they were homogeneously distributed in bone. Radioautographs show this is not true (Arnold, 1951). Only a portion of the alpha particle bombardment is effective in depressing bone marrow function, because of the uneven distribution, and because the alpha particles are ejected at random, and some must necessarily be absorbed in the bone itself. No estimate was made of the per cent of alpha particles that were effective. The comparison would also imply that only that portion of Co^{60} radiation absorbed in the bone marrow was effective in depressing bone marrow function.

4.4 Relative Biological Effectiveness and Specific Ionization

No sharply defined relation between specific ionization and RBE is found in the data assembled in the present paper (Table 12). With increasing specific ionization an increase is found in RBE, but no numerical relation was established. In Table 13, taken from Failla (1953), recommendations for RBE values to be associated with various ion densities are given. The values measured in the present study were not in absolute agreement with those presented in Table 13; a value less than 1 and greater than 1 was found for a gamma and a beta radiation, respectively. However, when the value for the specific ionization and RBE of the tritium beta radiation was compared with the same specific ionization and RBE in Failla's recommendations, there was no discrepancy. In the case of thermal neutrons the effect was due to radiations of differing specific ionization. The gamma radiation resulting from thermal neutron capture by hydrogen has a specific ionization lower than that of 250-KV X rays. The protons and alpha particles resulting from thermal neutron capture by nitrogen and boron, respectively, are radiations with high specific ionizations. The hydrogen gamma rays deliver about 60 per cent of the rep dose $\left[(0.505/0.855) \times 100\right]$, but if the RBE of this radiation is 0.8, then the rem contribution of hydrogen gammas is only 47 per cent of the rem dose. The remaining 40 per cent of the rep dose contributed by the protons and alpha particles resulting from the thermal neutron reactions with nitrogen and boron contribute 52 per cent of the rem dose.

The RBE for the proton and alpha radiations may be calculated by

subtracting the rem/sec. value of the hydrogen gammas from the total rem/sec. of the thermal neutrons and dividing the remainder by the sum of the rep/sec. values of the alpha and proton components:

$$\frac{0.971 - (0.505 \times 0.8)}{0.327 + 0.023} = 1.6$$

The RBE for these combined radiations is thus 1.6. The average specific ionization of a 0.6 Mev proton is about 2,000 ion pairs/micron and that for a 2.4 Mev alpha particle is >4,000 ion pairs/micron (Fig. 8).

Table 13 shows that the RBE of these radiations should be between 10 and 20 if these suggested values are valid for the system under study (depression of bone marrow function).

The data in the present study suggest that RBE increases with specific ionization up to a point and then no further, and, perhaps, a decrease follows.

The relation between specific ionization and RBE is not clearly defined by the data assembled in Table 14. The table contains data concerning mammalian systems only, because it is felt that radiation effects on microorganisms, plants, invertebrates and nonmammalian vertebrates are not so susceptible to extrapolation to human systems. The value of nonmammalian data is unquestionable and such data are necessary for studying the mechanism of radiation effects, but the extrapolation of such data to human tolerance values is, at best, questionable. For a review covering all biological materials, see Zirkle (1954).

Several facts worthy of comment appear in the table.

1. The importance of time factor selected is shown; e.g., in item 9, the RBE varies with the length of post-irradiation time selected.

2. Dose rate is a factor in evaluation of RBE. Comparison of items 21 and 23 illustrates this point.

3. The choice of tissue selected to measure the effect of radiation will affect the RBE. Compare items 32 to 34 and 45 to 46.

4. A few items have exceptionally high RBE values and deserve special mention:

Item 24. Fast neutrons from uranium fission are compared with Ta^{128} gamma radiation. The Ta^{128} gamma data are sparse (2 levels of radiation) and even if the data are valid, the value given may be reduced (see paragraph 5 below) by multiplying by a factor of 0.6 for comparison with 250-KV X radiation.

Item 25. This is the highest mammalian RBE found. Boag says, "It is possible that the non-uniform neutron dose distribution in Mitchell's exposure facility may have had some influence on his results (owing to the existence of possible 'hot spots')."

Items 36, 37. The effect of fast neutrons is compared with Ra gamma radiation. The values may be reduced by multiplying by a factor of about 0.6 for comparison with 250-KV X radiation. It also appears that while the mean lethal γ-radiation dose was approximately the same for irradiation

in vitro and in vivo, the mean lethal neutron dose is greater in vitro than in vivo. This suggests the possibility that the dosimetry for the neutron exposures may have been faulty.

5. Radiations with a specific ionization of the order of 10 ion pairs/μ (γ rays, high energy X- and β rays) are about 0.6 times as effective as 200, 250-KVP X rays (items 1 to 5, 26, 38, 43 to 46, etc.)

6. Radiations with a specific ionization greater than 200 have an RBE greater than 1 when compared with 250-KV X rays, but no fixed relation exists. The data for mouse lethality are arranged in the table in order of increasing RBE's but no regular increase in the relevant specific ionization values is evident.

7. The RBE values for α radiation, 3,000 ion pairs/μ (items 10, 28, 39), are less than 2. This is consistent with the suggestion of Gray (1946), Boag (1953), and Storer et al. (1954) that a plot of RBE against specific ionization would result in a curve that would rise, reach a maximum, and then decline. Such a curve has been reported by Sayeg (1954) for irradiated yeast cells.

Attempts have been made to explain the mechanism of action of radiations on biological materials which would account for the relation between RBE and specific ionization. The target theory, whose foremost proponent was Lea (1947), has been modified as more information has been accumulated. Simply stated, the target theory proposes that each biological entity (e.g., a cell) has a "sensitive volume" which may or may not

differ from the physical dimensions of the cell; this is the target. An ionizing particle must pass through the target in order to produce a radiation effect. The effect is produced by the ionization of one or more atoms within the target. The discovery of a number of radiomimetic substances (Loveless and Revell, 1949; Auerbach, 1949), the modification of radiosensitivity with protective agents (Brues and Patt, 1953) and with changes in oxygen tension (Gray, 1951) have all led to modifications of the target theory. The indirect action theory of Dale (1954) and the "migration" or "diffusion" model of Zirkle and Tobias (1953) are variants of such modifications wherein account is taken of indirect radiation effects due to radicals or toxins produced by ionizing particles.

Since water is the major single constituent of biological materials, the results of irradiating water have been the subject of numerous experiments (Gray, 1954; Hart, 1954; Dewhurst et al., 1954), and the products of the irradiation of water are thought to be responsible for the effects of ionizing radiations. However, specific details are lacking and many of the ions and radicals suggested as agents contributing to the biological effects of radiations have as yet no more concrete basis than theory. As more progress is made in this difficult field, and as the events that permit normal cells to grow and reproduce themselves are more clearly understood, the effects of ionizing radiations on biological material will become more subject to prediction on the basis of rational knowledge rather than empirical knowledge.

Chapter 5

SUMMARY AND CONCLUSIONS

Male Sprague-Dawley rats were exposed to external radiations of a 250-KVP X-ray machine and to the mixed radiations in the thermal column of a homogeneous reactor. The effect of these radiations on bone marrow function was measured by comparing the uptake of Fe^{59} by the red blood cells of the exposed animals to that of unirradiated controls. These data were used to determine the RBE of the thermal column radiations.

Using the same indicator of bone marrow function, the RBE of tritium beta radiation compared with Co^{60} gamma radiation was determined. The effects of Pu and Ra on bone marrow function were also measured with the same indicator. From these studies it may be concluded that

(a) The RBE of thermal neutrons for depression of bone marrow function in rats was 1.14 compared with 250-KVP X rays.

(b) The RBE of the 4 Mev gamma radiation compared with 250-KVP X rays was 0.6.

