BNL-29783
CONF-810673--3

FOURTH SYMPOSIUM ON NEUTRON DOSIMETRY
GSF, Munich-Neuherberg, 1-5 June 1981

MASTER

NEUTRON DOSIMETRY IN BORON NEUTRON-CAPTURE THERAPY

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ABSTRACT

The recent development of various borated compounds and the utilization of one of these ($Na_2B_{12}H_{11}SH$) to treat brain tumors in clinical studies in Japan has renewed interest in neutron capture therapy. In these procedures thermal neutrons interact with ^{10}B in boron containing cells through $^{10}B(n,\alpha)^7Li$ reaction producing charged particles with a maximum range of approx. 10 μm in tissue. Borated analogs of chlorpromazine, porphyrin, thiouracil and deoxyuridine promise improved tumor uptake and blood clearance. The therapy beam from the Medical Research Reactor in Brcokhaven contains neutrons from a modified and filtered fission spectrum and dosimetric consequences of the use of above mentioned compounds in conjunction with thermal and epithermal flures are discussed in the paper.

One of the important problems of radiation dosimetry in capture therapy is determination of the flux profile and, hence, the dose profile in the brain. This has been achieved by constructing a brain phantom made of TE plastic. The lyoluminescence technic provides a convenient way of monitoring the neutron flux distributions; the detectors for this purpose utilize ^6Li and ^{10}B compounds. Such compounds have been synthesized specially for the purpose of dosimetry of thermal and epithermal beams. In addition, standard lyoluminescent phosphors, like glutamine, could be used to determine the collisional component of the dose as well as the contribution of $^{14}N(n,p)^{14}C$ reaction. Measurements of thermal flux were compared with calculations and with measurements done with activation foils.

Some of the borated compounds used in the therapy are themselves lyoluminescent and can be used as dosimeters. The use of boron containing compounds would permit to avoid the need for correction due to the different slow neutron cross sections of boron and lithium, the latter being the 'active' part of lyoluminescent phosphor, lithium pyruvate.

This work was supported by the National Cancer Institute Grant no. RO1-CA 22749 and the U.S. Department of Energy under contract no. DE-AC02-76CH00016. Lyoluminescence studies were supported by a grant from the Commission of European Communities.

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1. INTRODUCTION

Utilization of the $^{10}B(n,\alpha)^{7}Li$ reaction for neutron capture therapy (NCT) provides potentially optimal conditions for radiotherapy. Physiological localization of boron in tumor permits selective irradiation of cancer cells within the radiation field, as the range of He and Li ions is about single cell diameter, approx. 10μm in the tissue. The high relative biological effect of the He and Li ions increases the radiosensitivity of hypoxic cells which may be present in tumor and allows a possible increase in the effective dose delivered to tumor by the incident neutron beam.

1.1. Past results

Previous clinical trials of neutron capture therapy were carried out at Brookhaven National Laboratory, Upton N.Y., and at the Massachusets General Hospital, Boston, Mass. Water soluble boron compounds were used, which did not localize in tumor. The blood-brain barrier was used to exclude these compounds from normal brain during the treatment of brain tumors. Clinical efforts were terminated in 1961, as survival was not prolonged following NCT.

The consensus was that two major problems contributed to poor results. These are:

(a) High blood concentration measurements indicated that blood was not cleared and that ^{10}B concentration exceeded that in tumor.

(b) Poor neutron penetration. The exponential attenuation of the thermal beam used (half-value layer approx. 1.5 cm) made it difficult to treat tumor at depth, particularly with high blood-boron concentrations in surface tissues. Viable tumor was found at depth following NCT (1). Further, normal tissue tolerance was exceeded for surface tissues, (2).

1.2. New developments

Improvements have been made both in the ratio of ^{10}B in tumor to ^{10}B in blood and in neutron flux density distributions. The first factor is due to the use of compound $Na_2B_{12}H_{11}SH$ developed in Boston (3). The relevant ratios vary between 1 and 2 (4,5).

Use of epithermal neutron beams provided improved depth-dose distributions, (6). (Fig.1). Clinical trials of NCT have been in progress for some time in Japan (7). On average an extension of survival is by a factor of approx. 3. An epithermal beam is under development in Japan to improve neutron penetration (8).

1.3. Future developments

The full potential of NCT is thought to reside in the use of 3rd generation boron compounds, showing physiological uptake in tumor, which would clear the blood to a significant extent, lowering the dose to normal tissues and improving the therapeutic ratio. A number of biomolecules have been shown to provide selective and robust

accumulations in tumor and may serve as improved vehicles for transport of boron to tumor. These are moieties of phenothiazines, nucleosides, porphyrins, steroids, liposomes, antibodies and thiouracil, all of which have borated analogs reported in the literature.

2. METHODS

Components of the mixed radiation field from thermal and epithermal beams have been measured previously in an anthropomorphic phantom with TE chambers, Au and Na foils, Si diodes and LiF dosimeters, so that the dose components could be separated (6,9).

3. RESULTS

Mixed field components of the thermal and epithermal beams are shown in Figs. 2 and 3 (6). Evaluation of these beams for therapy must involve numerous parameters: absolute ^{10}B concentration, ^{10}B ratio, depth in tissue, RBE, oxygen enhancement ratio (OER) and LET. Concentrating on physical parameters, an advantage factor, defined as the ratio of tumor dose to maximum normal tissue dose, can be evaluated. Fig. 4 shows this factor estimated for absorbed dose at a depth of 4 cm for various ^{10}B ratios and for ^{10}B concentrations in tumor of 35 and 70 μg of ^{10}B per gram of tissue. An epithermal beam in the current trials in Japan gives ^{10}B ratio of approx. 2 for concentration of 35 $\mu g/g$.

4. SIGNIFICANCE OF NEW COMPOUNDS

The new boron compounds should yield an improved ^{10}B ratio, as selective binding to the tumor allows clearance from blood. Chlorpromazine (CPZ) represents this behaviour. Binding to melanin, the pigment of melanoma, with a biological $T_{1/2}$ of approx. 10 days, allows clearance from blood (10) (Fig.5). If the borated analog of CPZ behaves in the same manner, for multiple doses of CPZ the ^{10}B ratios would exceed 10 and the absolute concentration can reach 70 $\mu g/g$, (11). Consequent advantage factors, based on absorbed dose, would thus exceed 2 at 4 cm depth in an epithermal beam (Fig.4), far in excess of currently available therapeutic modalities. Higher boron concentrations may be available from borated nucleosides and porphyrins. Advantage factors for ^{10}B concentration of 350 $\mu g/g$ are shown in Fig. 6 for ^{10}B ratio of 10. It can be seen that factors of 5 would be obtained and for depth of more than 2 cm epithermal beam is superior.

Taking into account the RBE's for the beam components (1 for gamma-rays, 2 for protons from recoils and from $^{14}N(n,p)^{14}C$ reaction, 3.7 (12) for charged particles from $^{10}B(n,\alpha)^{7}Li$ reaction) effective dose depth curves are generated for thermal and epithermal beams (Figs. 7 and 8). These curves represent the biological response of tissues to the neutrons beam in absence and presence of ^{10}B. Advantage factors are available in the range of 2 to 20 for depths up to 8 cm.

