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RECENT ADVANCES IN NEUTRON CAPTURE THERAPY (NCT)

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Ralph G. Fairchild

Medical Department
Brookhaven National Laboratory
Upton, New York 11973

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Abstract

The application of the $^{10}B(n,\alpha)^{7}Li$ reaction to cancer radiotherapy (Neutron Capture therapy, or NCT) has intrigued investigators since the discovery of the neutron. This paper briefly summarizes data describing recently developed boronated compounds with evident tumor specificity and extended biological half-lives. The implication of these compounds to NCT is evaluated in terms of Therapeutic Gain (TG). The optimization of NCT using band-pass filtered beams is described, again in terms of TG, and irradiation times with these less intense beams are estimated.

1. Desirable Characteristics for Radiation Therapy

According to cancer statistics, mortality is ~50% when averaged over all cancers. Thus depsite the combined attack of surgery, chemotherapy and radiotherapy, there is abundant room for impovement, including treatment of primary site tumors.

Conventional radiotherapy suffers from an inability to deliver a dose sufficient to insure prevention of regrowth. This is in part a consequence of the fact that the treatment volume must be expanded to include regions which might contain malignant extensions of growth; delivered dose is then limited to the tolerance of normal tissue within the treatment volume. Cancer therapy is based on the hope that as normal tissues are carefully irradiated with exposures up to but not exceeding their tolerance, curative levels will be achieved in tumor. Regions exist in the treatement volume where tumor and normal tissue doses are the same; nevertheless an advantage, or therapeutic gain (TG), is thought to exist as a result of differential repair and/or repopulation rates. The failure of radiotherapy attests to the fact that these conditions may only occasionally obtain. Additional problems are of course encountered when remote metastatic disease remains undetected and untreated.

In principle, it would be desirable to direct cytotoxic agents to cancer cells via specific physiological pathways. Biomolecules targeted to tumors could be tagged with radioactive isotopes emitting short-range particles (β^-, α, β^+, Auger cascades) which would limit dose to these cells. Consequently, tumor dose would no longer be limited to the tolerance level of surrounding tissues, and in addition, remote metastatic sites would be targeted automatically. The treatment of well-differentiated thyroid carcinoma with I-131 is a good example of this. A tumorcidal dose is given, while restricting normal tissues to less than 2% of that given to tumor. Another possible example is the treatment of melanotic melanoma with S-35-labeled thiouracil (TU). Following the experimental findings that TU was taken up selectively in growing melanoma (1), studies have shown that dose rate of ~60 rads per hour would be obtained in murine melanoma and that complete tumor regression followed the administration of such doses (2).

The above two examples may however be unique, as in practice it is found that essential normal cell pools such as bone marrow and intestinal epithelium usually compete for cytotoxic materials with an effectiveness equal to or greater than that of tumor. The result is that toxic levels are reached in normal tissues before lethal amounts can be delivered to tumor. The situation is further complicated by the fact that molar concentrations of therapeutic agents are usually 10^4-10^6 times those required for diagnosis, so that physiological pathways can easily be saturated before useful amounts of agent are delivered.

Utilization of a two-component therapeutic modality such as is employed with NCT has the advantage that ^{10}B is stable and thus not inherently toxic. Competing uptake of boronated compounds in cell pools such as bone marrow and gut does not limit therapy so long as these tissues are excluded from the treatment volume. In principle, multiple sites may be treated as long as normal tissues with high boron content are protected from the activating neutron beam. Since products from the $^{10}B(n,\alpha)^7Li$ reaction have ranges limited to ~1 cell diam-

eter, conditions ideal for radiotherapy can be obtained, assuming that cancer cells can be selectively targeted with therapeutic amounts of boron. In addition, the highly ionizing particles have advantages commonly accorded to high LET radiation (i.e., little or no repair, greater effectiveness against hypoxic cells, and a constant radiosensitivity throughout the cell cycle.

2. Past and Current Clinical Trials of NCT

In view of the potentially optimum conditions available for radiotherapy with NCT, it is not surprising that great interest has been shown in trying to realize these benefits. Initial clinical trails in the period from 1951-1961 were unsuccessful due to radiation nearosis in normal brain tissues, resulting from boron concentrations in blood which were higher than that in tumor. Also, viable tumor was found at depth due to rapid attenuation of the incident thermal neutron beam (3). More recent clinical studies in Japan which were started in 1968 by Dr. Hatanaka have shown better results, with an evident increase in average survival of patients with brain tumors, relative to conventional treatment (4). These encouraging findings are due in part to a "2nd generation" compound $Na_2B_{12}H_{11}SH$ which shows an improved tumor/blood concentration ratio of $\sim$1.5 (4).