(c) The RBE of tritium beta radiation compared with Co^{60} gamma rays was 1.59 ± 0.11.

(d) On the basis of rep delivered to total bone, assuming uniform distribution, Pu was about two times as effective and Ra was about 0.1 as effective as Co^{60} in depressing bone marrow function. The difference in deposition of the two elements was thought to be the most important factor in the difference in effectiveness of Ra and Pu. The results did

not permit the estimation of the RBE of Pu and Ra alpha particles in comparison with the gamma radiation of Co^{60}. They did, however, provide a relative comparison of the effectiveness of the modes of deposition of the two substances with regard to depression of bone marrow function.

(e) With increasing specific ionization there was an increase in the value of RBE. However, no RBE above 2 was found although there was a more than 40-fold increase in specific ionization.

(f) A survey of literature on RBE in mammalian systems shows no consistent relation between RBE and specific ionization. RBE values plotted against specific ionization may pass through a maximum and then decrease as specific ionization increases.

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TABLE 1

WHOLE BLOOD VOLUME OF THE RAT MEASURED WITH Fe^{59} LABELED RED BLOOD CELLS

Rat Weight (gm.)	Whole Blood Volume (cc.)	cc./100 Gm. Body Wt.
185	10.98	5.94
240	14.98	6.24
240	13.30	5.54
194	12.89	6.64
222	12.20	5.50
188	11.94	6.35
192	10.88	5.67
218	12.40	5.69
154	10.40	6.75
176	9.96	5.69
241	12.87	5.34
223	12.44	5.58
227	13.57	5.97
194	10.83	5.58
271	14.90	5.50
131	8.01	6.11
245	14.45	5.89
240	13.53	5.64
235	13.93	5.93
313	16.30	5.21
119	8.36	7.02
Average		5.89
S.E. = $\sqrt{\frac{\sum(x-\bar{x})^2}{n-1}}$		0.46

TABLE 2

PERCENTAGE OF Fe^{59} APPEARING IN RED BLOOD CELLS OF MALE AND FEMALE RATS

Animals	Average Wt. (gm.)	Fe^{59} in Red Blood Cells (per cent)	S. E.
Young Males	141	59.13	7.21
Old Males	350	57.21	9.32
Females	216	59.47	8.21
Young Males[(a)]	155	60.14	3.46

(a) 2 cc. blood withdrawn prior to Fe^{59} injection.

TABLE 3

DOSAGES AND EFFECT OF X RADIATION ON PERCENTAGE OF NORMAL Fe^{59} UPTAKE BY RED BLOOD CELLS OF RATS

Group		Dose (r)	Exposure Time (sec.)	Fe^{59} Uptake(a) (per cent of normal)	S.E. of Fe^{59} Uptake
Series 1	Series 2				
1		50	41.3	76.8	6.8
	1	50	41.3	78.2	10.0
	2	69	57.0	69.3	12.0
	3	95	78.5	62.4	12.7
2		100	82.6	53.0	9.3
	4	131	108.2	47.3	11.2
3		150	123.9	26.9	8.7
	5	181	149.5	34.7	10.4
4		200	165.2	20.3	3.7
5		250	206.6	18.3	2.9
	6	250	206.6	10.3	2.6

(a) For first series Fe^{59} uptake in red blood cells of controls equaled 57.1 per cent.

In second series Fe^{59} uptake in red blood cells of controls equaled 59.1 per cent.

TABLE 5

EXPOSURE TIMES AND EFFECT OF 4 MEV GAMMA RADIATION ON PERCENTAGE OF NORMAL Fe^{59} UPTAKE BY RED BLOOD CELLS OF RATS

Group	Exposure Time[a] (sec.)	Fe^{59} Uptake[b] (per cent of normal)	S. E. of Fe^{59} Uptake
1	106.6	86.24	14.2
2	204.0	76.17	17.2
3	281.0	67.71	22.8
4	388.0	47.35	12.9
5	536.0	43.40	8.3
6	741.0	23.72	8.3

(a) Operating power level was 25 KW.

(b) Fe^{59} uptake in red blood cells of controls equaled 63.47 per cent.

TABLE 6

EXPOSURE CONDITIONS AND EFFECT OF TRITIUM BETA RADIATION ON PERCENTAGE OF NORMAL Fe^{59} UPTAKE BY RED BLOOD CELLS OF RATS

Group	T Injected/200 Gm. Body Wt.(μc.)	Expected T Conc. in Body Water (μc./ml.)	T Conc. in Drinking Water (μc./ml.)	T Conc. in Urine (μc./ml.)	Dose (rep)	Fe^{59} Uptake[a] (Per Cent of Normal)	S.E. of Fe^{59} Uptake
1	36.0	240	320	254	314	38.8	11.7
2	42.5	278	371	293	362	34.5	15.8
3	47.5	317	422	342	423	19.9	13.2
4	54.7	365	486	368	455	16.5	8.3
5	63.4	422	563	413	511	12.6	6.2
6	72.0	480	640	514	636	4.1	1.4

(a) Fe^{59} uptake in red blood cells of controls equaled 59.4 per cent.

TABLE 7

EXPOSURE CONDITIONS AND EFFECT OF Co^{60} GAMMA RADIATION ON PERCENTAGE OF NORMAL Fe^{59} UPTAKE BY RED BLOOD CELLS OF RATS

Group	Source-Cage Distance (cm.)	Dose (r)	Fe^{59} Uptake(a) (per cent of normal)	S. E. of Fe^{59} Uptake
1	142	302	59.7	14.3
2	131	354	54.0	22.4
3	119	404	50.8	20.7
4	109	468	43.7	21.4
5	101	579	29.4	14.5
6	91	632	25.7	7.8

(a) Fe^{59} uptake in red blood cells of controls equaled 59.5 per cent.

TABLE 8

EFFECT OF PLUTONIUM INJECTION ON PERCENTAGE OF NORMAL Fe^{59} UPTAKE BY RED BLOOD CELLS OF RATS

Group	Pu Injected (μg./100 gm. body wt.)	Pu in Bone (μgm./gm.)	Dose to Bone (rep)	Fe^{59} Uptake(a) (per cent of normal)	S. E. of Fe^{59} Uptake
1	20.3	1.56	140.8	58.64	15.12
2	27.1	2.16	195.0	50.39	15.06
3	35.6	2.62	236.0	38.01	9.46
4	49.1	3.21	289.3	26.84	8.37
5	66.1	3.98	358.3	25.03	10.88
6	89.8	5.91	531.9	15.22	4.00

(a) Fe^{59} uptake in red blood cells of controls equaled 65.09 per cent.

TABLE 9

EFFECT OF RADIUM INJECTION ON PERCENTAGE OF NORMAL Fe^{59} UPTAKE BY RED BLOOD CELLS OF RATS

Group	Ra Injected (μgm./gm. body wt.)	Ra in Bone (μgm./gm.)	Dose to Bone (rep)	Fe^{59} Uptake(a) (per cent of normal)	S. E. of Fe^{59} Uptake
1	8.5	0.52	1,052	69.88	11.28
2	11.7	0.70	1,416	61.11	13.11
3	16.6	0.96	1,942	55.57	10.70
4	22.0	1.34	2,711	54.43	9.04
5	31.1	1.80	3,641	50.47	8.53
6	42.1	2.60	5,259	45.13	6.63

(a) Fe^{59} uptake in red blood cells of controls equaled 61.56 per cent.

