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THE DESIGN OF AN EXPERIMENT TO STUDY CARCINOGENESIS AND HEMATOLOGICAL EFFECTS IN MICE IRRADIATED BY ENERGETIC HEAVY IONS

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ABSTRACT

The design of an experiment to study the incidence of cancer and hematological effects in mice irradiated by heavy ions is described. A beam of fully stripped C^{6+} ions of energy 250 MeV/amu was produced by the Bevatron. Mice were irradiated in groups of 12 by rotating them through a wide beam (11.4 cm FWHM) once per minute. At a beam intensity of 10^8 ions/pulse irradiations of 250 animals to doses of 200 rad were completed in a few hours -- an efficient use of accelerator beam time. The average LET of the radiation was 17 ± 2 keV/μm. Radial and longitudinal variations in dose were less than 10%. Estimates of tissue entrance dose from measurements with an ionization chamber and thermoluminescent dosimeters were in agreement to about 1%.

KEY WORDS

Dosimetry, Carcinogenesis, Heavy ions.

I. INTRODUCTION

The recent development of high-energy heavy ion beams at the Bevatron (1) has made feasible many hitherto impossible radiobiological experiments. One example would be studies of the biological effects resulting from the whole body irradiation of small animals by radiations of well-defined high linear energy transfer (LET).† Hitherto such studies have been made by irradiating animals with neutrons of a few MeV in energy (2). Such experiments have the disadvantage that the charged particles resulting from neutron interactions in tissue have a wide range in LET, making their interpretation difficult.

Upton and his colleagues (3,4) have reported the overall RBE for leukemogenesis produced by acute fast neutron exposures to be in the range 0.7 to 1.0. This is a surprisingly low value, when compared to RBE's used to determine other carcinogenic effects of neutron irradiation. It might be explained, if confirmed, by the speculation that perturbations in the microscopic dose distribution near the bone/bone-marrow interface result in relatively low absorbed dose in the bone marrow when the animal is irradiated by neutrons. Such an effect would not be expected in animals irradiated by heavy charged particles whose principal mechanism for energy disposition is due to ionizing-collision energy losses. The RBE for leukemia induction by high-energy charged ion beams is therefore of

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†To avoid uncertainties wherever the term linear energy transfer (LET) is used in this report, it will refer, unless otherwise stated to the "stopping power" for the particles in tissue, which is for our purposes approximated by water, and is usually given in units of keV/μm.

considerable interest.

By the autumn of 1972 an adequate beam intensity of carbon ions was available from the Bevatron (~ 10^8 C^{6+} ions per pulse) to permit the design of experiments involving irradiation of a few hundred animals in the dose range 0-200 rad.

Fully stripped carbon ions of energy 250 MeV/amu have a range of 12.8 cm in water (tissue) -- considerably greater than the length of an adult RF mouse (about 7 cm). In passing through a mouse they change in LET by about 35% -- from 14 keV/μm to 20 keV/μm. A small proportion of the heavy ions will fragment in passing through the animal, producing particles of smaller LET than the primary ions. Since the quantity of tissue traversed by the ions (~ 7 g cm^{-2}) is small compared to the interaction length of ions in tissue (~ 19 g cm^{-2}), (5) the variation in absorbed dose and variation in LET along the irradiated animals will be quite small. Calculations based upon the data of Steward et al (6,7) indicate a variation of less than 20% in absorbed dose. Subsequent measurements by Maccabee et al (8) have shown the change in absorbed dose and LET in animals as small as RF mice to be quite small. Consequently, an experiment was designed to study the incidence of both granulocytic leukemia and thymic lymphoma following irradiation by carbon ions.

This paper describes two aspects of our experiments -- firstly, the physical design of the irradiation of more than 200 RF mice to a heavy ion beam, and secondly, the dosimetry techniques utilized. The radiobiological data resulting from this experiment will be published in a separate paper.

II. HEAVY ION EXPOSURE DETAILS

A. Exposure Requirements

The major requirements for the animal irradiations were:

- Absorbed doses up to 200 rad.
- The radial and longitudinal variations in absorbed dose distribution in the animals should be less than 20%.
- The mean LET of the particle beam should be close to 20 keV/μm and should not change by more than 20% from the mean through the animal.
- The time spent in the irradiation cages, time spent in the beam, and the total time taken to irradiate all the animals should be as short as possible in order to minimize the trauma to the animals.

These requirements were met by using a carbon ion beam of energy of ~ 250 MeV/amu at an upper flux of 2.5×10^7 particles sec^{-1}. A large irradiation field was used to permit the simultaneous irradiation of several animals.

B. Beam Conditions

Fully stripped C^{6+} ions were extracted from the Bevatron at an energy of 253.2 MeV/amu and transported to the experiment. Energy losses in scintillators and beam windows degraded the beam energy to 252.2 MeV/amu at the experiment. Beam transport steering and focusing elements (M7 and Q5A,B in Fig. 1) were adjusted to produce a beam spot as wide as feasible in the horizontal direction. Figure 2 shows the spatial distribution of beam intensity determined from the density of x-ray film exposed at the location of the experiment. The beam intensity was not great

enough to allow defocusing as a means of creating a large (but uniform) irradiation field. Such a method would have undesirably wasted too much of the available beam. Neither was it practicable to produce a beam whose intensity was symmetrical about the beam axis (see Fig. 2). However, an effective axial beam-symmetry was achieved by the simple expedient of rotating the mice about the beam axis during irradiation. (See Section II-C.) This technique resulted in a radial beam intensity distribution that was approximately Gaussian in shape (see Fig. 3).

In the early experiments the beam intensity distribution was determined with either x-ray film or thermoluminescent dosimeters. In more recent exposures, beam set-up has been facilitated by means of a pair of multi-wire proportional chambers (9). These chambers provide a visual display of the integrated beam intensity distribution projected in the vertical and horizontal directions. Figure 4 shows a typical display. With these chambers, almost any desired beam size may be obtained by adjusting the quadrupole magnets (Q5A,B) of the beam transport system (Fig. 1).

C. Details of Animal Irradiation

The mice to be irradiated were placed in light-weight cylindrical cages (7 cm long x 2.53 cm diameter) made of Lucite. Twelve cages were loaded into a Lucite wheel, which was rotated one revolution per minute during irradiation. Nine mice were irradiated at a distance of 5 cm from the center of the irradiation wheel, while the remaining three were irradiated at a distance of 1.9 cm from the wheel center (see Fig. 5). Animals were irradiated with their bodies aligned parallel to the beam axis, facing upstream (see Figs. 6, 7). The incident carbon ion beam had an energy of 252 MeV/nucleon, but after passing through an ionization

chamber and the upstream cap of the mouse cage was degraded to an energy of 250 MeV/nucleon. The beam energy leaving the animals was approximately 159 MeV/nucleon (taking the average "thickness" of a mouse to be 7 g/cm^2). Corresponding mean values of linear energy transfer in tissue at the entrance to and exit from the animal are 14.2 keV/μm and approximately 18.9 keV/μm, respectively. It is adequate for the purposes of this experiment to take the mean LET as 16.6 ± 2 keV/μm.

The radial dose-distribution across the rotating wheel shown in Fig. 3 was measured with ^{7}LiF thermoluminescent dosimeters. Reasonable agreement was obtained between the radial dose distribution across the rotating animal cage measured directly by thermoluminescent dosimeters and that inferred from spatial beam distribution measured with x-ray film. The beam distribution is smooth and over the range of sizes used in our experiment, is approximately Gaussian in shape. How well the distribution is approximated by a Gaussian distribution may be seen from the example given in Fig. 8. In the case shown, a Gaussian distribution with standard deviation 4.85 cm (corresponding to a full width at half maximum of 11.4 cm) describes the data well.

If a Gaussian beam distribution across the experiment is assumed, the rate of absorbed dose deposition in tissue, D(r), at distance r from the beam axis is given by:

$$D(r) = 9.2 \times 10^{-6} \frac{fN(dE/dx)\ e^{-r^2/2\sigma^2}}{\sigma^2} \qquad (1)$$

where D is measured in rad/h

f is the pulse repetition frequency (pulses/s)

N	is the beam flux (particles/pulse)
(dE/dx)	is the mass stopping power of tissue in MeV $g^{-1}cm^2$
σ	is the standard deviation of the Gaussian distribution (cm).

Substituting values typical of our experiment into Eq. (1):

$f = 0.25$ pulses/s

$N = 10^8$ particles/pulse

$(dE/dx) = 140$ MeV g^{-1} cm^2

$\sigma = 4.85$ cm.

We obtain a maximum dose rate D(0) of 1.4×10^3 rad/h, corresponding to dose rates of 22 rad/min and 14 rad/min to mice in the inner and outer cages respectively. Exposures resulting in absorbed dose in the range 50-200 rad therefore took between 5-20 minutes beam time. Transfer of animals and setting up between irradiations took about five minutes. Since 12 animals are simultaneously irradiated, experiments that require the irradiation of 250 animals to doses of 200 rad may be completed in a few hours at ion beam fluxes of 10^8/pulse at the Bevatron. This is an efficient use of accelerator beam time.

III. DOSIMETRY

A. General

Thermoluminescent dosimeters were used throughout this experiment to study both the characteristics of the radiation field and the absorbed dose distribution within the experimental animals.

^{7}LiF chips (1/8 in. x 1/8 in. x 0.035 in., mass ~ 25 mg) produced by Harshaw

Chemical Company (TLD-700) were convenient for our purposes. New chips were used and before irradiation were annealed at a temperature of 400°C for one hour followed by two hours at 100°C in accordance with the manufacturer's recommended procedures. The chips were annealed at 100°C for 10 minutes before reading to eliminate any small contribution to measured thermoluminescent output from low temperature peaks in the glow curve which are susceptible to fairly rapid fading (10). The dosimeters were read using a Mark IV Series 1100 TLD reader produced by the Radiation Detection Company (11); nitrogen was passed through the reader at a rate of about 4 ft^3/h during measurement.