5. ALTERNATIVE NEUTRON SOURCES

Extended biological half-lives relax the requirements for intense

sources for NCT. Protracted irradiations may indeed allow selective repairs in normal tissues traversed by lower LET irradiations in the incident beam. Work by Zamenhof et al.(12) has shown that monoenergetic neutron beams with energies as low as 37 eV provide thermal neutron flux-density distributions similar to those of Figs. 3 and 8. The use of beams with incident energies less than 10 keV will eliminate tissue dose from proton recoils (curve H in Fig.3). Filtered neutron beams with energies of a few keV (e.g. Sc filtered beams of 2 keV energy) (13) may provide therapy beams with dose distributions better than those shown in Figs. 2 and 3.

6. LYOLUMINESCENCE DOSIMETRY AND THERMAL FLUENCE MAPPING

In the thermal and epithermal neutron radiation fields, lyoluminescent phosphors containing ^{10}B or ^{6}Li provide means of mapping the thermal flux and measure the neutron component of the total dose. The lyoluminescent response is proportional to the concentration of the nuclide undergoing the (n,α) reaction and to the thermal fluence. Among the boron compounds tried for this purpose were lithium borates, phenylboric acid, amylboric acid, butylboric acid and furanylboric acid. The last four compounds were tried in organic solvents as they are very sparsely, if at all, soluble in water. The response was considered unsatisfactory, because of an extremely low lyoluminescence yield. The borated analogs of compounds mentioned in para.1.3 were not available for trials but it can reasonably be expected that they will show a marked lyoluminescent response, because the unmodified compounds are all lyoluminescent.

Many compounds of lithium were also tried as potential thermal neutron phosphors. Particular attention was concentrated on the lithium salts of organic acids because they are easy to prepare from enriched reagents. The following compounds were investigated: tris-lithium citrate tetrahydrate, lithium formate monohydrate, lithium acetate dihydrate, lithium lactate, lithium oxalate and lithium pyruvate. The last three compounds in this list were particularly good lyoluminescent phosphors. The thermal neutron response of ^{6}lithium pyruvate is shown in Fig.9 . It was used to measure the thermal neutron flux density profile in a simple brain phantom, 12 x 12 x 12 cm block of TE plastic, embedded in a larger lucite block. The phantom was placed in front of the patient irradiation port in the Medical Research Reactor in Brookhaven. Dosimeters were placed along the central axis, two positions irradiated at a time, separated by 3 to 5 cm to minimize the 'shadowing effect'. Gamma ray component of the field, measured with a graphite+CO_2 chamber was subtracted from the response of dosimeters. All exposures were carried out at power level of 5 MW for duration of 1 min. The corresponding thermal fluence was approx. 2×10^{13} neutr./cm^2 . The results for two types of dosimeters used are shown in Figs.10 and 11. The measured dose profile shows good agreement with the calculated profile as well as with the results of measurements employing activation detectors.

In the almost entirely thermal radiation field of the patient irradiation facility at MRR in Brookhaven the response of lyoluminescent phosphors containing ^{10}B or ^{6}Li must be the same. However, in the presence of pronounced epithermal component use of the ^{10}B compounds is superior to the measurements with ^{6}Li because ^{10}B is a pure 1/v absorber, unlike ^{6}Li. Obviously, in a radiation field containing epithermal or fast neutrons, suitable corrections must be made for the response of ^{6}Li. The present

measurements were corrected for the non-thermal response using data from (14). The fast component of the neutron radiation field can be measured using one of tissue equivalent lyoluminescence phosphors, e.g. mannose. More information on the LL measurements with various phosphors can be found in (15) and the description of read-out equipment is given in (16).

It is important to realize, that in neutron fields containing both the thermal and epithermal components it is possible to reconstruct the 'therapeutic profile'. This profile is the plot of the dose delivered to the tissue from the capture reactions in boron or lithium. If the nuclide used for this mapping is the same as the nuclide used for the therapy, then the pecularities of the spectral content of the neutron beam, effects of further thermalization are automatically accounted for in the response. Thus the use of boron compounds for mapping the radiation fields in boron therapy offers a method of exact predicting of the physical response of irradiated tissues to the neutron fluxes. In addition, amino acid based lyoluminescent phosphors, e.g. glutamine or valine, can measure the dose received by the tissue not containing boron compounds. In resolving the components of the dose in the mixed radiation field it is necessary to take into account the dependence of the response of LL phosphors on the LET of radiation, which are given in (15).

7. REFERENCES

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LIST OF CAPTIONS

Fig.1 Total absorbed dose to tissue containing 35 μg ^{10}B per gram of tissue, in the epithermal and thermal beams. For comparison, depth dose curves for 1 and 6 MeV neutron beams are included.

Fig.2 Mixed radiation field components from a thermal neutron beam incident upon an anthropomorphic phantom head. Reactor power 5 MW (ref.6)

Fig.3 Same as fig.2 but for an incident epithermal beam .

Fig.4 Advantage factors at 4 cm depth in tissue for a thermal and epithermal neutron beams. Factors are given for ^{10}B concentrations in tumors of 35 and 70 μg of ^{10}B per gram of tissue.

Fig.5 Chlorpromazine (CPZ) distribution in BALB/C mice carrying Harding-Passey melanoma. Distributions are given at 48 hours following single IP injections of ^{35}S labeled CPZ. Doses of CPZ were : 5, 25, and 50 μg of CPZ per mouse.

Fig.6 Advantage factors are shown for various depth in tissue assuming a ^{10}B tumor concentration of 350 $\mu g/g$ and a ratio of boron in tumor to boron in blood of 10.

Fig.7 Effective dose rate in tissue from an incident thermal neutron beam. RBE's for gamma rays (=1), protons (= 2) and charged particles from $^{10}B(n,\alpha)^{7}Li$ reaction (= 2.7) were applied to absorbed dose distributions in Fig.2. The lower curve (TOTAL, NO B-10) represents effective dose to tissues from the neutron beam alone, with no boron present.

Fig.8 Same as Fig.7, except that the values of RBE's were applied to the curves in Fig.3

Fig.9 Dose response curve of lithium pyruvate, containing lithium enriched to 97% with ^{6}Li. The material was dissolved in water.

Fig.10 Depth dose profile from thermal neutrons measured with disc-shaped dosimeters containing ^{6}Lithium pyruvate. The results were corrected for self-shielding and for the contribution of epithermal neutrons to ^{6}Li response. Broken line : calculated values.

Fig.11 Same as Fig.9, but for rod-shaped dosimeters containing the same material.