TABLE 10

EXCRETION, DEPOSITION, AND RECOVERY OF RADIUM AND PLUTONIUM

	Per Cent Excreted in Urine		Per Cent Excreted in Feces		Per Cent Deposited in Skeleton		Per Cent Deposited in Soft Tissues	
Day	Ra	Pu	Ra	Pu	Ra	Pu	Ra	Pu
1	6.80	0.51	13.15	1.02	--	--	--	--
2	0.86	0.17	6.38	2.86	--	--	--	--
3	0.37	0.09	1.75	2.90	--	--	--	--
4	0.27	0.08	1.08	2.67	--	--	--	--
5	0.15	0.25	0.82	2.90	60.06	66.77	2.02	14.16
Total[a]	8.45	1.10	23.18	12.35	60.06	66.77	2.02	14.16

(a) Total recovery of Ra and Pu was 93.71 and 94.38 per cent of injected dose, respectively.

TABLE 11

RBE OF THERMAL COLUMN RADIATIONS FROM THE LOS ALAMOS HOMOGENEOUS REACTOR WHEN COMPARED TO 250-KVP X RAYS

Biological System Studied	RBE of Thermal Neutrons	RBE of 4 Mev Gamma Radiation	Reference
Lethality in mice	1.51	0.53	13
Spleen weight loss in mice	1.55	0.60	52
Thymus weight loss in mice	1.73	0.80	52
Lens opacity production in mice	15.00	1.02	106
Testicular atrophy in mice	1.3	--	107
Mitotic index in mice	1.5	--	104

TABLE 12

SPECIFIC IONIZATION OF VARIOUS RADIATIONS

Radiation	Ion Pairs/μ Tissue	RBE*
X ray, 250-KV	$\sim$80[a]	1.0
Co^{60} Gamma	$\sim$10[a]	1.0
4 Mev Gamma	$\sim$10[a]	0.6
Tritium Beta	$\sim$180[b]	1.59
0.6 Mev Proton	$\sim$2000[b]	1.6
2.4 Mev Alpha	$>$4000[b]	1.6

(a) Gray (1947).

(b) Lea (1947).

* Values from present study.

TABLE 13

RBE OF RADIATIONS ACCORDING TO AVERAGE SPECIFIC IONIZATION IN WATER[a]

	RBE
X rays, Electrons, and Positrons of Any Specific Ionization	1
Heavy Ionizing Particles	
Average Specific Ionization (ion pairs/μ of water)	
100 or less	1
100-200	1-2
200-650	2-5
650-1500	5-10
1500-5000	10-20

(a) Taken from Failla (1953). These values were recommendations to be used as guides in setting up tolerance values.

TABLE 14

RBE VALUES OF RADIATIONS OF DIFFERING SPECIFIC IONIZATION
FOR MAMMALIAN SYSTEMS

Notes to Table 14

The first column contains a number for reference. The second column indicates the biological end point used to determine RBE. "Takes" indicates the successful transplantation of a tumor. The other items are self-explanatory. The third column gives the types of radiations that are compared for effectiveness. X radiation is indicated by X followed by a number which gives the kilovoltage applied across the tube. Alpha, beta, and gamma radiations are followed by the symbol for the element which is their source or by the energy of the particles. Fast neutrons are indicated by the method they are produced; e.g., Be(d,n)B indicates the bombardment of a beryllium target with deuterons to produce fast neutrons and boron, and U fission indicates fission neutrons. Thermal neutrons are produced in a reactor.

The fourth column gives the specific ionization in ion pairs per micron. These values can be only approximations. The variation found in the specific ionization of fast neutrons is due to the variations in energy of the bombarding particles. Most values for specific ionization come from Gray (1947) and Lea (1947).

The fifth column gives the RBE. In general, when a radiation has a specific ionization of 80 to 100 ion pairs/micron it is arbitrarily assigned an RBE of 1. When this is not possible, the least effective radiation is assigned an RBE of 1.

The sixth column contains a reference number to the Bibliography.

The seventh column contains letter symbols referring to the following:

A. Fast neutron exposures measured in "n" units. The factor 2.5 has been used to equate roughly "n" to rep. (Aebersold and Anslow, 1946, but see also Boag, 1953.)

B. Assumes Ra gamma filtered by 0.5 mm. Pt is 8.47 r/mgm.-hr. (White, Marinelli, and Failla, 1940.)

C. RBE is probably higher. The effect of an unmeasured gamma ray contaminant is not subtracted from the mixed radiation.

TABLE 14

MOUSE

No.	End Point	Radiations	Ion pairs/μ	RBE	Ref.	Notes
1	Lethality	X, 200 KV	80	1.0	11	
		γ, Ra	~10	0.3-0.48		
2	Death, 3 weeks' daily exposure	X, 200 KV	80	1.0	89	
		X, 20 MV	~10	0.49		
3	LD_{50}^{30}	X, 250 KV	80	1.0	13	
		γ, Pile	~10	0.53		
4	Lethality	X, 200 KV	80	1.0	99	
		β, Na^{24}	~10	0.73		
5	Survival Time	X, 200 KV	80	1.0	88	
		X, 20 MV	~10	0.78		
6	Death, 1 week daily doses	X, 200 KV	80	1.0	89	
		X, 20 MV	~10	0.84		
7	LD_{50}^{30}	X, 250 KV	80	1.0	16	
		β, tritium	180	1.0		
8	Early death	X, 200 KV	80	1.0	68	A,C
		Be(d,n)B	600	1.2		
9	Lethality, 5 days	X, 250 KV	80	1.0	51	
		Thermal column radiations	380	2.04	51	
	30 days	Thermal column radiations		1.38		
	30 weeks	Thermal column radiations		1.41		
	1 year	Thermal column radiations		1.33		
10	LD_{50}^{30}	X, 186 KV	90	1.0	60	
		α, Rn	3000	1.4		

TABLE 14
(continued)

MOUSE

No.	End Point	Radiations	Ion pairs/μ	RBE	Ref.	Notes
11	Reciprocal of life span	X, 200 KV	80	1.0	67	A,C
		Be(d,n)B	560	1.5		
12	LD_{50}^{30}	X, 250 KV	80	1.0	54	
		Fast neutrons, 14 Mev	200	2.16		
13	Early death	X, 200 KV	80	1.0	70	A,C
		Be(d,n)B	600	1.6		
14	LD_{50}^{30}	X, 250 KV	80	1.0	13	
		Thermal neutrons	400	1.7		
15	LD_{50}	X, 200 KV	80	1.0	32	C
		Be(d,n)B	700	2.3		
16	Lethality, acute exposure	X, 185 KV	90	1.0	30,31	A
		Be(d,n)B	700	3.2		
17	Lethality, chronic exposure	X, 185 KV	90	1.0	30,31	A
		Be(d,n)B	700	3.2		
18	LD_{50}^{30}, acute exposure	γ, Ta^{128}	~10	1.0	57	A
		U fission	>1000	3.6		
19	LD_{50}, single exposure	X, 180 KV	90	1.0	111	
		D, 170 Mev	90	4.0		
20	LD_{50}^{30}	X, 200 KV	80	1.0	47	A
		Be(d,n)B	300	4.1		
21	LD_{50}^{30} exposure time 1.5 hr.	γ, Co^{60}	~10	1.0	113	
		U fission	>1000	4.4		
22	Total dose chronic exposure at 50% death	X, 185 KV	90	1.0	29,30	A
		Be(d,n)B	700	5.2		
23	LD_{50}^{30}	γ, Co^{60}	~10	1.0	113	
		U fission	>1000	6.25		

TABLE 14
(continued)