B. Dosimetry for Animal Irradiations

1. General. Various techniques of dosimetry were used throughout the animal irradiations for the following purposes:

(a) Preparatory inspection of the irradiation field: x-ray film, thermoluminescent dosimeters and wire chambers (Sections II-B and II-C)

(b) Absolute dose estimates: nitrogen ionization chamber and thermoluminescent dosimeters (Section III-B-3 and Appendix B)

(c) Batch consistency: Because each dose group of animals was necessarily irradiated in batches it was necessary to ensure that each batch was exposed to identical radiation intensity. An air ionization chamber was used for this purpose and its use is described in Section III-B-2 and Appendix C.

In addition to monitoring the irradiation from run to run with an ionization chamber, thermoluminescent dosimeters were placed on the upstream face of at least one animal cage in each irradiation batch. Thermoluminescent dosimeters were also used to determine the longitudinal distribution of absorbed dose in a mouse phantom (see Section III-B-5). From the batch dosimeters and the measured dose distribution the midline absorbed dose to the experimental animals could be determined.

2. In-Beam Dosimetry; Ionization Chamber. A parallel plate air ionization chamber was used to monitor the animal irradiations from batch to batch. The chamber used was designed by Howard (12) to present a minimum quantity of material (~ 0.047 g cm^{-2}) in the ion beam path. The chamber was constructed with a central collecting electrode of circular cross section (2 cm diameter) surrounded by several annular electrodes. Throughout the irradiations, charge was collected from the largest annulus (8 cm i.d.; 10 cm o.d.). Spacing between the collector electrodes was 1 cm (see Fig. 9).

Use of the ionization chamber also permitted an independent estimate of the absorbed dose to the irradiated animals. As shown in Appendix C, the dose at distance r from the beam axis $D(r)$ is given by:

$$D(r) = \frac{10^5}{2\pi\sigma^2}\left(\frac{W_t s_a}{\rho x}\right) \cdot Q(r_1 r_2) \frac{e^{-r^2/2\sigma^2}}{[e^{-r_1{}^2/2\sigma^2} - e^{-r_2{}^2/2\sigma^2}]} \qquad (2)$$

where $Q(r_1,r_2)$ is the charge collected by an annular chamber of internal radius r_1, outer radius r_2 operating in a radiation field that decreases in a Gaussian manner with distance from the beam axis, with standard

deviation σ.

W	is the energy required to create an ion pair (eV)
${}_tS_a$	is the ratio of particle stopping in tissue to that in water
ρ	is the density of air in the chamber (g/cm^3)
x	is the electrode separation (cm)

No definitive value of W (the energy required to create an ion pair) has yet been published for carbon ions in nitrogen, although plans are underway at Berkeley to measure this parameter [13]. Myers (14) quotes values of W in nitrogen of 34.6±0.03, 36.39±0.04 and 36.6±0.5 eV for γ-rays, α-particles and protons respectively. We assume a value of W=36 eV in this paper. From the data of Steward et al (6,7) we find ${}_tS_a = 1.14$. The chamber was designed with a collector electrode separation, x, of 1 cm. Substituting these values into Eq. (2) we obtain the dose at distance r from the beam axis at the experiment:

$$D(r) = 6.54 \times 10^5 \, F \, \frac{Q(r_1, r_2)}{\rho \, \sigma^2} \, \frac{e^{-r^2/2\sigma^2}}{[e^{-r_1^2/2\sigma^2} - e^{-r_2^2/2\sigma^2}]} \qquad (3)$$

Where F is a geometrical factor that accounts for the dilution of the beam because the animals were irradiated approximately 10 cm behind the ionization chamber. The factor F can be readily determined experimentally.

3. <u>In Beam Dosimetry; Thermoluminescent Dosimeters</u>. The determination of the sensitivity response of ^7LiF thermoluminescent dosimeters to ^{60}Co γ-rays is described in Appendix B.

The dosimeter response, τ, in arbitrary units of thermoluminescence (TLU) was measured as 1.20 ± 0.01 TLU/Roentgen for ^{60}Co γ-rays.

The energy absorption per g resulting from an exposure of 1 R in any material, f, provided there is no significant perturbation of the photon field, is:

$$f = 86.9 \frac{(\mu/\rho)m}{(\mu/\rho)\ air} \quad \text{ergs g}^{-1} \tag{4}$$

where the (μ/ρ)'s are the mass-energy absorption coefficients of the medium and air. The response of the dosimeter to ^{60}Co γ-rays per rad is then: τ/f_m where f_m is the appropriate value in ^{7}LiF.

Attix (15) has calculated a value f = 0.805 rad/R for ^{60}Co γ-rays in ^{7}LiF giving the response of our dosimeters, τ', as

$$\tau' = 1.49 \pm 0.01 \text{ TLU/rad} \tag{5}$$

The response of thermoluminescent dosimeters is known to be a function of the linear energy transfer (LET) of the incident radiation (10). The thermoluminescent response per rad absorbed decreases when the energy deposition is due to particles of specific energy loss less than about 50 MeV cm^2/g (16). The dosimeter response as a function of LET, is normally expressed as an efficiency, ε, relative to the response from ^{60}Co γ-rays.

Jähnert (16) has reported measurements of ε in ^{7}LiF protons and alpha particles of various energies. For protons of energy 13.3 MeV (21 keV/μm in LiF) he measured an efficiency relative to ^{60}Co of 0.86 ± 0.04. Jähnert has proposed two alternative theoretical models, both of which fit his experimental data well in the LET range 0.02 - 300 keV/μm (see Fig. 10). At a LET of 11.6 keV/μm in LiF, Jähnert predicts a value of ε of 0.90 ± 0.02. Tochilin et al (17) have reported measurements using normal

LiF thermoluminescent detectors which might be expected to respond in a similar manner to ^{7}LiF dosimeters. (The isotopic abundance of ^{7}LiF in natural lithium is 92.6%). At a LET of 11 keV/μm in LiF, Tochilin et al measured an efficiency of 0.88 ± 0.05. We will use a value of $\epsilon = 0.89$ in this paper and thus the dosimeter response to 1 rad deposited in ^{7}LiF by 250 MeV/amu carbon ions is: 1.33 TLU/rad in LiF. For 250 MeV/nucleon carbon ions:

$$S_{LiF} = 116.4 \text{ MeV cm}^2/\text{g}$$

$$S_{\substack{\text{tissue} \\ \text{(water)}}} = 142 \text{ MeV cm}^2/\text{g}$$

and it follows the dosimeter response per rad in tissue is then

$$1.33 \times \frac{116.4}{142} = 1.09 \text{ TLU/rad in tissue}^{*}$$

4. Intercomparison of In-Beam Dosimetry Techniques. Excellent agreement was obtained between estimates of entrance dose obtained from measurements with the ionization chamber and thermoluminescent dosimeters.

In our first experiment the density of nitrogen in the ionization chamber was determined to be 1.21×10^{-3} g cm^{-3} at the time of irradiation. Charge was collected on an annulus with r_1 and r_2 respectively 4 and 5 cm. From measurements of the beam profile at the experiment (Fig. 3) and at the ionization chamber (Fig. 11) the parameter F was determined as 0.924. The beam had a width, σ, of 4.85 cm. Substituting into Eq. (3) we obtain:

$$D(r) = 1.69 \times 10^{8} \; Q \; e^{-r^2/47.04} \text{ rads/coulomb}$$

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*To convert dosimeter response in TLU to rads in tissue (water) multiply by 0.916.

Where Q is the charge collected (in coulomb) on the annular electrodes (i.d. 8 cm and o.d. 10 cm).

In our experiment two series of animal irradiations were carried out. The first with $Q = 6 \times 10^{-7}$ coulomb, and the second with $Q = 1.2 \times 10^{-6}$ coulomb. Table I summarizes the estimates of entrances doses in tissue (water) to animals irradiated in 1.9 cm and 4.8 cm from the beam axis. These estimates of absorbed dose derived from the ionization chamber measurement are judged to be accurate ± 10%.

Use of the ionization chambers to monitor batch-to-batch exposures made it possible to ensure equal exposure to within ± 0.4%.

Table II gives a summary of the response of a dosimeter placed on the upstream face of the mouse cages for each irradiation. These values of entrance dose in tissue (water) are judged to be accurate to ± 5% and are in good agreement with the values estimated from ionization chamber measurements summarized in Table I. The absolute accuracy of the ionization chamber measurement largely depends upon the value of W assumed, while the accuracy of the thermoluminescent dosimeters depends upon the value of ε used.

We intend to independently measure values of W for a number of heavy ions over a wide range of energy at the Lawrence Berkeley Laboratory. We also intend to make measurements of ε for a variety of ions over a wide range of LET in ^{7}LiF.

5. Longitudinal Absorbed Dose Distribution in Experimental Animals. A cylindrical Lucite (methyl-methacrylate resin, $\rho = 1.19$ g cm^{-3}) phantom was fabricated to study the longitudinal absorbed dose distribution in the irradiated mice. Figure 12 shows the construction

of this phantom which was 1.09 in. diameter and 6 in. long. Dosimeters were placed by means of radial holes along the longitudinal axis of the cylinder at suitable intervals [generally 0.5 in. but every 0.25 in. in in the region of the Bragg peak (see Fig. 8)] and the radial hole was plugged with Lucite. This phantom was not only greater than the length of a mouse (approximately 6 cm Lucite equivalent), but also significantly longer than the range of 250 MeV/nucleon C^{6+} ions (approximately 10.8 cm in Lucite) so that a rough measure of beam energy could be obtained from the phantom measurements.