As described below, "3rd generation" compounds have been shown to have a significantly increased physiological selectivity for tumor, relative to $Na_2B_{12}H_{11}SH$. It is anticipated that when such compounds are used in conjunction with the increased tissue penetration of epithermal neutron beams, marked increase in therapeutic efficacy should be obtained.

3. New Compounds for Boron Transport to Tumor

From the vast array of diagnostic tests available, it is clear that numerous biomolecules show an affinity for tumor, for one reason or another. Only a few of these show a selectivity and concentration robust enough to be useful for therapy. The various classes of compounds which have shown some evidence of being useful for NCT are summarized briefly below:

3.1 Steroids

A number of groups have synthesized boronated steriods (5). However, to date no data has been presented indicating that it will be possible to deliver boron concentrations adequate for therapy. (With currently available neutron beams a concentration of $\geq$15 μg ^{10}B/g would be needed; see below.)

3.2 Antibodies

The use of boronated antibodies is a potentially powerful method because of its general applicability. A number of reports have shown that sufficient boron can be attached to antibodies ($\sim$1000 ^{10}B atoms/antibody; ref. 5). More recently, preliminary data have indicated that such conjugates retain their biological activity and selectivity *in vitro* (22). Significant difficulties may however be encountered in uniformly targeting antigen sites with sufficient numbers of these large conjugates *in vivo*.

3.3 Liposomes

The possibility of directing potentially cytotoxic agents via liposomes conjugated with monoclonal antibodies (MABs) has been investigated with some indication of success (10). Preliminary studies have shown that boron can be incorporated in liposomes. Depending upon the liposome diameter, it should be impossible to direct therapeutic amounts of boron to tumor while addressing only a few of the $\sim 10^6$ available antigen sites per cell (11).

3.4 Nucleosides

Schinazi et al. have synthesized a boronated analog of thymidine (DBDU) (ref. 6), which is evidently incorporated in DNA (7). It has been estimated that a 5% substitution (DBDU for Tyd) would be adequate for NCT (8). Studies are now underway to see if an incorporation of 5% or more can be attained.

3.5 Melanin Affinic Agents (Chlorpromazine; Thiouracil).

The pigment melanin in melanotic melanoma provides a physiological handle that should be useful for NCT (1). It is known that the N-substituted phenothiazines such as chloropromazine (CPZ) as well as a "false precursor" in the biosynthetic pathway of melanin, thiourcil (TU), are bound to melanin. Numerous efforts are underway to synthesize a boronated analog of these two molecules (5,9); it is anticipated that this facet of NCT will eventually find clinical application.

3.6 Porphyrins

The potential carrying capacity of porphyrins for boron is higher than that of any of the other compounds under investigation. In addition, it appears to be taken up equally well by all tumors, and therefore may have broader applicability than, say, the melanin-affinic agents. Thus boronated porphyrins may represent one of the most direct approaches to providing adequate amounts of boron for NCT. Preliminary data obtained by some investigators have demonstrated the evident feasibility of this method (13,14).

3.7 Amino Acids

Various boronated amino acids are being synthesized and tested by investigators in Europe, Japan and the U.S. (5). In particular, we have found p-borono-phenylalanine as initially reported by Mishima (9) to have a selective accumulation in murine melanoma, with a concomitant clearance from normal tissues. Following single i.p. injections, absolute concentrations of ~ 30 µg ^{10}B per gram tumor can be obtained, with a tumor/blood concentration ratio of ~ 10. Use of the L-form of this compound has allowed background boron concentration to be reduced by a factor of ~ 2 (ref. 15). The above distribution should make this compound clinically useful.

3.8 $Na_4B_{24}H_{22}S_2$

Recent studies have indicated that the dimer $Na_4B_{24}H_{22}S_2$ has greater biological activity than the monomer $Na_2B_{12}H_{11}SH_1$. Multi-day infusions with osmotic pumps have provided a tumor uptake of up to ~25 μg ^{10}B per gram, with tumor/blood ratios of ~6. Various measurements show little or no accumulation in normal brain, making this form of sulfhydryl boron hydride a prime candidate for use in the treatment of glioblastoma.