MOUSE

No.	End Point	Radiations	Ion pairs/μ	RBE	Ref.	Notes
24	Reduction of life span, daily doses	γ, Ta^{128}	~10	1.0	57	A
		U Fission	>1000	14.0		
25	LD_{50}^{30} dose given in 48 hr.	γ, Ra	~10	1.0	81	
		$Be^{9}(\alpha, n)C^{12}$	600	32.0		
26	"Takes," Sarcoma 180	X, 200 KV	80	1.0	108	
		γ, Ra	~10	0.68-0.81		
27	Chromosome abnormalities in Sarcoma 180	X, 120 KV	100	1.0	74	
		X, 180 KV	90	1.0		
		X, 400 KV	40	1.0		
28	Tumor regression Lymphosarcoma	X, 186 KV	90	1.0	60	
		α, Rn	3000	1.0		
29	"Takes," Sarcoma 180	X, 200 KV	80	1.0	68	A,C
		Be(d,n)B	600	2.0		
30	"Takes," mammary carcinoma	X, 200 KV	80	1.0	67	A,C
		Be(d,n)B	560	2.0		
31	Chromosome abnormalities, lymphoma	X, 200 KV	80	1.0	75	A
		Be(d,n)B	420	2.3		
32	"Takes," Lymphosarcoma	X, 220 KV	80	1.0	6	A
		Be(d,n)B	250	3.0		
33	"Takes," Lymphoma	X, 220 KV	80	1.0	6	A
		Be(d,n)B	250	2.3		
34	"Takes," mammary carcinoma	X, 220 KV	80	1.0	6	A
		Be(d,n)B	250	2.4		
35	Chromosome abnormalities, Lymphoma	X, 220 KV	80	1.0	76	A
		Be(d,n)B	250	2.4-3.5		
36	Regression of mouse carcinoma 2146 (in vivo)	γ, Ra	~10	1.0	46	
		D(d,n)He	>1000	24.0		

TABLE 14
(continued)

MOUSE

No.	End Point	Radiations	Ion pairs/μ	RBE	Ref.	Notes
37	"Takes," mouse carcinoma 2146 (in vitro)	γ, Ra	~10	1.0	46	
		D(d,n)He	>1000	9.5		
38	Changes in WBC counts in normal and leukemic mice	X, 184 KV	90	1.0	33	
		β, Na^{24}	~10	0.64		
39	Depression of leucocyte count	X, 186 KV	90	1.0	60	
		α, Rn	3000	1.0		
40	Depression of leucocyte count	X, 200 KV	80	1.0	68	A,C
		Be(d,n)B	600	1.2		
41	Depression of leucocyte count, acute exposure	X, 185 KV	90	1.0	30,31	A
		Be(d,n)B	700	3.2		
42	Depression of leucocyte count, repeated exposure	X, 185 KV	90	1.0	30,31	A
		Be(d,n)B	700	3.2		
43	Greying of hair	X, 200 KV	80	1.0	19	
		X, 20 MV	~10	0.7		
44	Greying of hair	X, 150 KV	100	1.0	5	
		β, 17 Mev	~10	0.6		
45	Spleen wt. loss	X, 250 KV	80	1.0	52	
		γ, Pile	~10	0.8		
46	Thymus wt. loss	X, 250 KV	80	1.0	52	
		γ, Pile	~10	0.6		
47	Spleen wt. loss	γ, Ra	~10	1.0	116	
		β, tritium	180	1.26		
48	Thymus wt. loss	γ, Ra	~10	1.0	116	
		β, tritium	180	1.47		
49	Spleen wt. loss	X, 250 KV	80	1.0	52	
		Thermal neutrons	400	1.55		

TABLE 14
(continued)

MOUSE

No.	End Point	Radiations	Ion pairs/μ	RBE	Ref.	Notes
50	Spleen and thymus wt. loss	X, 250 KV	80	1.0	53	
		Fast neutrons, 14 Mev	200	1.6		
51	Thymus wt. loss	X, 250 KV	80	1.0	52	
		Thermal neutrons	400	1.73		
52	Spleen wt. loss	γ, Co^{60}	~10	1.0	113	
		U fission	>1000	4.-5.		
53	Cataract production single exposure	X, 200 KV	80	1.0	32	A
		Be(d,n)B	700	4.0		
54	Cataract production multiple exposure	X, 200 KV	80	1.0	32	A
		Be(d,n)B	700	6.0		
55	Production of lens opacities, 30 weeks	X, 250 KV	80	1.0	51	
		Thermal column	380	9.73		
56	Production of lens opacities, 1 year	X, 250 KV	80	1.0	51	
		Thermal column	380	5.92		
57	Sterilization in males	X, 200 KV	80	1.0	97	A,C
		Be(d,n)B	700	2.0-2.4		
58	Testicular atrophy	X, 250 KV	80	1.0	107	
		Thermal neutrons	400	1.3		
59	Testicular atrophy	X, 186 KV	90	1.0	28	A
		Be(d,n)B	650	4.0		
60	Suppression of estrous	X, 185 KV	90	1.0	31	A
		Be(d,n)B	700	5.6		
61	Inhibition of mitosis	X, 185 KV	80	1.0	104	
		Thermal neutrons	400	1.7		

TABLE 14
(continued)

MOUSE

No.	End Point	Radiations	Ion pairs/μ	RBE	Ref.	Notes
62	Erythema and desquamation, tail skin	X, 117 & 190 KV	100 & 80	1.0	82	
		γ, Ra	$\sim$10	0.77		
63	Exudation, epilation, tail skin	X, 117 & 190 KV	100 & 80	1.0	82	
		γ, Ra	$\sim$10	0.63		

RAT

64	Lethality	X, 400 KV	40	1.0	38	
		β, 19 Mev	$\sim$10	0.6-0.8		
65	Decreased bone growth, bone marrow damage, skin damage	X, 200 KV	80	1.0	39, 40,	B
		X, 1 MV	15	1.0	72	
66	Bone growth	X, 400 KV	40	1.0	18	
		X, 24 MV	$\sim$10	0.6		
67	Inhibition of glycolysis in the retina	γ, Ra	$\sim$10	1.0	21	B
		β, Ra	$\sim$10	1.0		
		X, 200 KV	80	1.0		
68	Degeneration of cells in retina	γ, Ra	$\sim$10	1.0	100	
		Be(d,n)B	420	2.6		
69	Decrease in nucleic acid content of gut	X, 120 KV	100	1.0	27	A
		Be(d,n)B	570	2.5		
70	Abnormal mitoses, Walker carcinoma 256	X, 220 KV	80	1.0	77	A
		Be(d,n)B	250	2.4-4.3		
71	Abnormal mitoses, lymphosarcoma	X, 220 KV	80	1.0	77	A
		Be(d,n)B	250	2.4		
72	Fall in lymphocyte count	X, 900 KV	15	1.0	69	A
		Be(d,n)B	780	4.0		

TABLE 14
(continued)

RABBIT

No.	End Point	Radiations	Ion pairs/μ	RBE	Ref.	Notes
73	Lethality	X, 250 KV	80	1.0	47	A
		Be(d,n)B	300	4.1		
74	Changes in WBC counts	X, 200 KV	80	1.0	94	A
		Be(d,n)B	300	2.5		
75	Minimal erythema, ear	X, 30 KV	100	1.0	8	
		β, P^{32}	~10	0.3		
76	First signs of epilation	X, 30 KV	100	1.0	8	
		β, P^{32}	~10	0.25		
77	100% epilation	X, 30 KV	100	1.0	8	
		β, P^{32}	~10	0.22		

HUMAN

78	Skin erythema	X, 85 KV	100	2.9	35	B
		X, 200 KV	80	1.0		
		γ, Ra	~10	0.6		
79	Moist desquamation	X, 0.15 AEff	80	1.0	80	
		γ, Ra	~10	0.7-0.8		
80	Erythema	X, 200 KV	80	1.0	103	
		X, 1 MV	15	0.8		
81	Erythema	X, 200 KV	80	1.0	102	A
		Be(d,n)B	560	2.3		
82	Erythema	X, 200 KV	80	1.0	101	A
		Be(d,n)B	250	2.4		
83	Decrease in lymphocytes in bone marrow cultures	X, 200 KV	80	1.0	83	A
		X, 1 MV	15	1.0		
		β, P^{32}	~10	1.0		
		Be(d,n)B	250	1.6		