Figure 13 shows the longitudinal variation of dosimeter response through the phantom. It should be noted that this does not correspond exactly to the absorbed dose distribution because the dosimeter efficiency, which is a function of particle LET, changes along the length of the phantom (see Section II-C). At the Bragg peak this correction would be very large but this is of no consequence in our experiment because the Bragg peak was not developed in the animals (see Fig. 13). The dosimeter response is seen to be essentially constant to a depth of 6 cm in the phantom. Since the dosimeter efficiency does not change by more than 10% in the range of LET through the animal, we are probably justified in assuming the absorbed dose distribution along the animal to be constant to better than 10%.

A calculated depth-dose curve for 250 MeV/nucleon C^{6+} ions incident on Lucite is also shown (6,18) and is seen to be in fair agreement with the experimental data. The influence of secondary particles resulting from primary particle interactions is seen in the broadened Bragg peak and the finite dosimeter response beyond the ionization range of the incident carbon ions.

IV. SUMMARY

The experimental arrangement described in this paper is very efficient for the irradiation of large numbers of small mammals to the Bevatron heavy-ion beam. At a beam intensity of ~ 10^8 carbon ions/pulse, irradiations of 200 rad take less than 20 minutes. Irradiations of several hundred animals may be completed in less than eight hours. The radial and longitudinal variations in absorbed dose are less than 20% from the midpoint dose.

^{7}LiF thermoluminescent dosimeters are seen to be capable of good absolute accuracy in absorbed dose measurements and are extremely convenient for studying the dose distribution in irradiated animals.

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TABLE I

Estimates of entrance doses to animals from ionization chamber data.

Irradiation	Charge collected by ion chamber (μC)	Entrance dose (rad)	
		Inner mice	Outer mice
Run 1	0.60	94	62
Run 2	1.20	188	124

TABLE II

Summary of the response of a dosimeter placed on the upstream face of the mouse cages for each irradiation.

Irradiation	Ion chamber charge (μC)	Mean dosimeter response (TLU)		Entrance dose in tissue (rad)	
		Inner mice	Outer mice	Inner mice	Outer mice
Group 1	0.600	102±1	66.8±0.6	93.6±0.9	61.2±0.5
Group 2	1.200	203±4	135 ± 2	186 ± 4	124 ± 2

APPENDIX A
CALIBRATION OF ^{60}Co SOURCE OF γ-RAY IRRADIATION FACILITY

Calibration of our thermoluminescent dosimeters was carried out at the ^{60}Co irradiation facility of the Biomedical Division (19). This source had a measured activity of 1359 (± 68) Ci on 12 April 1972.

For our measurements the source strength was redetermined with a cavity ionization chamber (Victoreen Condenser R-meter Model 570) (20). This instrument had just been calibrated to an absolute accuracy of ± 5% by the National Bureau of Standards, Washington. Subsequent measurements with the instrument using a standard ^{60}Co source suggest that the instrument is, in fact, accurate to ± 1.5%.

Table A-1 summarizes measurements of exposure at several distances from the source. The source strength, Q, may be calculated from a measurement of exposure using the formula:

$$Q = \frac{60r^2E}{\Gamma t}$$

where r = distance from source in meters

E = measured exposure (r)

t = exposure time (min)

Γ = specific γ-ray constant (1.30 R $m^2 h^{-1}$ Ci^{-1} for ^{60}Co)

The individual measurements agree within 5% of the mean value for source strength of 1226 Ci. The accuracy of the mean is calculated to be ± 3.2% and the best value of the absolute source strength on 27 Oct. 1972 was:

$$1226 \pm 39 \text{ Ci}^{*}$$

The corresponding exposure rate at 1 meter from the source is 26.6R min^{-1}.

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*(This value is in good agreement with the value 1265 ± 63 Ci obtained by correcting the value of 1359 Ci measured on 12 April for radioactive decay.)

TABLE A-1

Absolute calibration of ^{60}Co source (27 October 1972).

Distance from source (cm)	Exposure time (min)	Measured exposure (Roentgen)[a]	Calculated source strength (Ci)
52	0.7	68.7	1225
100	2.8	70.7	1166
350	5.6	15.7	1288
		Mean	1226 Ci

[a]Corrected to standard temperature and pressure.

APPENDIX B

CALIBRATION OF THERMOLUMINESCENT DOSIMETERS BY γ-RAYS

The ^{7}LiF dosimeters were carefully calibrated with γ-rays in the response range expected due to carbon-ion irradiation. Table B-1 summarizes details of a typical series of calibration exposures.

The dosimeter response is a linear function of exposure in the response range of our experiment. This may be seen from Fig. 14 which shows the dosimeter readings plotted as a function of exposure; the response can be seen to be linear for exposures up to at least 500 R. (Calibrations subsequent to the one shown here have indicated linearity up to exposures close to 1000 R beyond which the response increases faster than linearity with exposure. The dosimeter readings corresponding to an exposure of 3000 R in Fig. 14 clearly demonstrates this supralinearity.)

A least squares analysis of the data of Table B-1 (but excluding the point at 3000 R) gives as the best value for dosimeter response, τ, as:

$$\tau = 1.20 \pm 0.01 \text{ TLU}^{*}/\text{Roentgen}$$

Calibrations were repeated over a period of several months and no significant change in dosimeter sensitivity was noted (after correction for changes in detector gain based on the reader light source calibration).

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*TLU = arbitrary thermoluminescent units.

TABLE B-1

Typical calibration exposures.

Distance from source (cm)	Exposure time (min)	Exposure (Roentgen)	Dosimeter reading (Relative units)
100	2.0	50.3	62.1
100	4.0	100.5	121
100	6.0	150.8	176
100	8.0	201.4	245
100	12.0	301.6	353
100	20.0	502.6	608
50	29.8	3000	4752
Control	--	0	0

TABLE B-2

^{7}LiF thermoluminescent dosimeter calibrations.

Date	Measured sensitivity TLU/ Roentgen	Measured light source reading	Sensitivity normalized to light source reading of 7.92
27 Oct 72	1.20 ± 0.01	7.92	1.20 ± 0.01
26 Feb 73	1.74 ± 0.03	11.0	1.25 ± 0.02
26 Apr 73	1.54 ± 0.01	10.0	1.22 ± 0.01
	1.56 ± 0.02	10.0	1.23 ± 0.01

APPENDIX C
ION CHAMBER OPERATION

I. General

Consider an air-filled parallel plate ionization chamber placed normal to a heavy ion beam. The total charge collected, Q, following the passage of N particles is:

$$Q = \frac{10^6 N \rho \times e(dE/dx)_{air}}{W} \text{ coulombs} \tag{7}$$

where $(dE/dx)_{air}$ is the appropriate stopping power of air (MeV $g^{-1}cm^2$)

ρ is the density of air in the chamber (g cm^{-3})

x is the plate separation (cm)

E is the electronic charge (coulomb)

W is the energy required to produce an ion pair

If the particle distribution is uniform the particle fluence Φ is given by:

$$\Phi = \frac{N}{A} \tag{8}$$

where A is the surface area of the ionization chamber plates.

The absorbed dose in tissue, D, resulting from irradiation by a fluence Φ of ions is:

$$D = 1.602 \times 10^{-8} \Phi (dE/dx)_{tissue} \tag{9}$$

where $(dE/dx)_{tissue}$ is the appropriate stopping power of tissue.

Combining Eqs. (7, 8) and (9) and substituting 1.602×10^{-19} coulombs for the electronic charge we obtain:

$$D = 10^5 \left(\frac{WQ}{m}\right) t S_a \tag{10}$$

Where D is in rad (in tissue)

W is in eV

Q is in coulomb

m is the mass of gas irradiated in the chamber (in g)

$_tS_a$ is ratio of stopping powers in tissue to air for the ions.

II. Annular Chamber Theory

Beam profile measurements on the rotating animal cages indicated a Gaussian distribution particle fluence $\Phi(r)$ of the form:

$$\Phi(r) = \Phi_0 e^{-r^2/2\sigma^2} \tag{11}$$

The total number of particles, N, in the beam is then:

$$\begin{aligned} N &= 2\pi \int_0^\infty \Phi_0 r \; e^{-r^2/2\sigma^2} \, dr \\ &= 2\pi \sigma^2 \Phi_0 \end{aligned} \tag{12}$$

The number of particles crossing an annulus between radii r_1 and r_2, $N(r_1,r_2)$ is given by:

$$\begin{aligned} N(r_1,r_2) &= 2\pi \Phi_0 \int_{r_1}^{r_2} r \, e^{-r^2/2\sigma^2} \, dr \\ &= 2\pi \sigma^2 \Phi_0 \left(e^{-r_1^2/2\sigma^2} - e^{-r_2^2/2\sigma^2} \right) \\ &= N\left(e^{-r_1^2/2\sigma^2} - e^{-r_2^2/2\sigma^2} \right) \end{aligned}$$

From Eq. (7) the charge collected following the passage of $N(r_1,r_2)$

particles, $Q(r_1,r_2)$, is given by:

$$Q(r_1,r_2) = \frac{10^6 \rho \times e(dE/dx)_{air}}{W} N(r_1,r_2) \qquad (14)$$

Combining Eqs. (12, 13) and (14) we obtain the maximum fluence Φ_0:

$$\Phi_0 = \frac{10^{-6} W Q(r_1,r_2)}{2\pi \sigma^2 \times e \rho (dE/dx)_{air} [e^{-r_1^2/2\sigma^2} - e^{-r_2^2/2\sigma^2}]} \qquad (15)$$

The corresponding maximum dose may be obtained by using Eq. (9). Finally the absorbed dose in tissue at distance r from the beam axis $D(r)$ is given by:

$$D(r) = \frac{10^5}{2\pi\sigma^2} \frac{W}{\rho x} \frac{t S_a}{} Q(r_1,r_2) \frac{e^{-r^2/2\sigma^2}}{[e^{-r_1^2/2\sigma^2} - e^{-r_2^2/2\sigma^2}]} \qquad (16)$$

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FIGURE CAPTIONS

Fig. 1. Schematic diagram of the beam transport system for the experiment. The heavy-ion beam is incident from the right. Animals were irradiated on the optical bench.