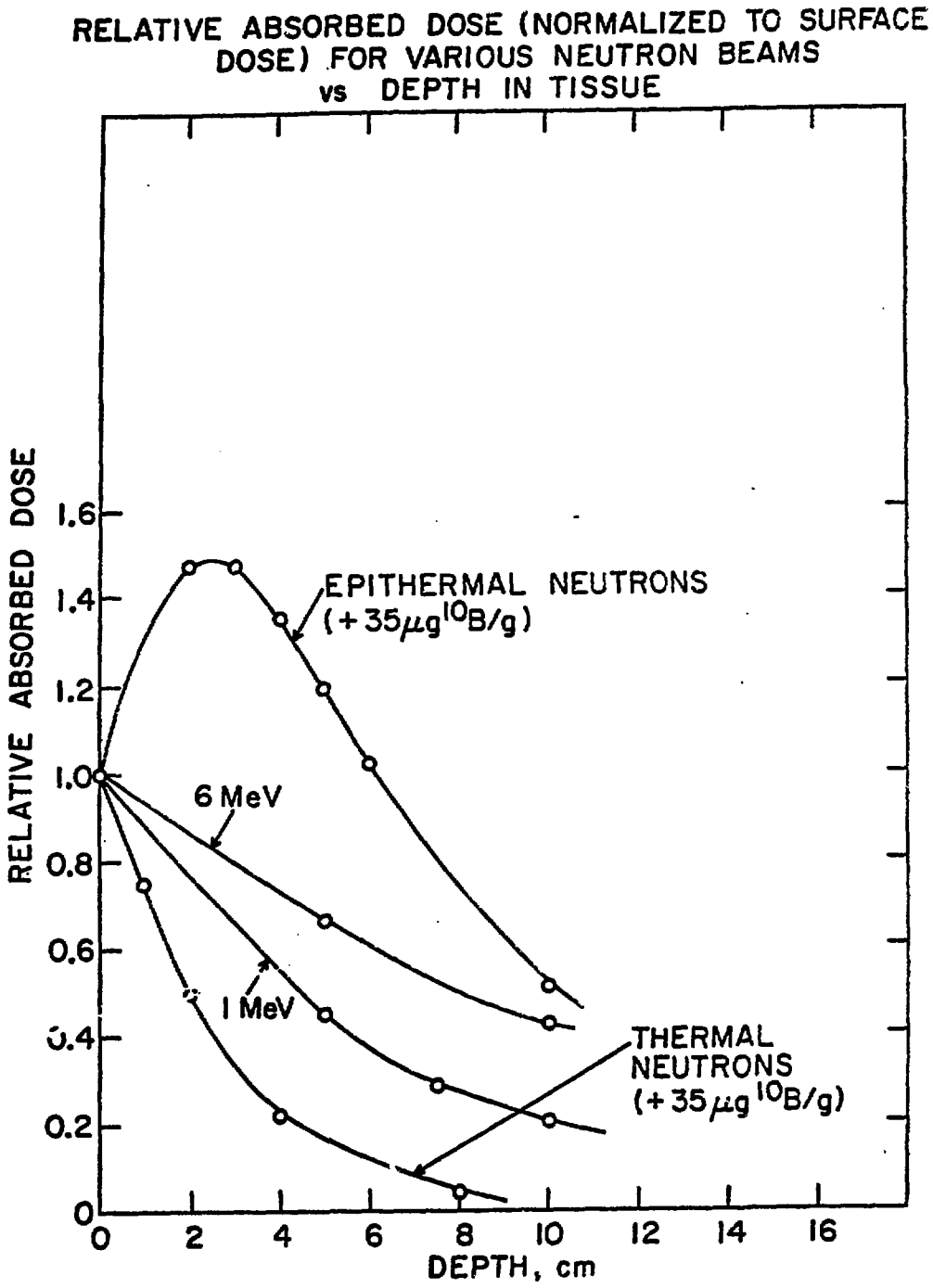
RELATIVE ABSORBED DOSE (NORMALIZED TO SURFACE DOSE) FOR VARIOUS NEUTRON BEAMS vs DEPTH IN TISSUE
RELATIVE ABSORBED DOSE
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
EPITHERMAL NEUTRONS
(+35μg 10B/g)
6 MeV
1 MeV
THERMAL
NEUTRONS
(+35μg 10B/g)
0
2
4
6
8
10
12
14
16
DEPTH, cm

FIGURE 1

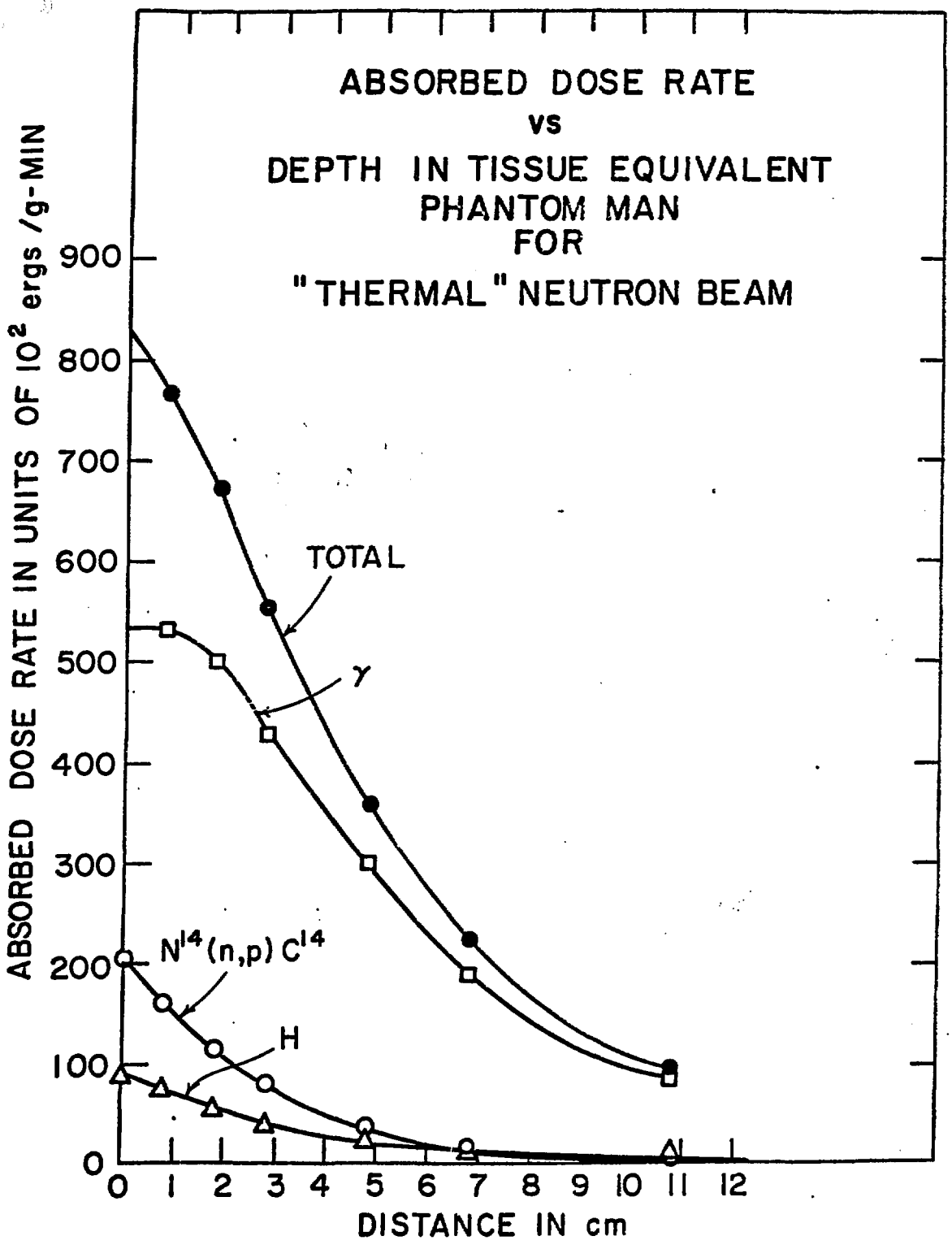
ABSORBED DOSE RATE
vs
DEPTH IN TISSUE EQUIVALENT
PHANTOM MAN
FOR
"THERMAL" NEUTRON BEAM
ABSORBED DOSE RATE IN UNITS OF 10^2 ergs /g-MIN
900
800
700
600
500
400
300
200
100
0
TOTAL
γ
$N^{14}(n,p)C^{14}$
H
0 1 2 3 4 5 6 7 8 9 10 11 12
DISTANCE IN cm