While a number of compounds listed aboved appear to have promise as vehicles for boron transport, the latter two (the L-form of p-boronophenylalanine and the dimer $Na_4B_{24}H_{22}S_2$), have demonstrated tumor and normal tissue distributions in mice which should provide therapeutic gains significantly in excess of those which are available with current conventional techniques.

4. Therapeutic Gain

From the above discussions, it is apparent that with at least two of the compounds under investigation, parameters are approaching those values considered desirable for radiation therapy. As noted previously, this is a two-component system in which a stable isotope (^{10}B) is physiologically targeted to tumor, and then activated with an external neutron beam. The second component is not without its own inherent toxicity, due to γ-rays generated by the $H(n,\gamma)D$ reaction, and protons from the $^{14}N(n,p)^{14}C$ reaction; additional adventitious radiations (fast neutrons and γ-rays) may accompany the incident beam in the form of contaminating radiations. Thus the boron dose to tumor must of necessity be superimposed upon a "background" dose delivered unavoidably to both tumor and normal tissues. While clinical trials of NCT have to date used a thermal beam, there is a consensus that future trials in the U.S. will include use of an epithermal neutrons. The latter will be employed in order to circumvent problems associated with the use of incident thermal neutrons, which are attenuated rapidly. Dosimetric aspects of thermal and epithermal beam have been reviewed in the context of the various parameters involved (i.e., boron concentration and tumor/normal tissue concentration ratio (^{10}B ratio), tumor depth, thermal neutron flux density and biological effect of the various mixed field components). Results are summarized in terms of the minimum ^{10}B concentration required (Table 1; from ref. 8)).

Absolute B concentrations and tumor/normal tissue ratios are listed in Table 2 for $Na_2B_{12}H_{11}SH$ (currently being used in clinical trials) and the two most promising compounds described in section 3 ($Na_4B_{24}H_{22}S_2$ and p-boronophenylalanine). From these data it is clear that for the latter 2 compounds:

a) absolute concentrations of B are adequate for therapy, and
b) boron has been cleared from blood (as well as normal brain).

Thus it is apparent that two of the prime requisites for successful NCT have been achieved.

Thermal beams are currently available, as well as a broad spectrum "epithermal" neutron beam obtained by filtering out thermal neutrons with a Cd filter, and transmitting the remaining "slowing down" or 1/E spectrum (8). Ther-

mal beams would be particulary advantageous for surface lesions, but their rapid attenuation in tissue limits their applicability at depth. The increased penetration of epithermal beams would, in conjunction with the improved compounds shown in Table 2, enable treatment of brain tumors at any depth through the use of bilateral irradiation. The therapeutic (TG) gain has been calculated assuming a ^{10}B concentration in tumor of 35 μg/g and a tumor/normal tissue (^{10}B) ratio = 10. Results are given in Fig. 1; a TG of 2 is obtained at all depths $\geq$2 cm. Depth dose distributions and RBE's etc. used in obtaining the TG are described in ref. 8.

Significant further gains should be accessible via development of essentially monoenergetic band-pass filtered beams which transmit neutrons in the epithermal neutron energy region ($\sim$0.5 to 10,000 eV), but restrict the fast neutrons which produce an undesirable dose to normal tissues from hydrogen recoils. The TG for a 2 keV scandium filtered beam is given in Fig. 2. As in Fig. 1, dose distributions and RBEs were the same as those in ref. 8. Because of the reduced dose from fast neutron produced H recoils, the TG approaches 4. The lack of high LET contaminating radiations in band-pass filtered beams also allows the possibility of reducing normal tissue damage from low LET radiations through fractionation. Thus the possibility exists that the TG of $\sim$4 would be doubled (see ref. 8).

While pure band-pass filtered beams have been produced at low intensities ($\sim 10^6$ n/cm^2-sec; ref. 18), similarly pure beams of intensities sufficient for NCT ($\sim 10^8$ n/cm^2-sec) have yet to be constructed (5). A number of efforts are now underway to provide such a beam at currently existing reactor facilities (5, 20, 23, 24).