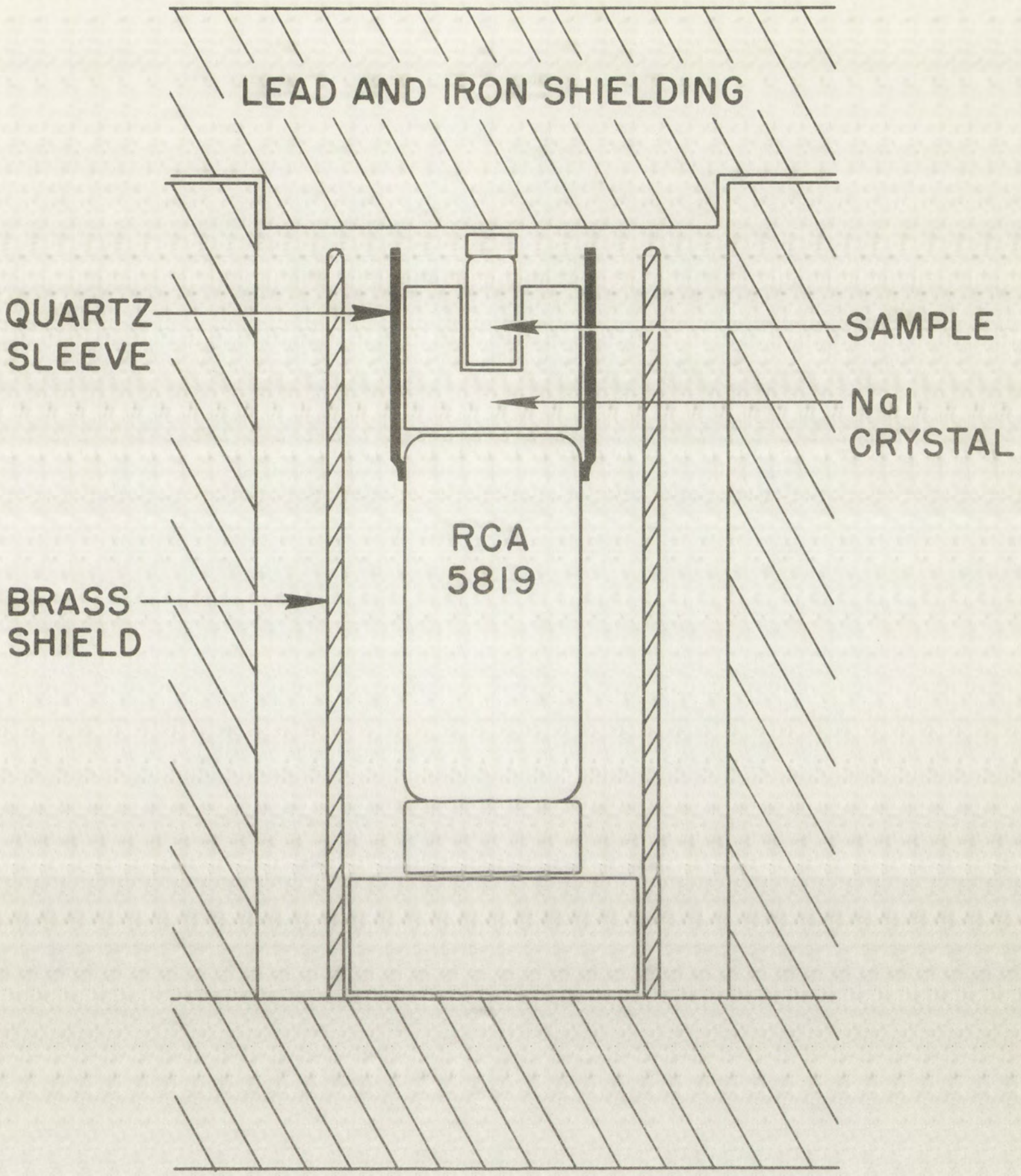

Fig. 1. Counting setup showing arrangement of sodium iodide scintillation crystal and RCA-5819 photomultiplier tube.

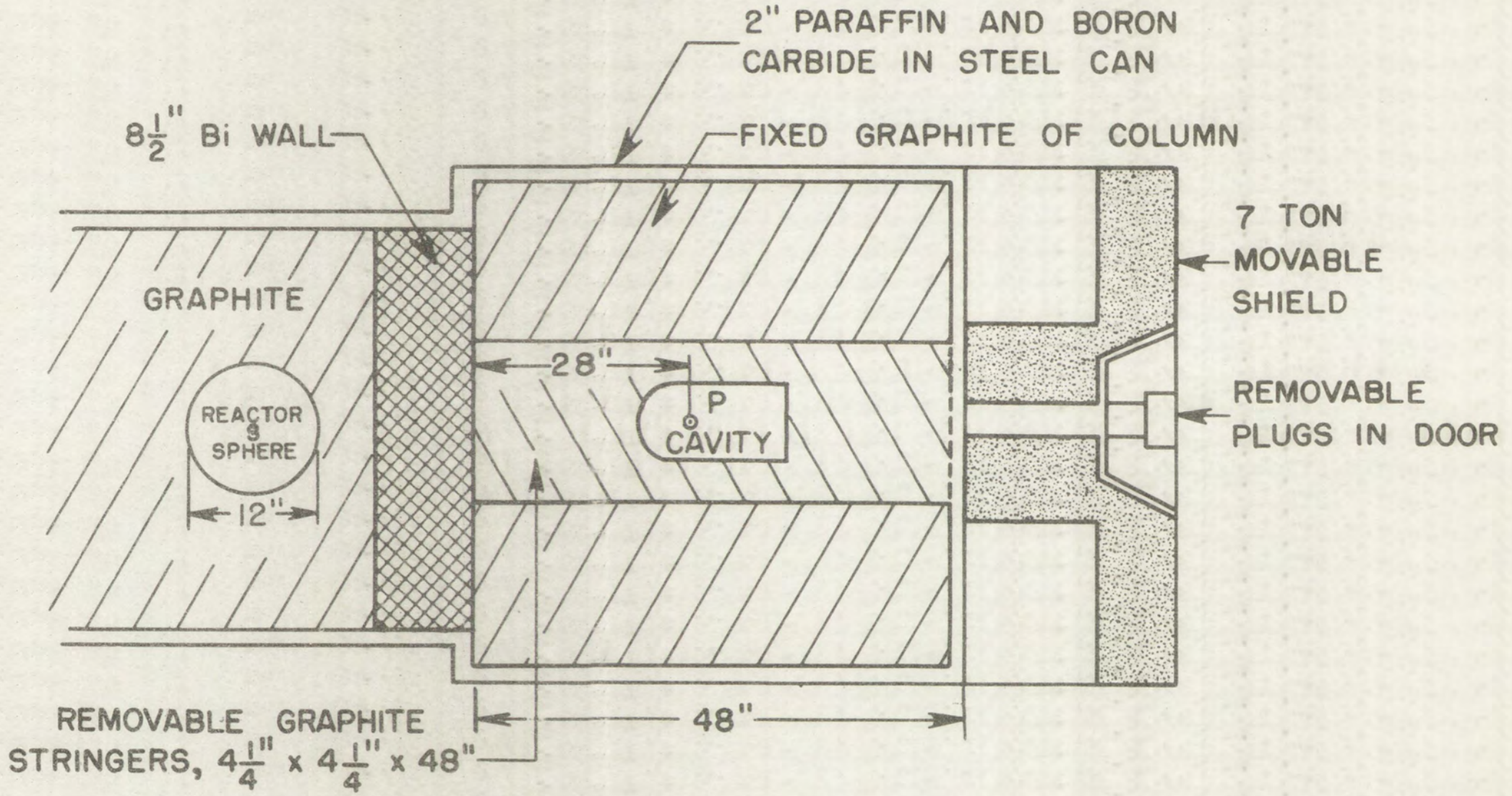

Fig. 2. North thermal column of the homogeneous reactor showing position of exposure cavity.