FIGURE 2

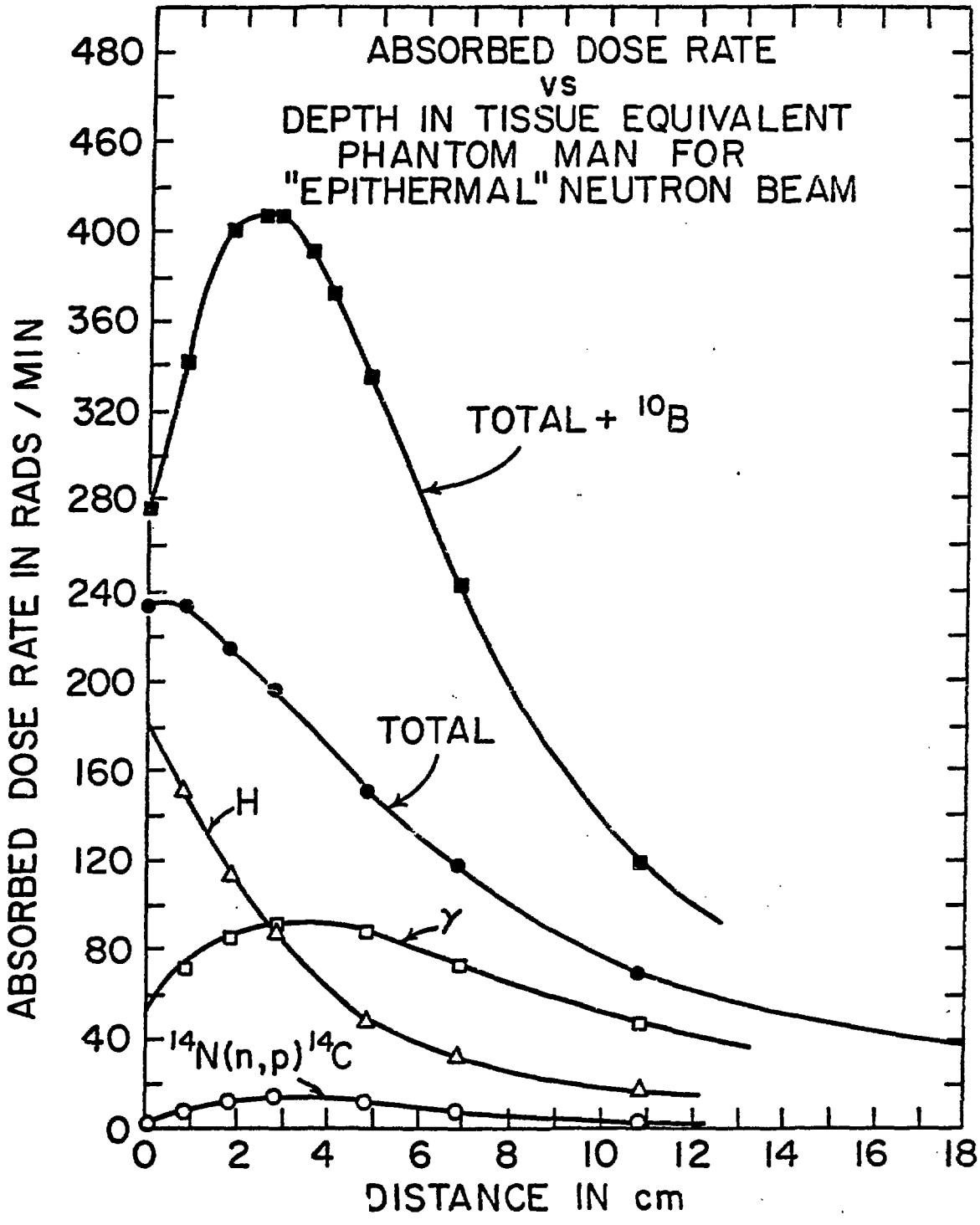
ABSORBED DOSE RATE
vs
DEPTH IN TISSUE EQUIVALENT
PHANTOM MAN FOR
"EPITHERMAL" NEUTRON BEAM
TOTAL + ^{10}B
TOTAL
H
γ
$^{14}N(n,p)^{14}C$
ABSORBED DOSE RATE IN RADS / MIN
DISTANCE IN cm
0
40
80
120
160
200
240
280
320
360
400
460
480
0
2
4
6
8
10
12
14
16
18

FIGURE 3

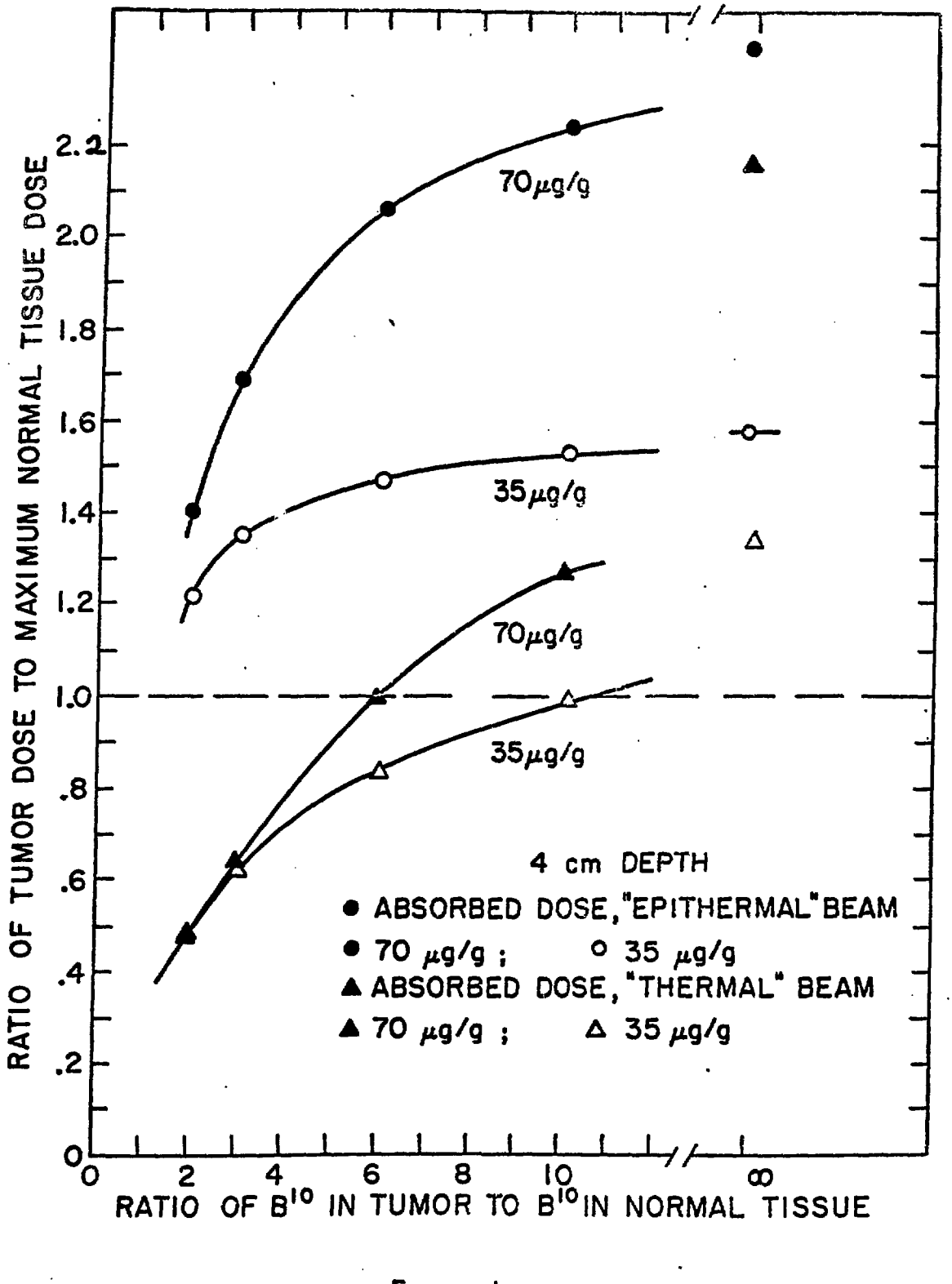
RATIO OF TUMOR DOSE TO MAXIMUM NORMAL TISSUE DOSE
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
.4
.2
0
70μg/g
35μg/g
70μg/g
35μg/g
4 cm DEPTH
● ABSORBED DOSE, "EPITHERMAL" BEAM
● 70 μg/g ; ○ 35 μg/g
▲ ABSORBED DOSE, "THERMAL" BEAM
▲ 70 μg/g ; △ 35 μg/g
0
2
4
6
8
10
∞
RATIO OF B10 IN TUMOR TO B10 IN NORMAL TISSUE