Fig. 2. Spatial distribution of ion beam experiment as measured with x-ray film.

Fig. 3. Dose distribution across rotating mouse cages (measured with thermoluminescent dosimeters -- a typical error is shown).

Fig. 4. Wire chamber displays -- horizontal (a) and vertical (b) beam profiles.

Fig. 5. Schematic diagram of irradiation wheel.

Fig. 6. Photograph of rotator in position on optical bench.

Fig. 7. Photograph of mice being irradiated in ion beam.

Fig. 8. Comparison of beam profiles measured with x-ray film, TLD, and calculated Gaussian distribution.

Fig. 9. Photograph of the annular ionization chamber used for dosimetry.

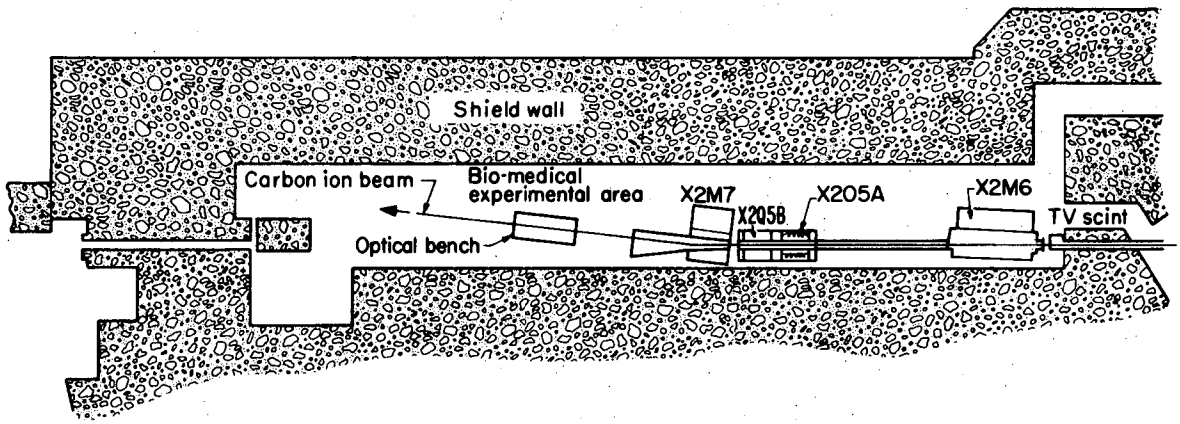
Fig. 10. Response of ^{7}LiF as a function of linear energy transfer.

Fig. 11. Horizontal beam profile at the ionization chamber.

Fig. 12. Diagram of lucite phantom.

Fig. 13. Thermoluminescent response and absorbed dose distribution in lucite mouse phantom. The calculated curve is of the absorbed dose distribution in lucite for a broad parallel beam of carbon ions with incident energy 251 ± 1.5 MeV/amu.

Fig. 14. The response of ^{7}LiF thermoluminescent dosimeters to ^{60}Co γ-rays.



XBL738-3764

Fig. 1

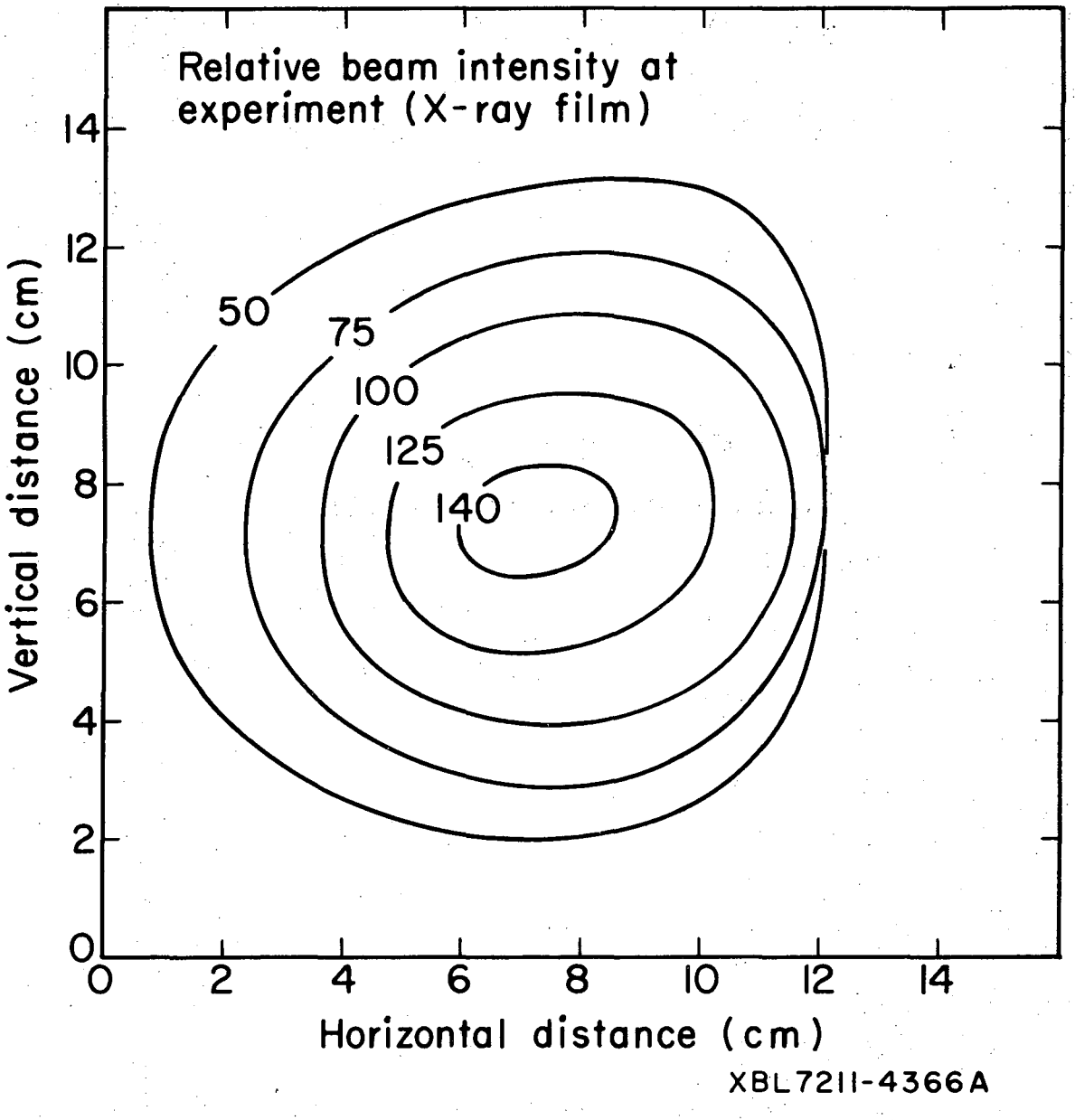

Relative beam intensity at
experiment (X-ray film)
50
75
100
125
140
Vertical distance (cm)
Horizontal distance (cm)
0
2
4
6
8
10
12
14
XBL7211-4366A