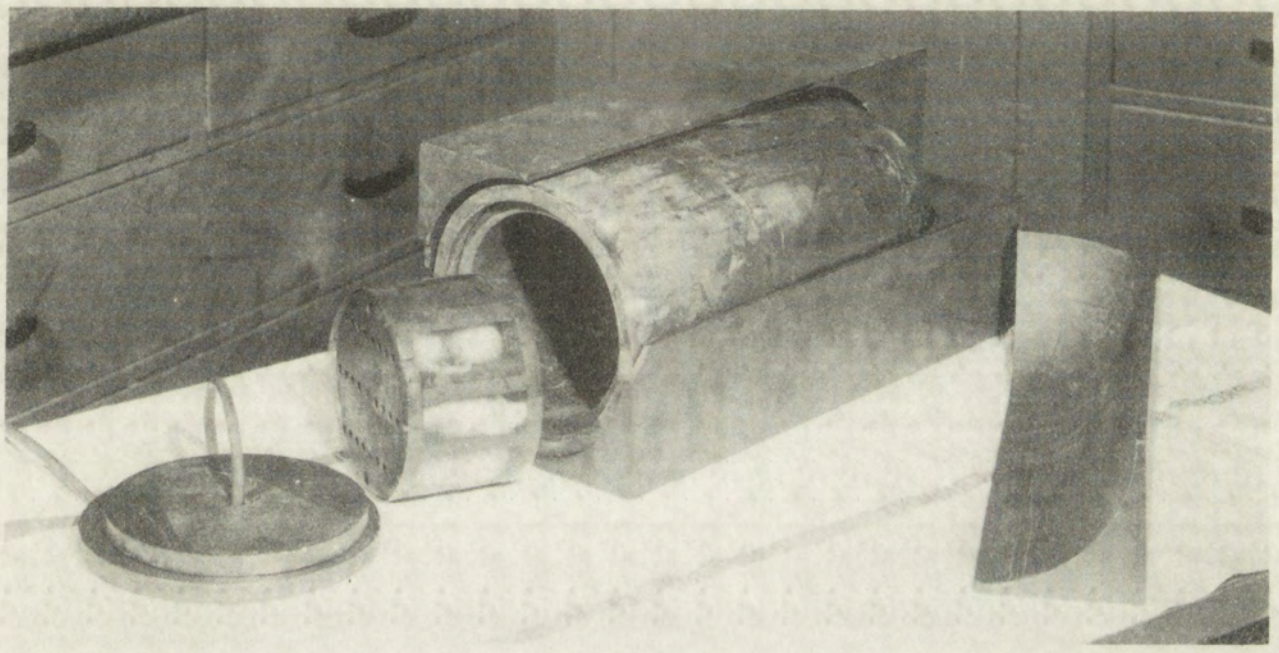

Fig. 3. Graphite exposure cavity showing an exposure cage, bismuth shells, and lid.

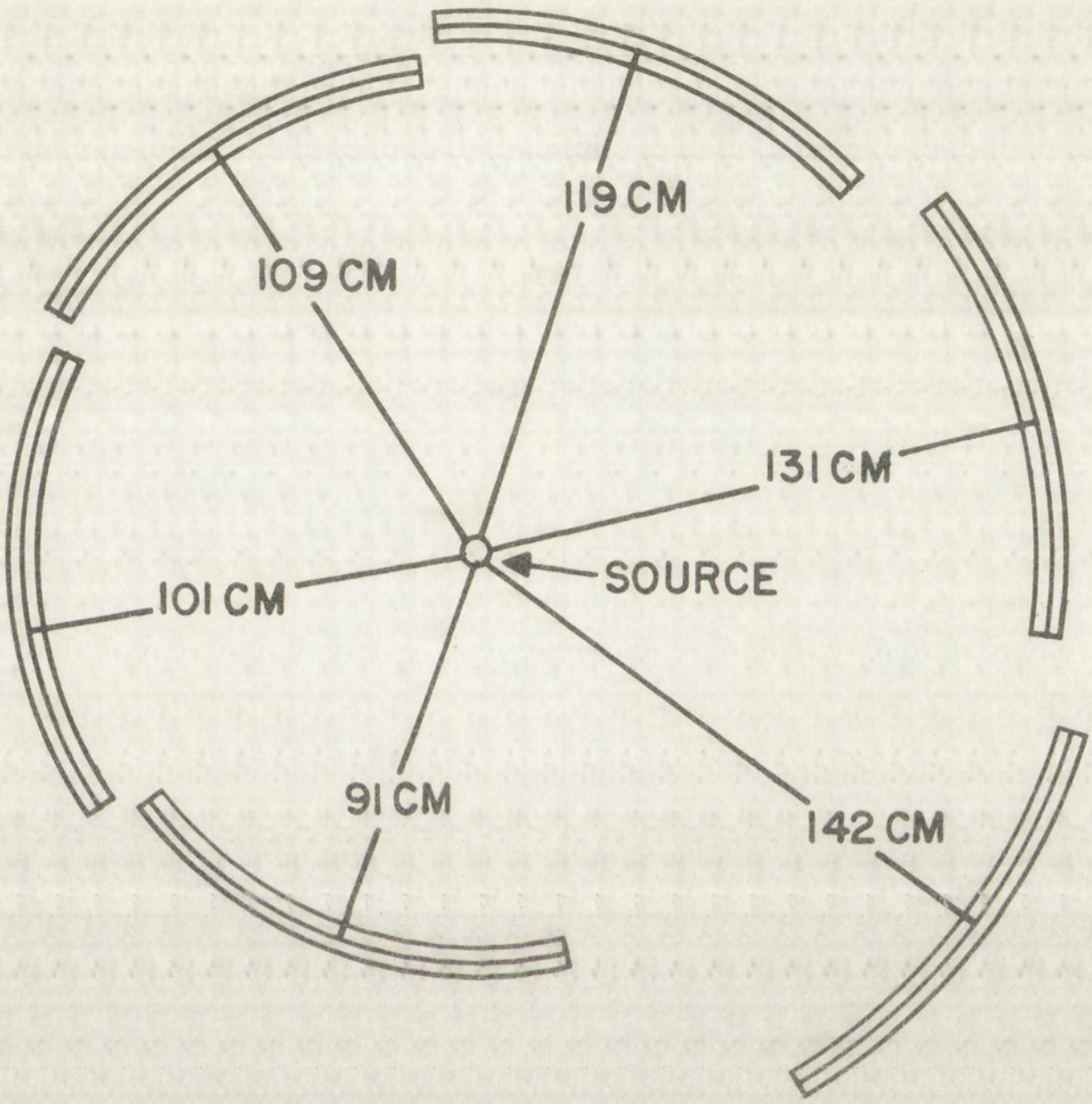

Fig. 4. Cage arrangement for exposure to Co^{60} gamma radiation.