FIGURE 4

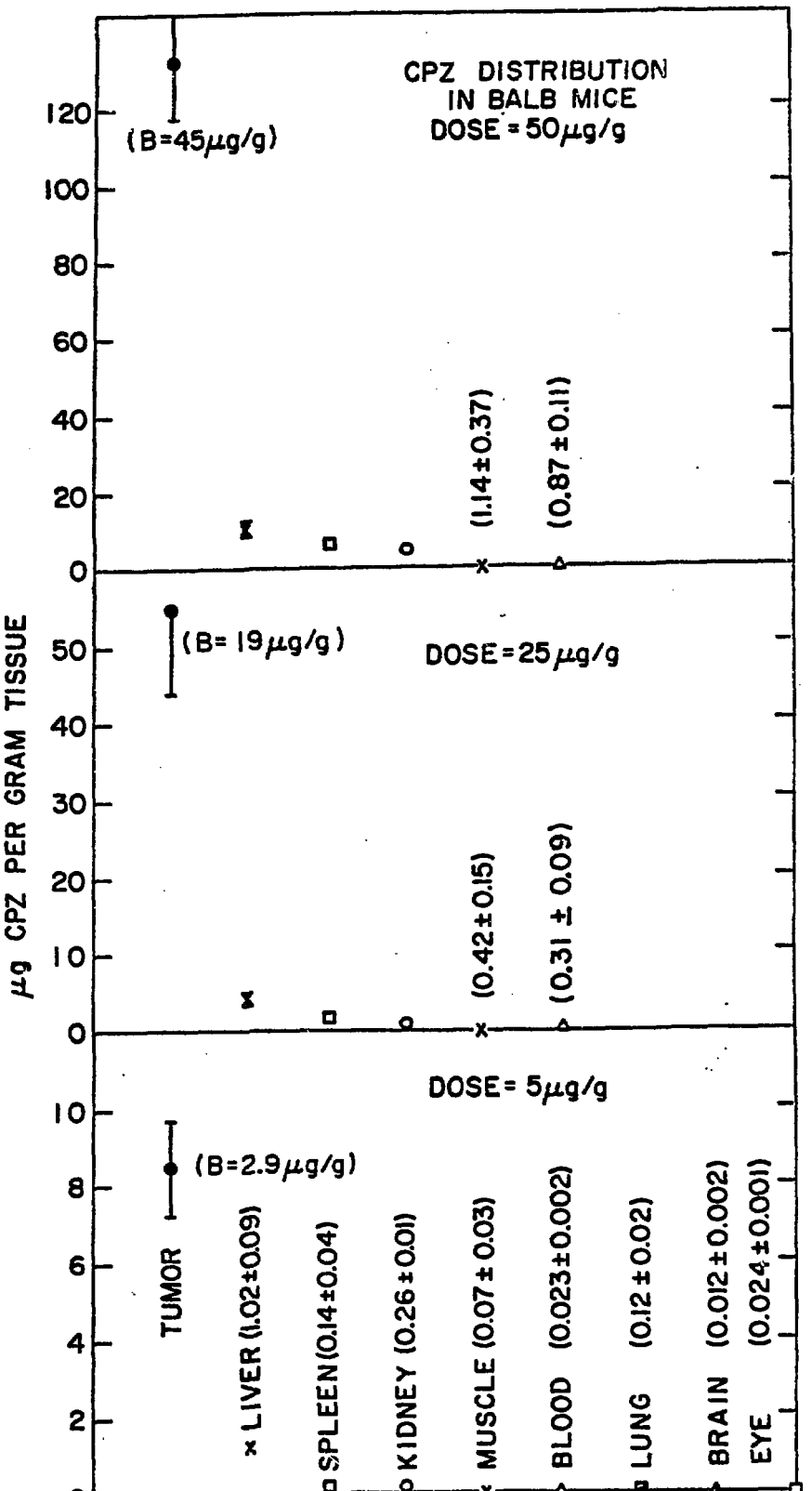
CPZ DISTRIBUTION
IN BALB MICE
DOSE = 50μg/g
(B=45μg/g)
(1.14±0.37)
(0.87±0.11)
DOSE=25μg/g
(B= 19μg/g)
(0.42±0.15)
(0.31 ± 0.09)
DOSE= 5μg/g
(B=2.9μg/g)
μg CPZ PER GRAM TISSUE
TUMOR
LIVER (1.02±0.09)
SPLEEN (0.14±0.04)
KIDNEY (0.26±0.01)
MUSCLE (0.07± 0.03)
BLOOD (0.023±0.002)
LUNG (0.12 ±0.02)
BRAIN (0.012±0.002)
EYE (0.024±0.001)