Fig. 2

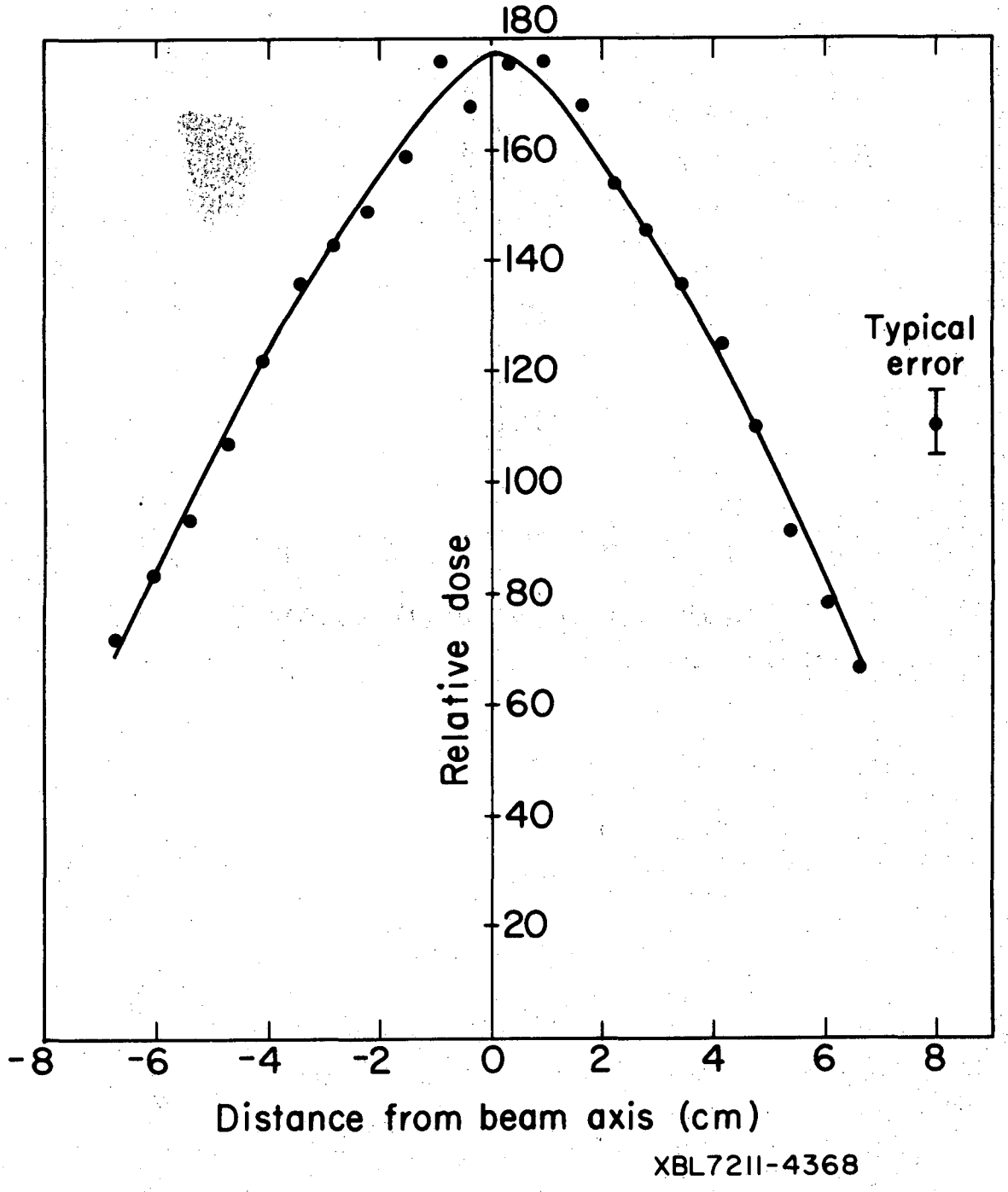
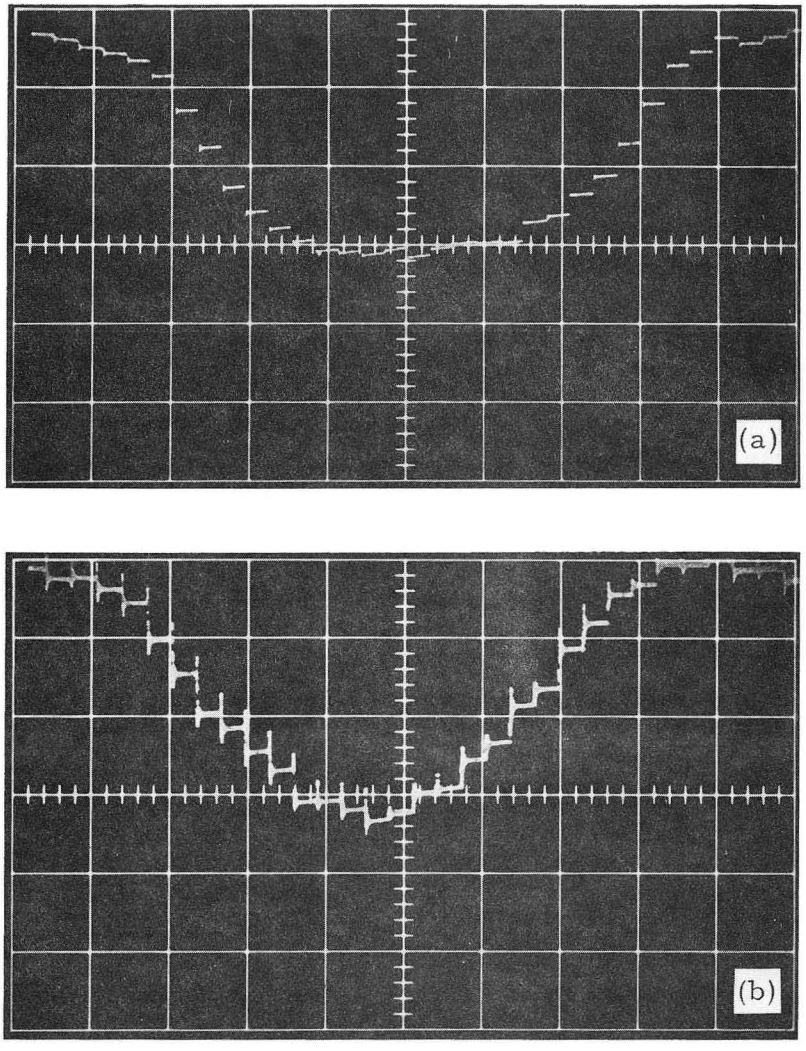
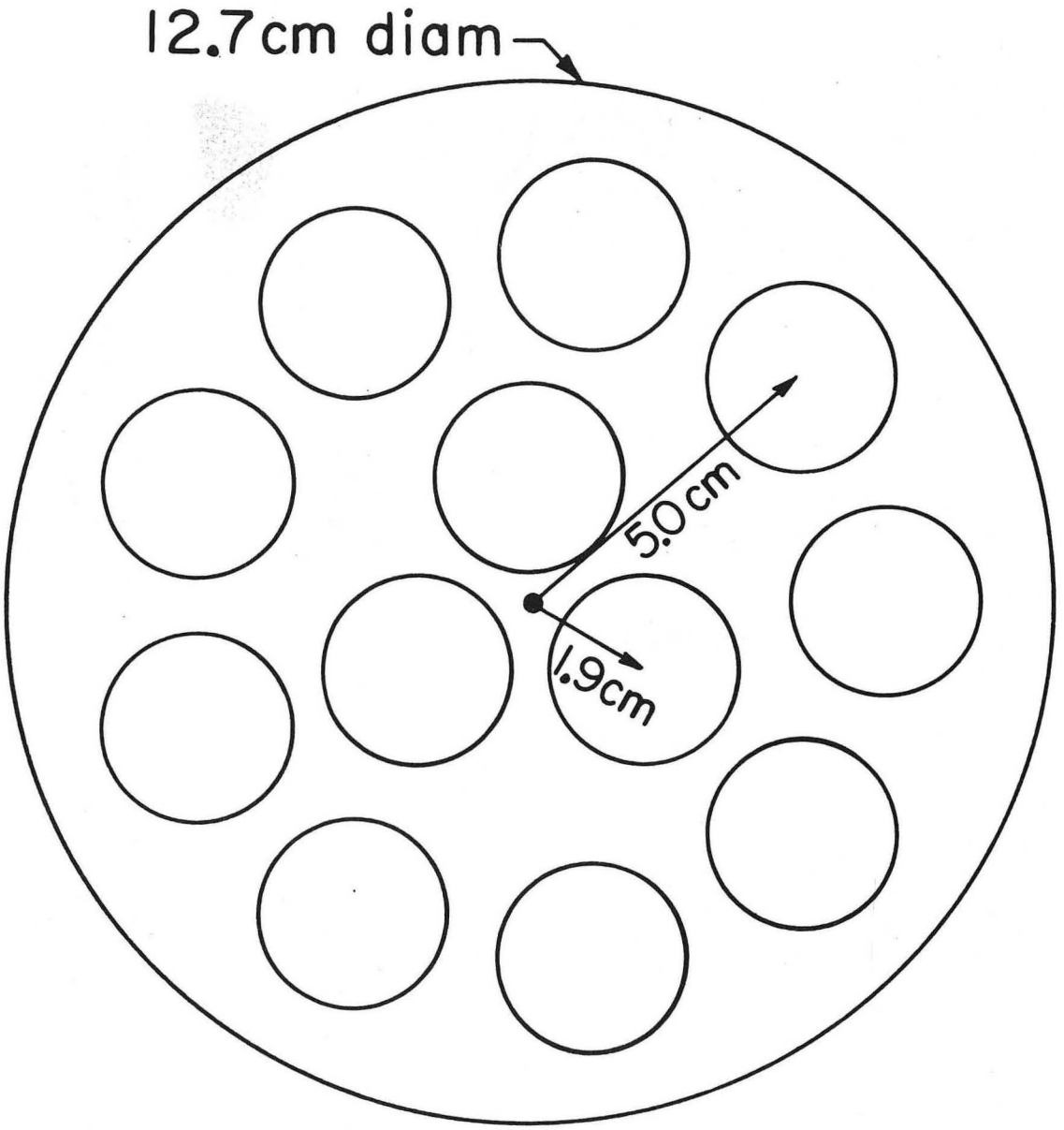

180
160
140
120
100
80
60
40
20
Relative dose
Typical error
-8
-6
-4
-2
0
2
4
6
8
Distance from beam axis (cm)
XBL7211-4368