5. Dose-Rates from Pass-Band Filtered Beams

While dose distributions from pass-band filtered beams offer real advantages, the latter will be inconsequential if dose rates are inadequate. The parameter of most importance is the peak thermal neutron flux density generated at depth in tissue by the incident epithermal neutron beam. Two measurements have been reported for this quantity, and they are summarized in Table 3 (refs. 19 and 20). Based on these data it would seem reasonable to assume that there is an approximate one-to-one correspondence between the intensity of the incident beam, and the peak thermal neutron flux density generated at depth in a head-sized phantom. Using depth-dose distributions evaluated for an assumed "pure" pass-band filtered beam (see Fig. 3; from Ref. 8), it is then possible to obtain an estimate of possible dose rates. The peak thermal neutron flux density producing the curves in Fig. 3 was 1.1 x 10^{10} n/cm^2-sec. Calculations have been made which show that the epithermal flux density expected from the MRR patient port using an iron filter (9 inches Fe, 6 inches Al, 3.75 inches S) and the full core as a source, is 4.4 x 10^8 n/cm^2-sec at 3 MW (ref. 21). (The latter power is the highest at which continuous operation is currently possible.) The dose rates in Fig. 3 would then have to be lowered by a factor of 25. This would produce dose rates in tumor and normal tissues as summarized in Table 4 (single beam, depth of 4 cm), based on a ^{10}B concentration of 35 μg ^{10}B/g in tumor and a ^{10}B ratio (T/normal tissue) of 10. The effective dose rate of $\sim$25 (rads x RBE), would produce 1,500 (rads x RBE) per hour to tumor, which would be clearly adequate for therapy. Since normal tissue tolerance for a sin-

gle dose is ∿ 2000 rads x RBE, irradiation times would have to be ≤ 6 hours, during which tumor would receive ≤ 7500 rads x RBE. It may well be that radiobiological and physiological considerations would argue for 2-5 separate fraction.

6. Summary

The development of new boronated compounds showing physiological binding to tumor allows clearance of B from normal tissue, and thus the requirements for successful NCT have hopefully been met. Therapeutic gains should now exist which significantly exceed those possible with conventional radiotherapy. The availability of such compounds should stimulate the development of band-pass filtered beams of sufficient purity and intensity to be employed for NCT.

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Table 1. Minimum ^{10}B concentration (μg ^{10}B per gram tumor)

	^{10}B Ratio					
	Without repair			With repair		
Beam	3	10	∞	3	10	∞
Thermal	not possible	36	17	not possible	28	13
Epithermal	16	15	14	17	16	16
2-keV	2.8	1.9	1.7	1.4	0.94	0.83

Table 2. Compounds for neutron capture theapy**

Compound	Test System	Tumor (μg B/g)	Administration	Time Post Start Hours	Concentration Ratios T/Blood	T/Brain	T/Muscle
$Na_2B_{12}H_{11}SH$	Humans	25	intra-aterial infusion	2-3	1.1		
$Na_2B_{12}H_{11}SH$	Mouse*	12†	i.p. infusion	∿ 200	1.4	4.4	
$Na_4B_{24}H_{22}S_2$ (Dimer)	Mouse*	24†	i.p. infusion	∿ 200	6	5	
p-borono phenyl-alanine	Mouse*	33	i.p. (single dose)	3	10	17	4

*Harding Passey Tumor in BALB/c mice
†Average of a number of experiments
**Reference 4, 15, 16

Table 3. Thermal neutron flux densities (ϕ_{th}) generated by total epithermal neutron beam (total) flux densities (ϕ_{TOT})

Reactor Source	$\phi(E)$ n/cm^2-sec	Φ_{TOT} n/cm^2-sec	Peak ϕ_{th} n/cm^2-sec	ϕ_{th}/ϕ_{TOT}
Brookhaven Medical Research Reactor (5 MW)	E > 10 keV = 0.3×10^{10} E < 10 keV = 1.5×10^{10}	1.8×10^{10}	1.1×10^{10}	0.6
Georgia* Research Reactor (5 MW)	E > 30 keV = 0.27×10^{7} E < 30 keV = 6.9×10^{7}	7.1×10^{7}	2.5×10^{8}	3.5

*Fast flux measured at 100 cm from Biological Shield Face; Peak Thermal flux in a phantom measured at 45 cm from the biological shield face.

Table 4. Dose rates from a "pure" band-pass filtered beam (depth of 4 cm, from a single beam), based on an incident epithermal neutron flux density of 4.4×10^8 (ref. 8, 21).