FIGURE 5

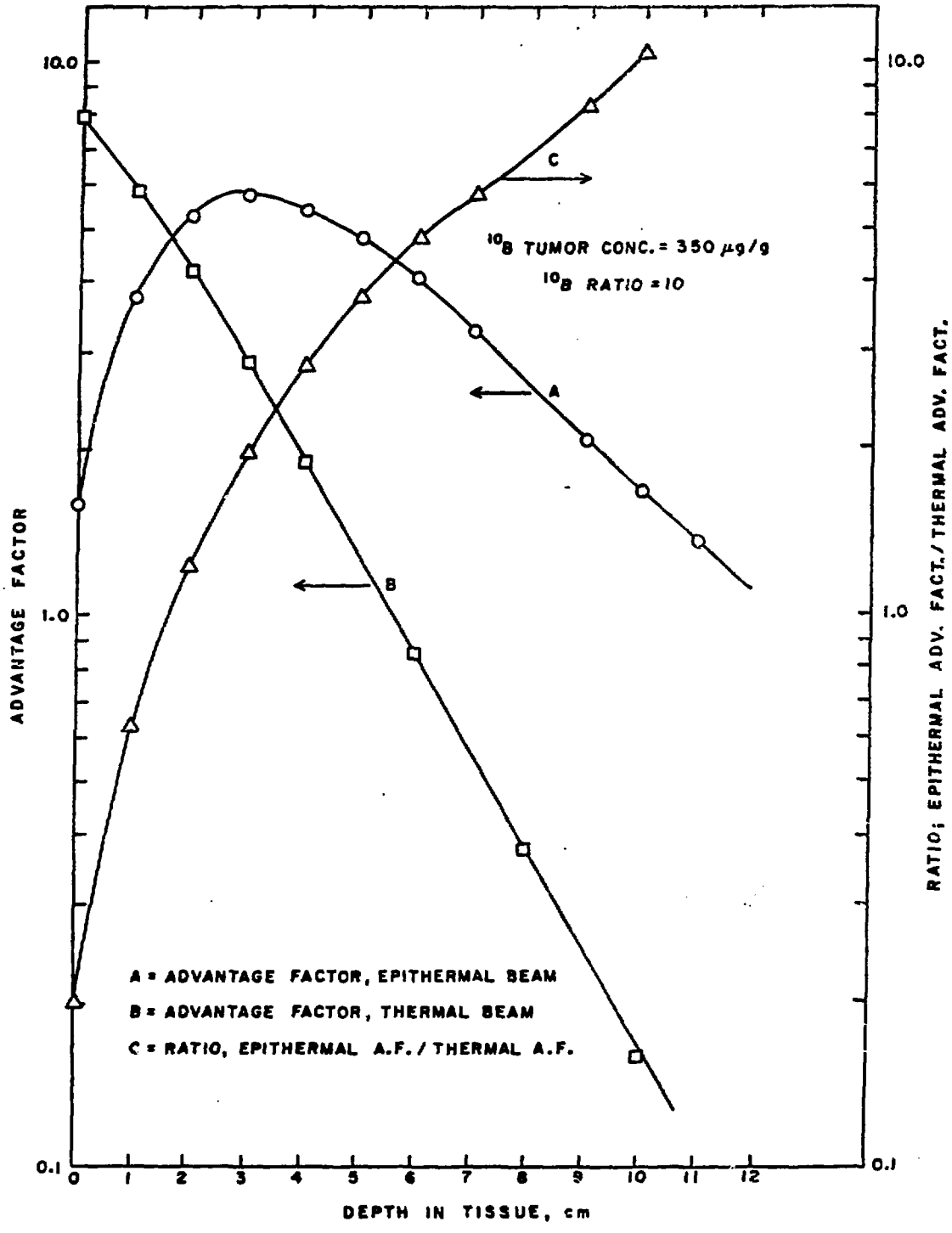
10.0
1.0
0.1
ADVANTAGE FACTOR
RATIO; EPITHERMAL ADV. FACT./THERMAL ADV. FACT.
C
^{10}B TUMOR CONC. = 350 μg/g
^{10}B RATIO = 10
A
B
A = ADVANTAGE FACTOR, EPITHERMAL BEAM
B = ADVANTAGE FACTOR, THERMAL BEAM
C = RATIO, EPITHERMAL A.F. / THERMAL A.F.
0 1 2 3 4 5 6 7 8 9 10 11 12
DEPTH IN TISSUE, cm

FIGURE 6

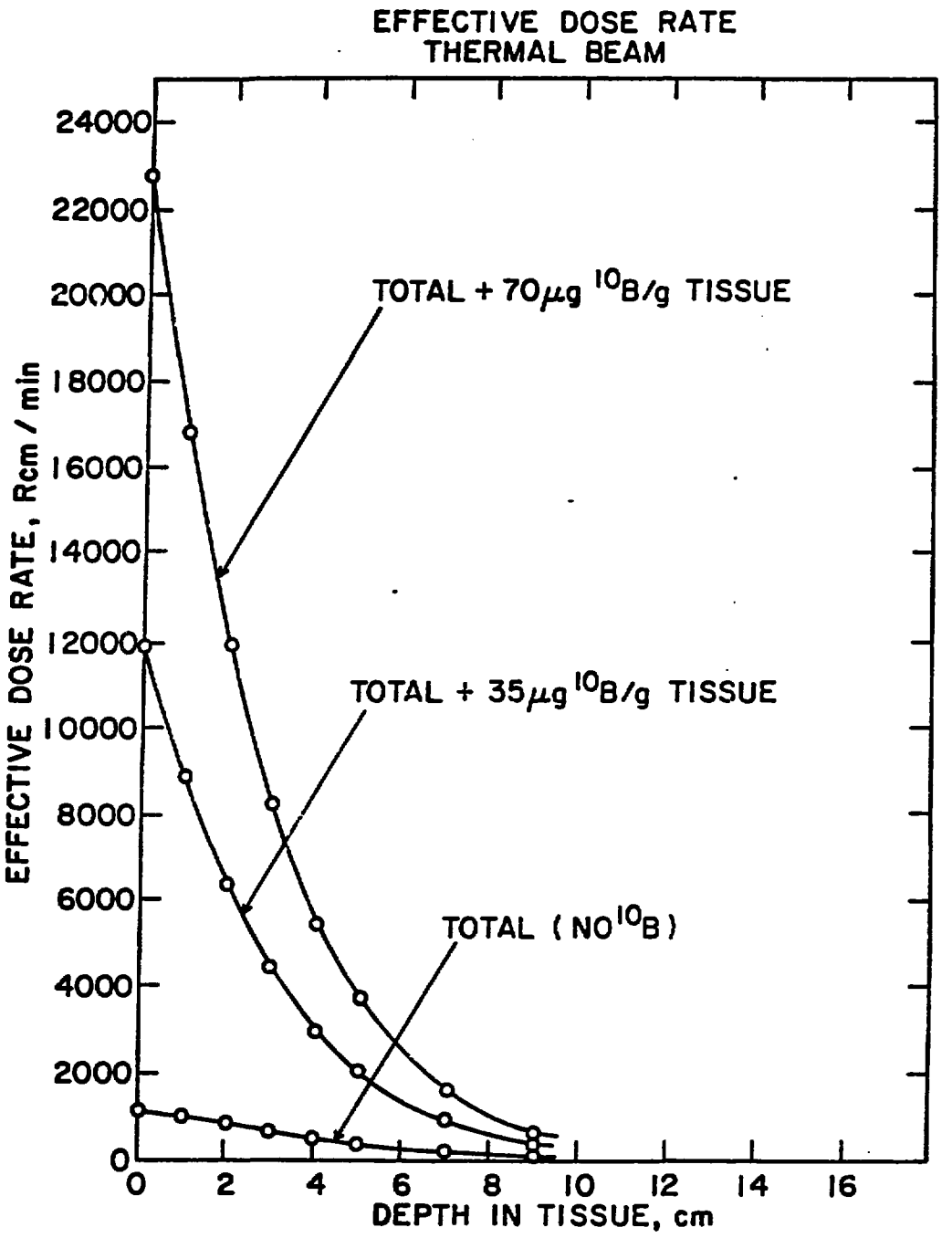
EFFECTIVE DOSE RATE
THERMAL BEAM
EFFECTIVE DOSE RATE, Rcm / min
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
TOTAL + 70μg ^{10}B/g TISSUE
TOTAL + 35μg ^{10}B/g TISSUE
TOTAL (NO ^{10}B)
0
2
4
6
8
10
12
14
16
DEPTH IN TISSUE, cm