Fig. 3



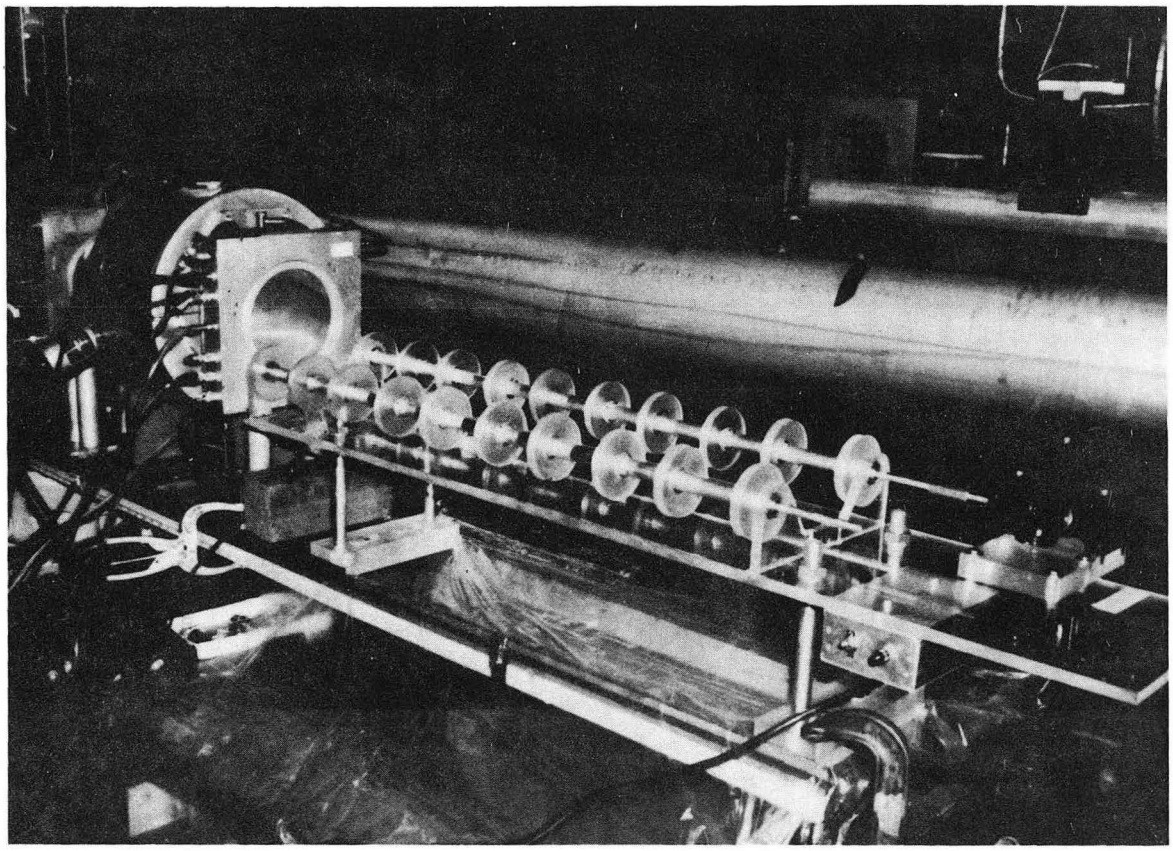
XBB 748-5521

Fig. 4



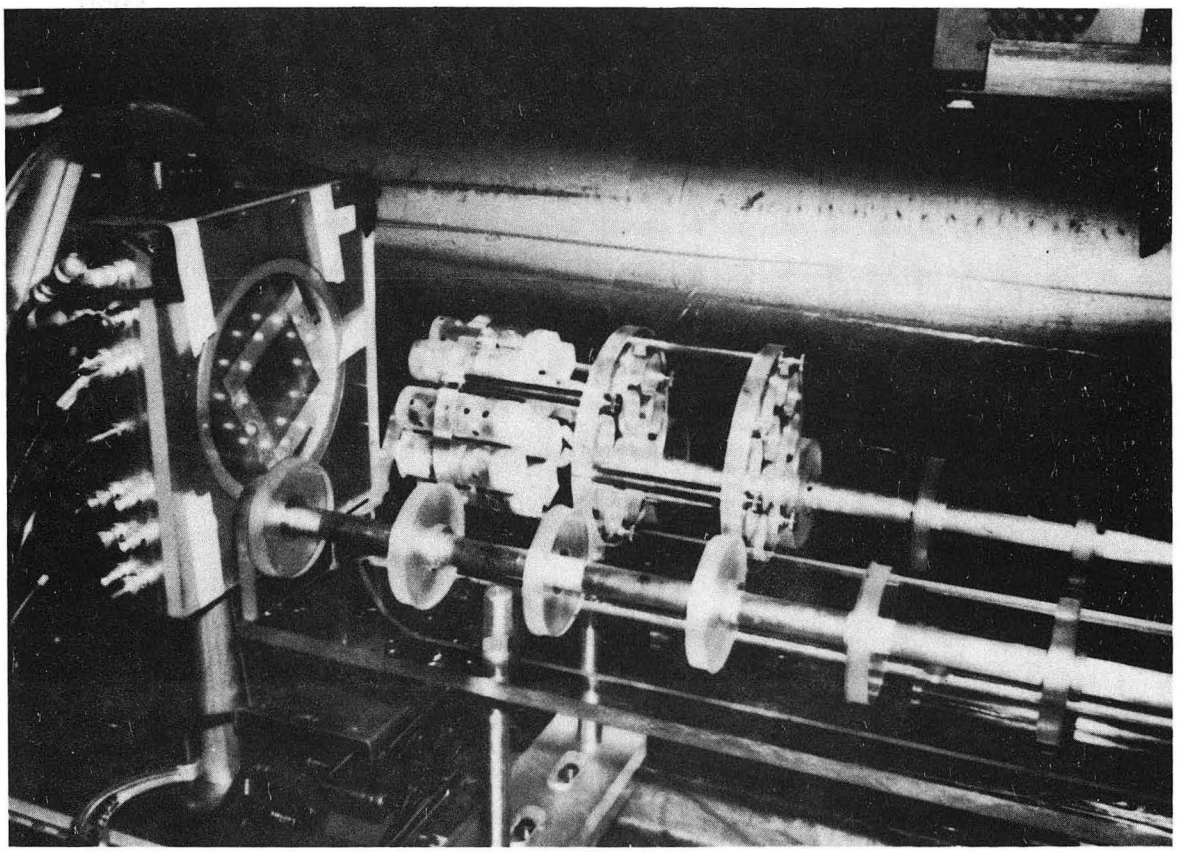
XBL738-3661

Fig. 5



XBB 744-2917

Fig. 6



XBB 744-2918

Fig. 7

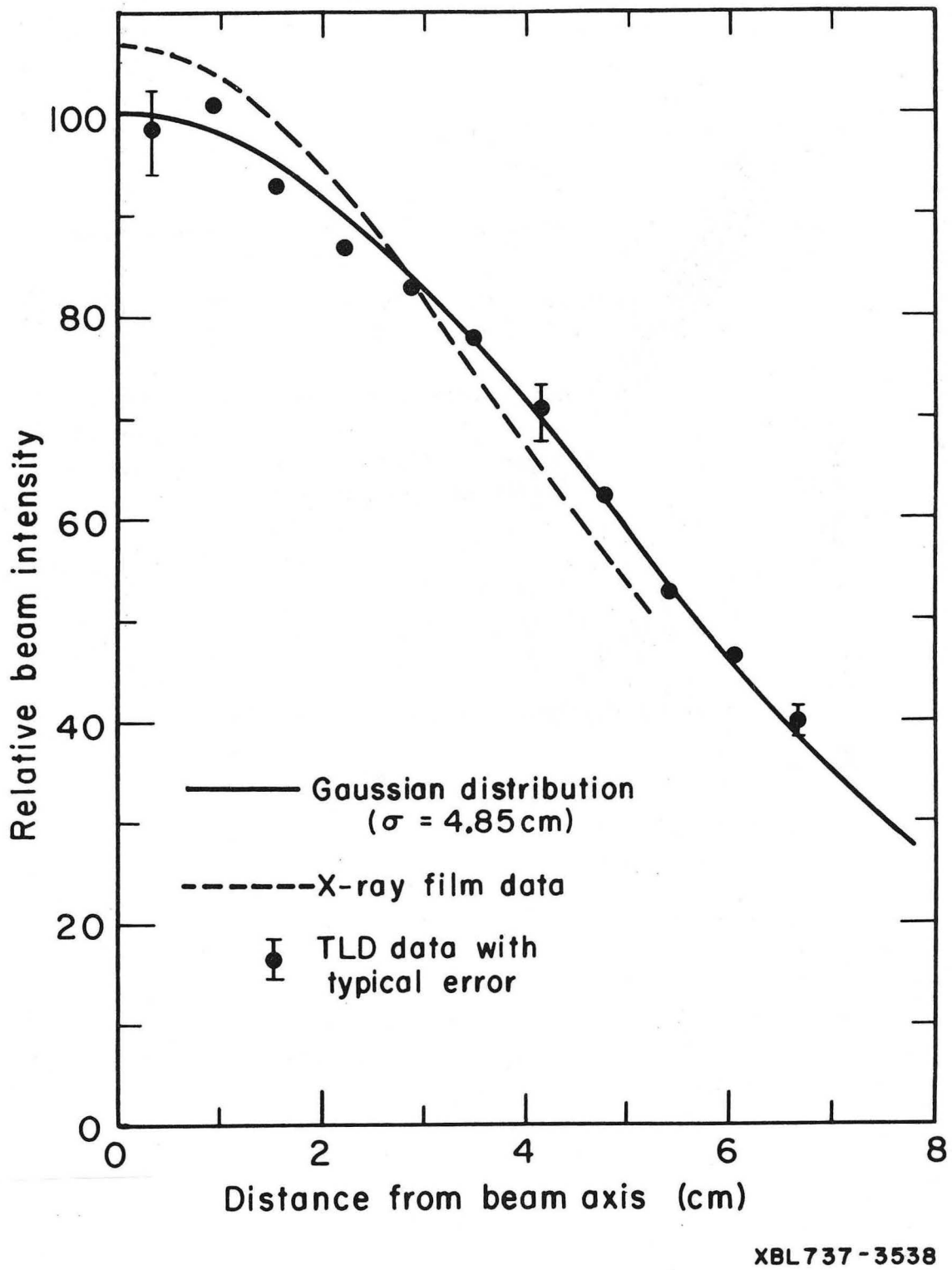

100
80
60
40
20
0
0
2
4
6
8
Relative beam intensity
Distance from beam axis (cm)
Gaussian distribution
(σ = 4.85cm)
X-ray film data
TLD data with
typical error
XBL737-3538