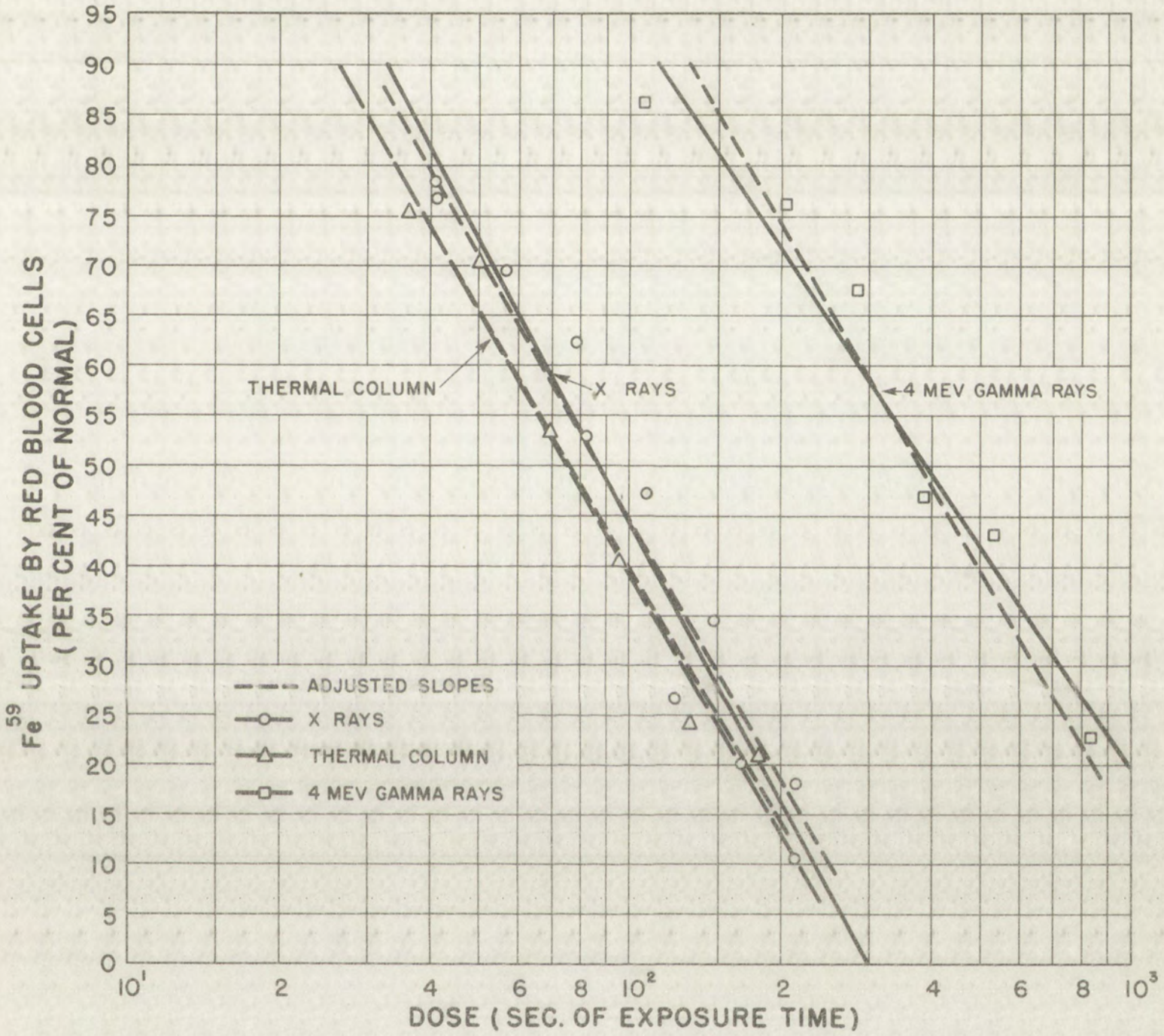

Fig. 5. Percentage of normal Fe^{59} uptake by red blood cells of rats exposed to X rays, thermal column radiation, and 4 Mev gamma rays.

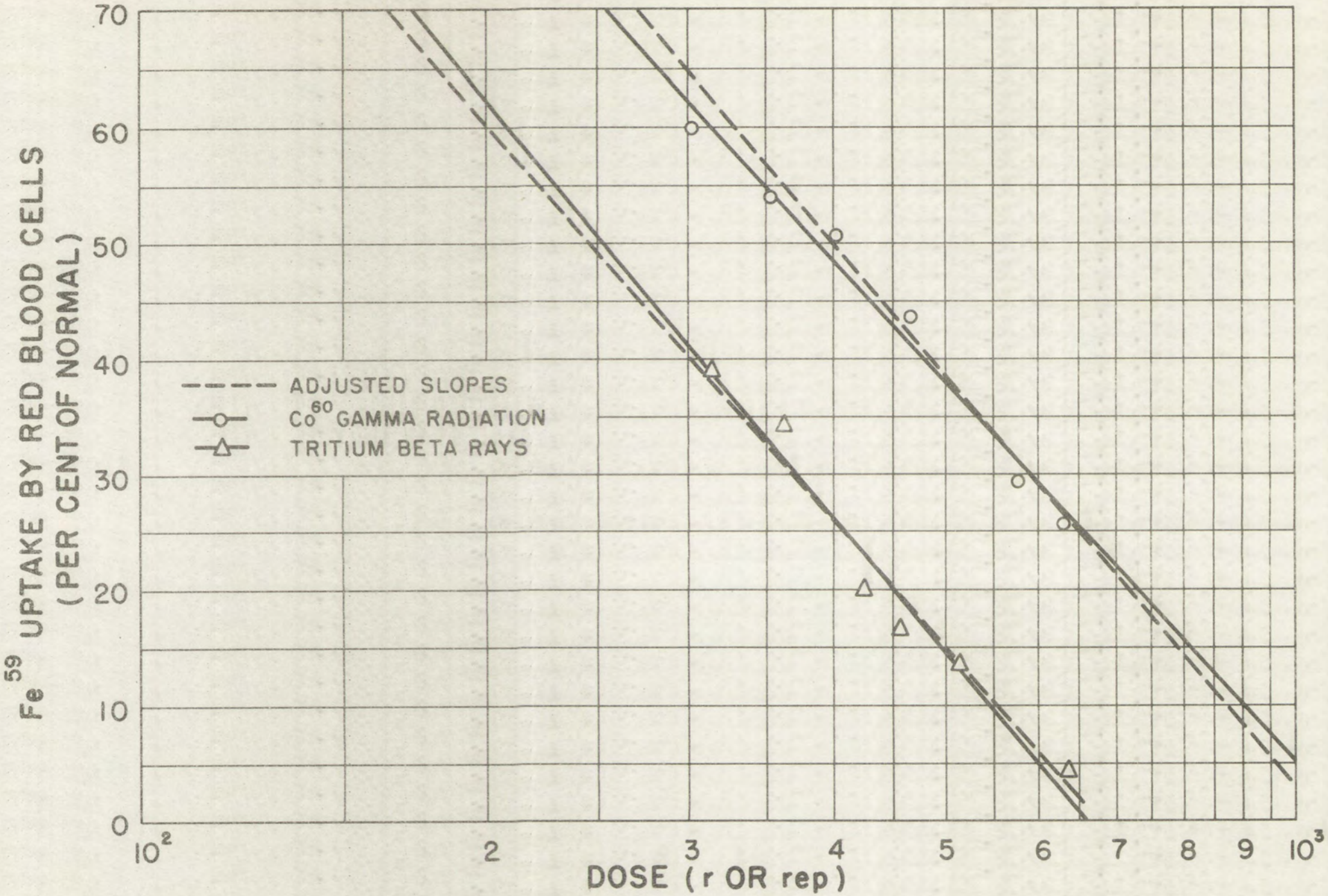

Fig. 6. Percentage of normal Fe^{59} uptake by red blood cells of rats exposed to Co^{60} gamma and tritium beta radiation.