FIGURE 7

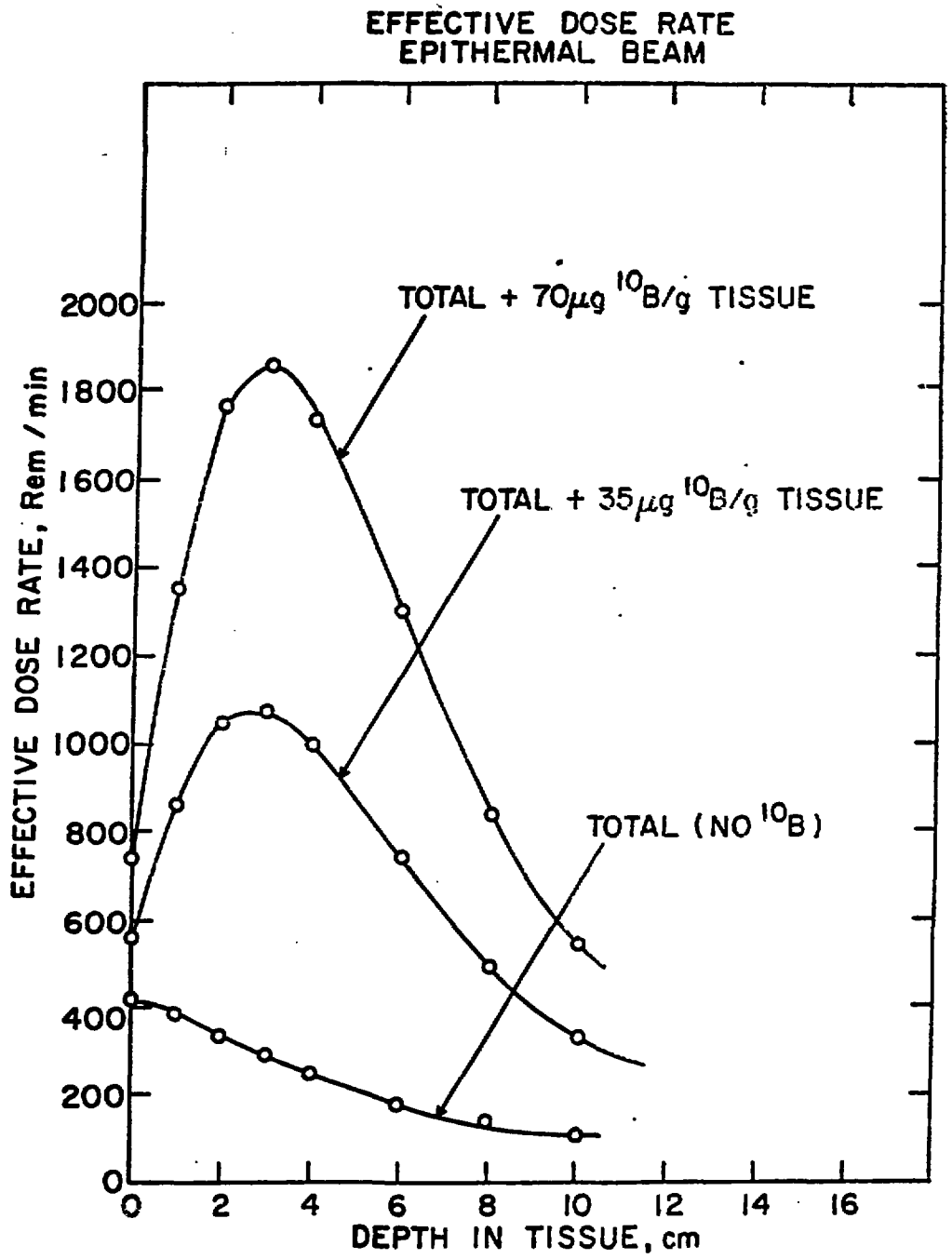
EFFECTIVE DOSE RATE
EPITHERMAL BEAM
TOTAL + 70μg ^{10}B/g TISSUE
TOTAL + 35μg ^{10}B/g TISSUE
TOTAL (NO ^{10}B)
EFFECTIVE DOSE RATE, Rem / min
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
16
DEPTH IN TISSUE, cm

FIGURE 8

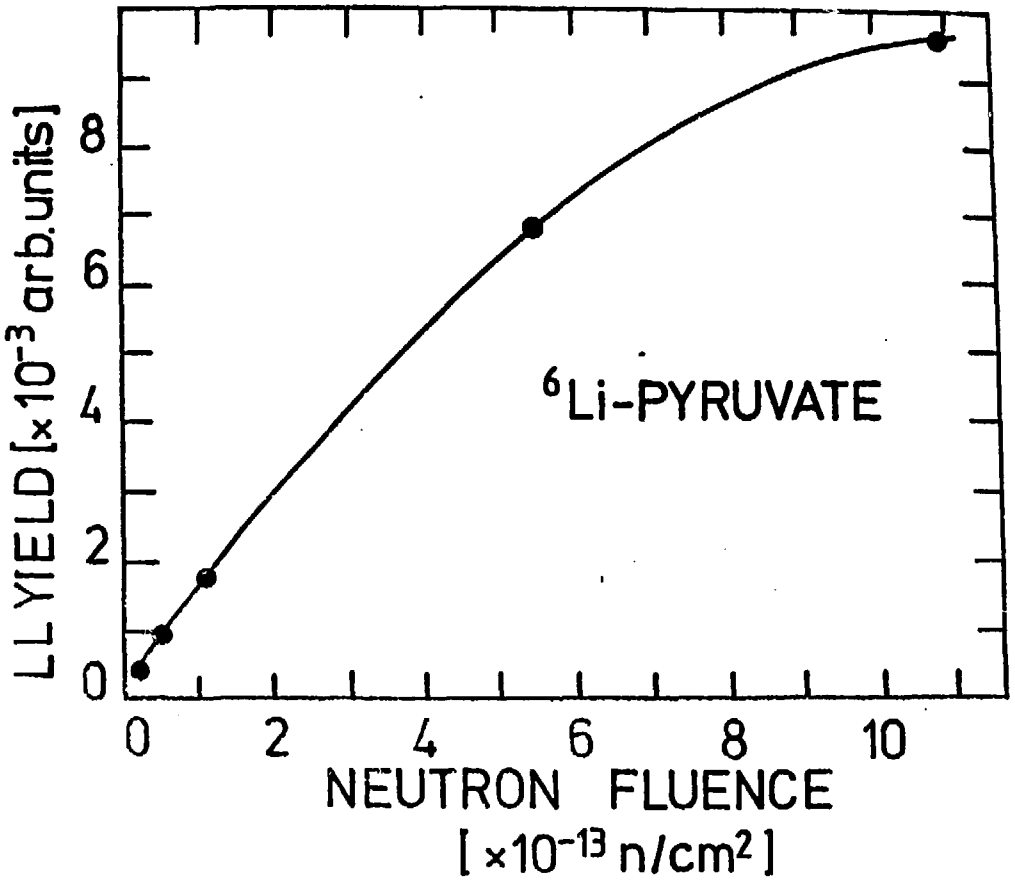
LL YIELD [×10⁻³ arb.units]
0
2
4
6
8
0
2
4
6
8
10
NEUTRON FLUENCE
[×10⁻¹³ n/cm²]
⁶Li-PYRUVATE