Fig. 8

TABLE 2 - ALLOCATION OF STATE GOVERNMENT PORTION[1] OF CETA TITLE II FUNDS FOR PUBLIC SERVICE EMPLOYMENT - FY 1974

U.S. DEPARTMENT OF LABOR
MANPOWER ADMINISTRATION

UNITED STATES BY STATE

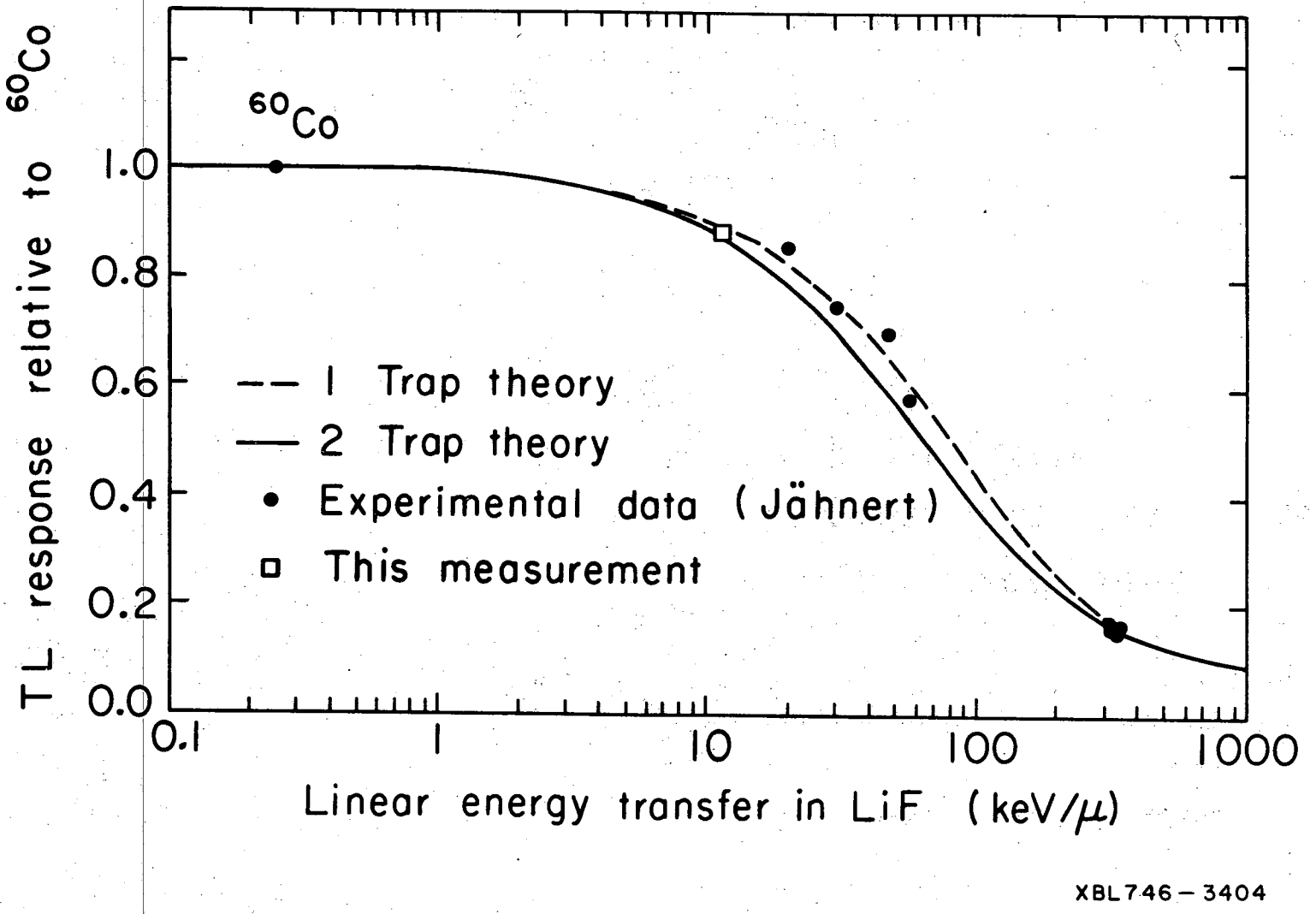
LAWRENCE BERKELEY LABORATORY
UNIVERSITY OF CALIFORNIA

STATE	TOTAL ALLOCATION (DOLLARS)	STATE	TOTAL ALLOCATION (DOLLARS)
Alabama	479,465	New Hampshire	311,234
Alaska	1,842,989	New Jersey	1,019,144
Arizona	140,500	New Mexico	1,330,479
Arkansas	852,774	New York	5,576,351
California	5,212,978	North Carolina	0
Colorado	205,078	North Dakota	1,368,400
Connecticut	769,000	Ohio	2,741,000
Delaware	1,266,312	Oklahoma	947,054
District Of Columbia	2,258,500	Oregon	2,544,293
Florida	2,914,400	Pennsylvania	2,049,722
Georgia	273,353	Rhode Island	2,038,887
Hawaii	738,350	South Carolina	1,200,383
Idaho	1,996,800	South Dakota	0
Illinois	1,379,359	Tennessee	1,334,332
Indiana	1,221,564	Texas	914,039
Iowa	494,300	Utah	1,854,100
Kansas	0	Vermont	1,552,279
Kentucky	2,236,856	Virginia	1,779,814
Louisiana	3,915,830	Washington	5,321,565
Maine	2,771,077	West Virginia	3,261,649
Maryland	909,364	Wisconsin	4,496,520
Massachusetts	10,849,185	Wyoming	0
Michigan	4,845,776		
Minnesota	4,793,023		
Mississippi	702,000	Puerto Rico	10,677,698
Missouri	314,600	A.Samoa-Guam-Trust Territories	345,300
Montana	1,860,200	Virgin Islands	246,700
Nebraska	0	Indian Reservations	1,855,000
Nevada	473,759		

1. FUNDS TO BE ADMINISTERED BY STATE GOVERNMENT FOR BALANCE OF STATE AREA

MEDIAN ALLOCATION BY STATE $ 1,368,000

MEAN ALLOCATION BY STATE $ 1,963,000



XBL746-3404

Fig. 10

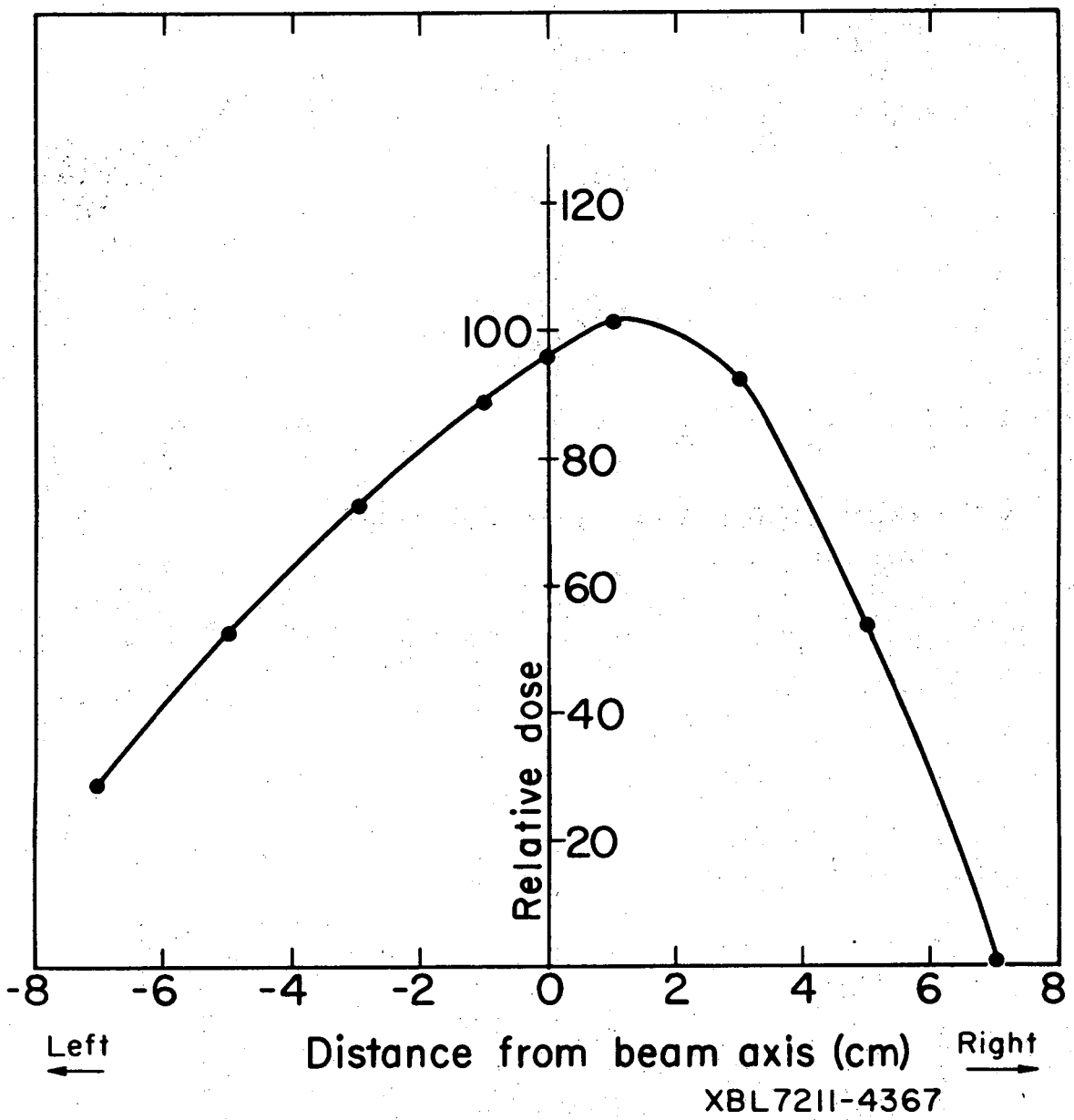
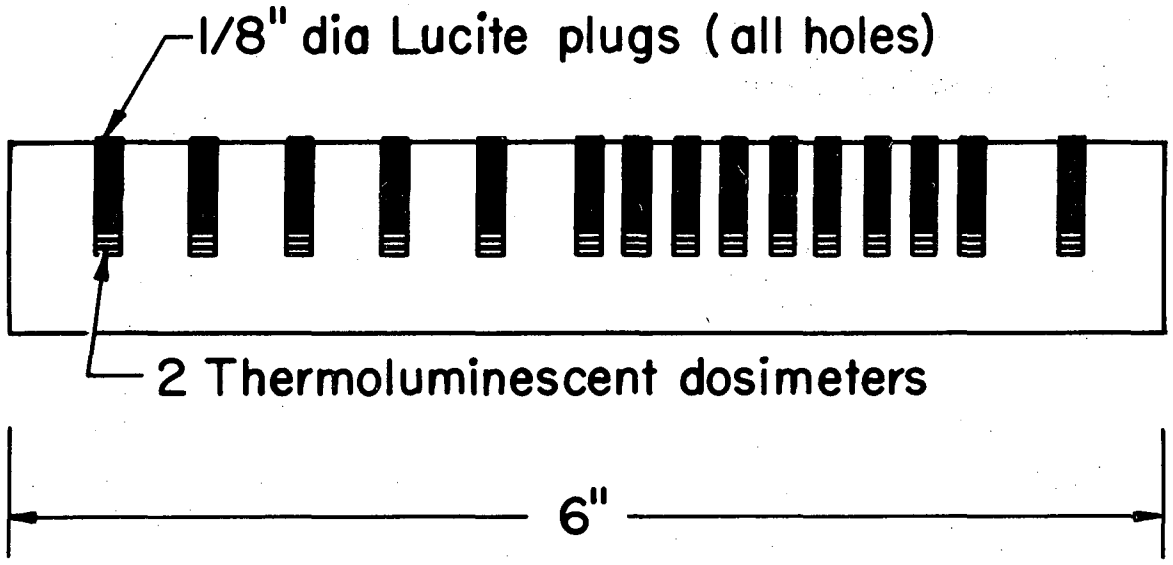