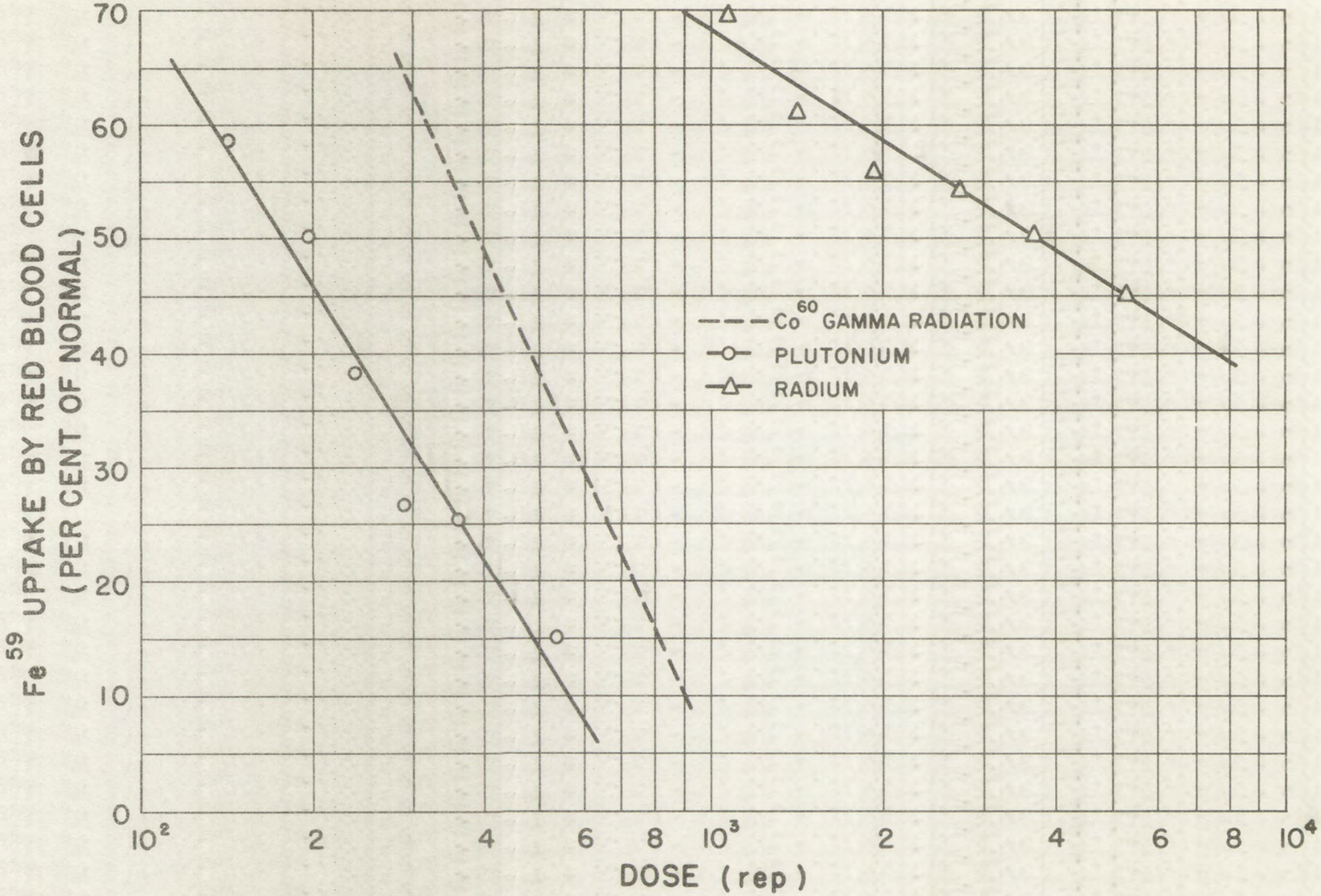

Fig. 7. Percentage of normal Fe^{59} uptake by red blood cells of rats injected with plutonium and radium.

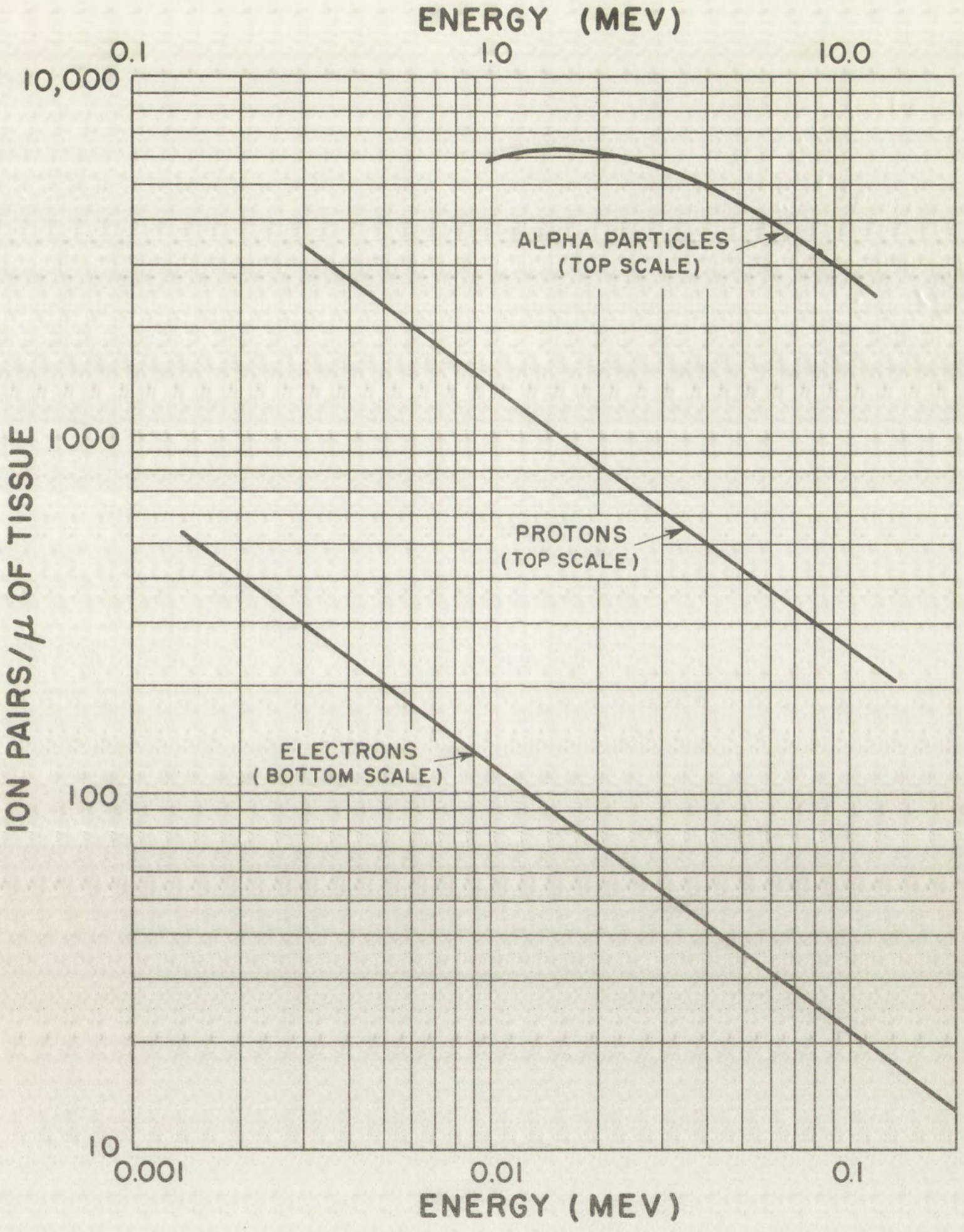

Fig. 8. Specific ionization of protons and alpha and beta particles as a function of energy (Plotted from data in Lea, 1947).

EV