FIGURE 9

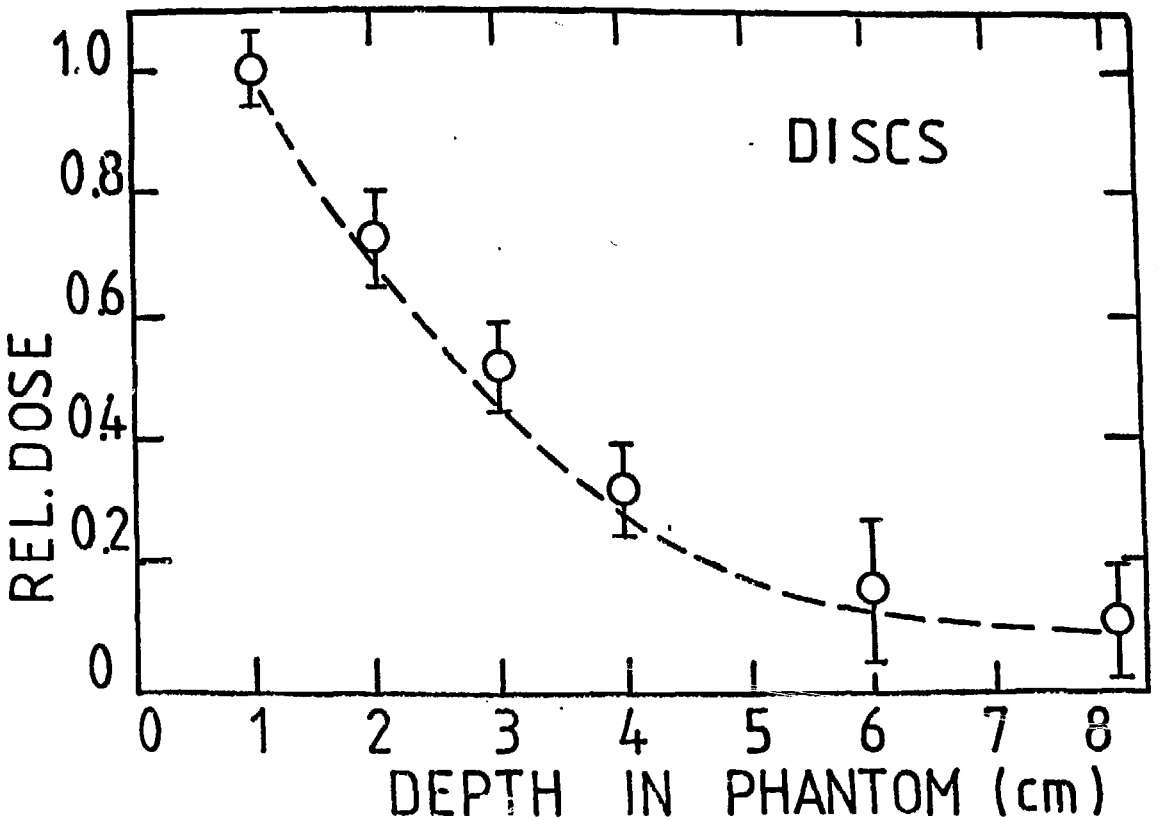

FIGURE 10

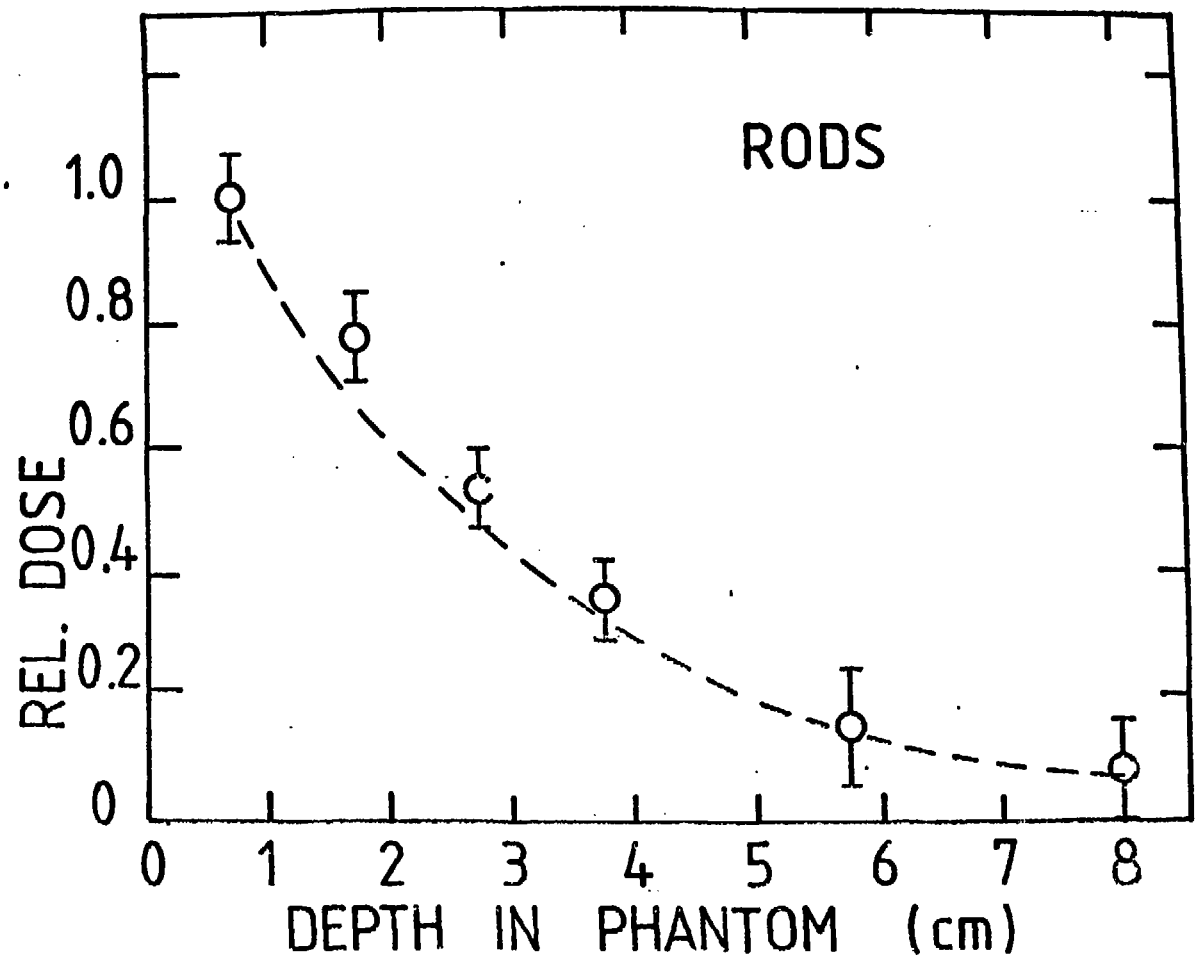

FIGURE 11