120
100
80
60
40
20
Relative dose
-8
-6
-4
-2
0
2
4
6
8
Left
Distance from beam axis (cm)
Right
XBL7211-4367

Fig. 11



XBL738-3663

Fig. 12

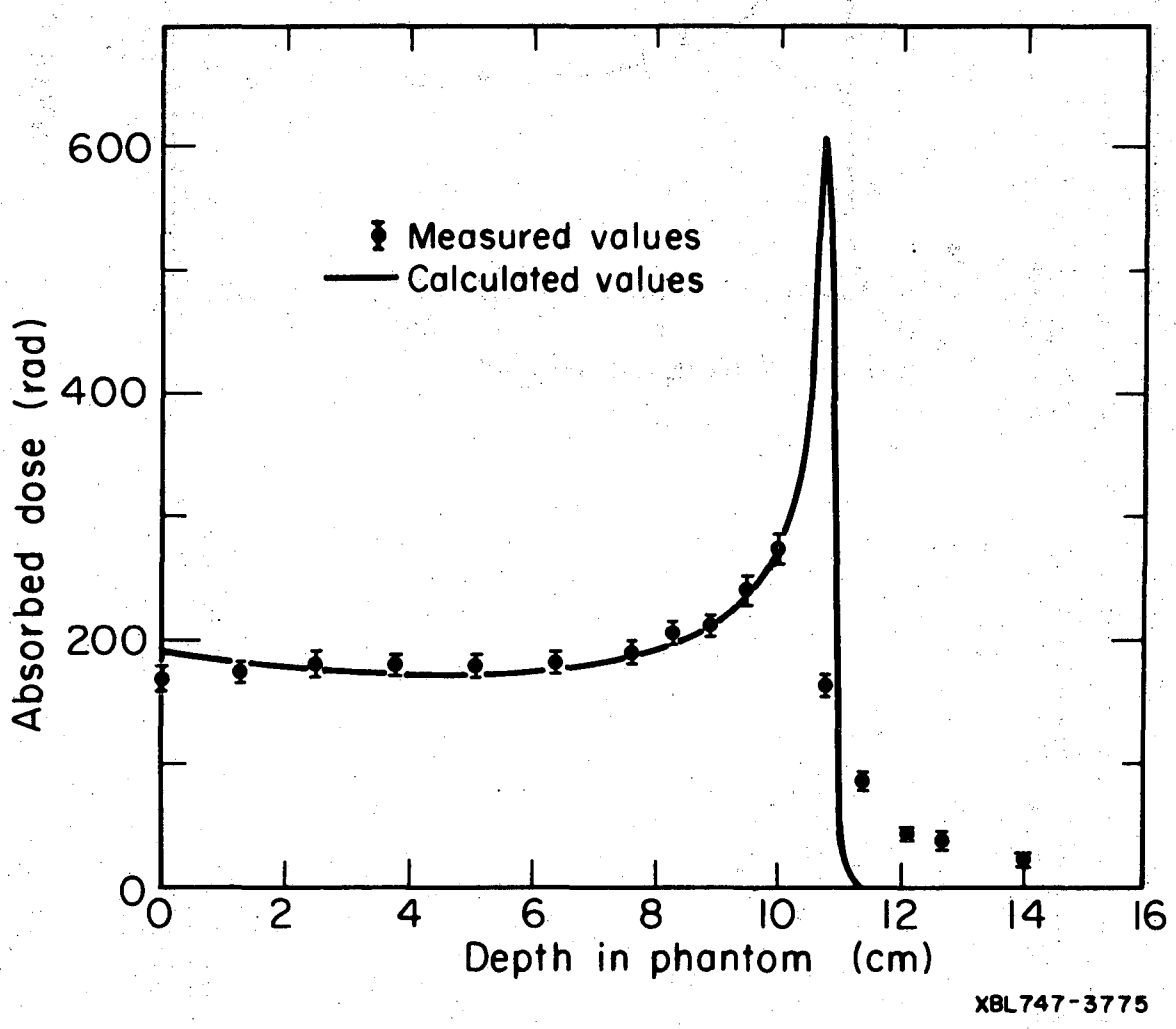

600
400
200
0
Absorbed dose (rad)
Measured values
Calculated values
0
2
4
6
8
10
12
14
16
Depth in phantom (cm)
XBL747-3775

Fig. 13

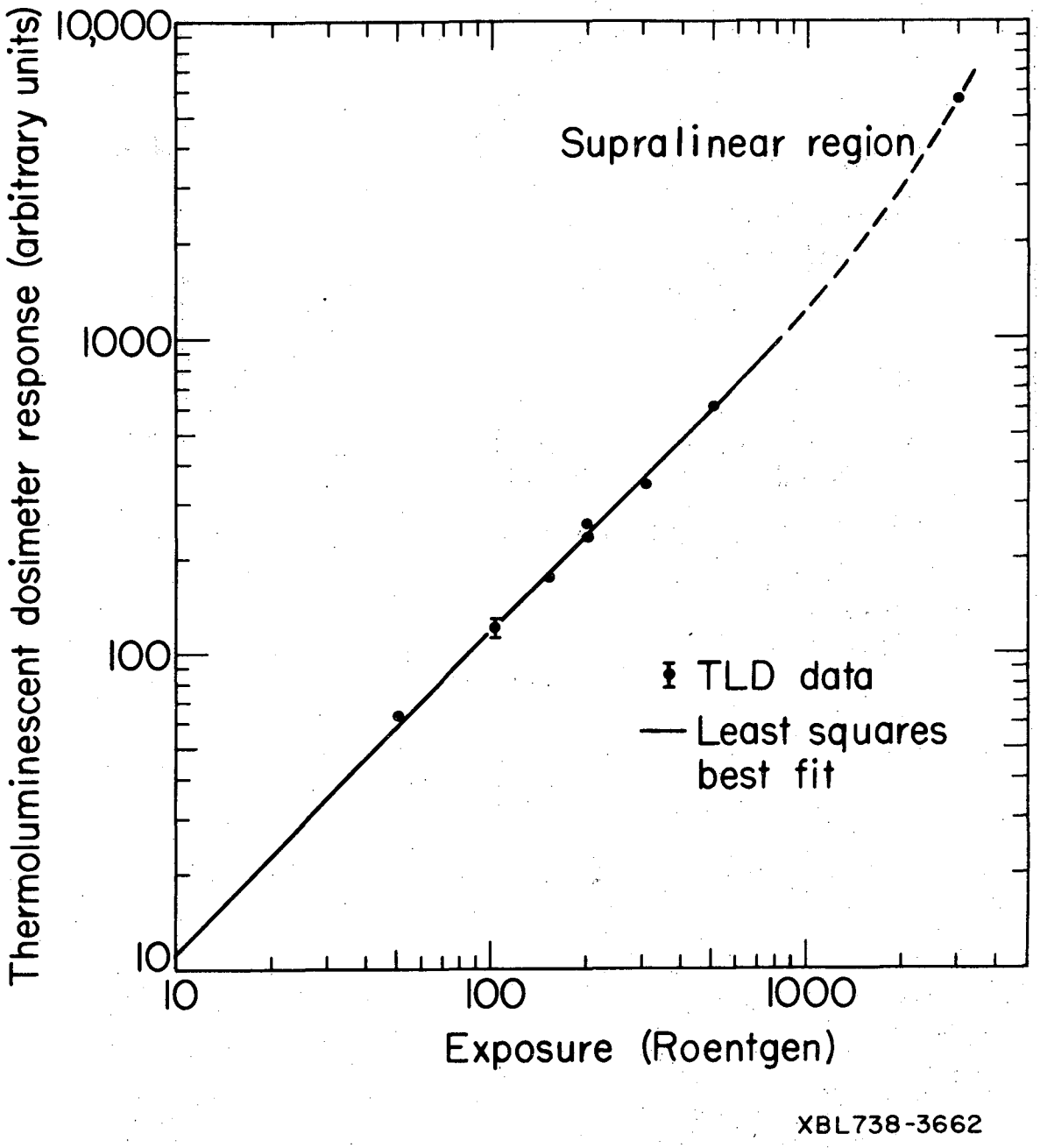

Thermoluminescent dosimeter response (arbitrary units)
10,000
1000
100
10
10
100
1000
Exposure (Roentgen)
Supralinear region
TLD data
Least squares best fit
XBL738-3662

Fig. 14

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