TOTAL DOSE RATE	
Tumor with 35 µg ^{10}B/g	Normal tissue with 3.5 µg ^{10}B/g
25 rads x RBE/min	7 rads xs RBE/min

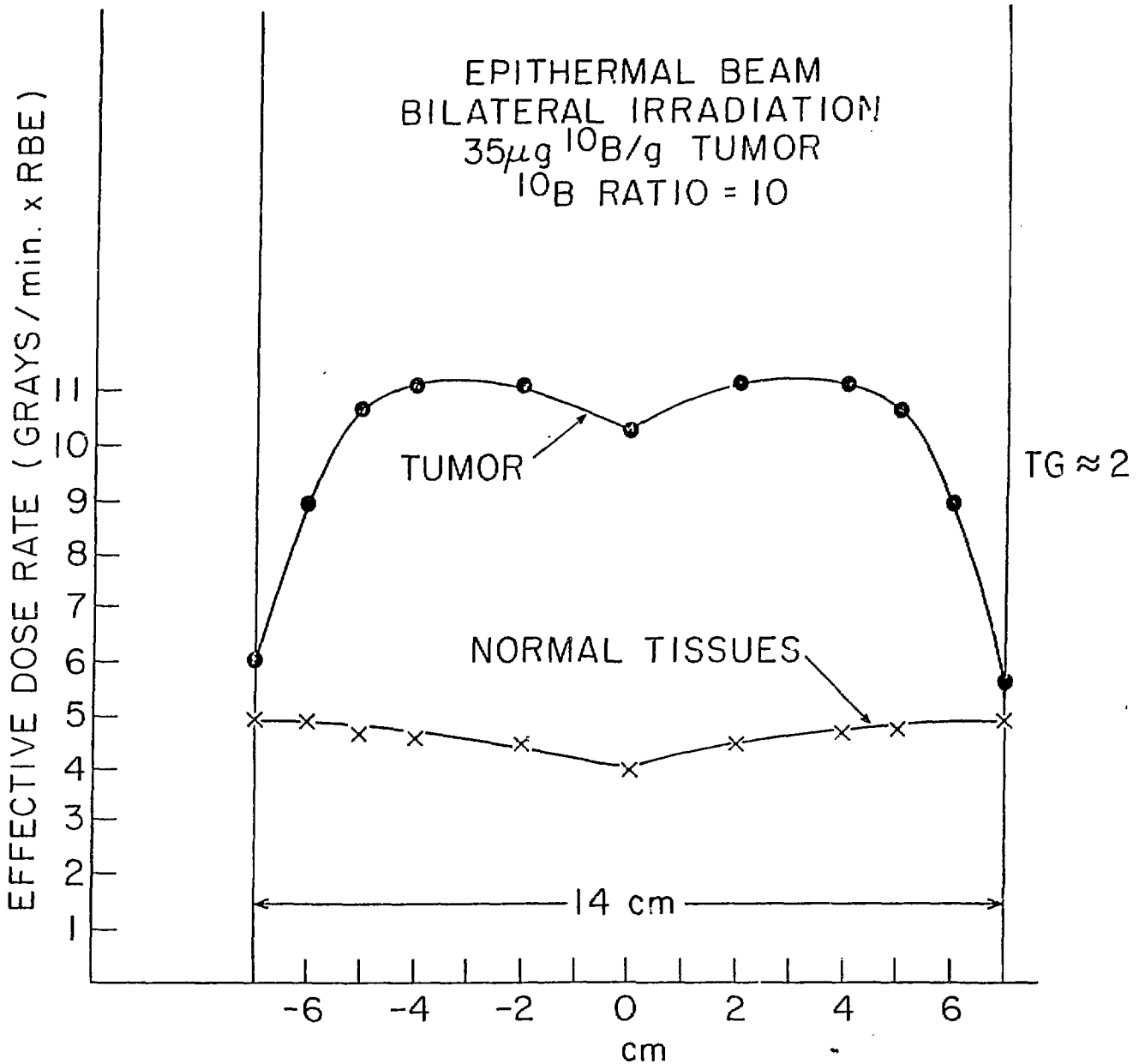
EPITHERMAL BEAM
BILATERAL IRRADIATION
35μg ^{10}B/g TUMOR
^{10}B RATIO = 10
EFFECTIVE DOSE RATE (GRAYS / min. x RBE)
11
10
9
8
7
6
5
4
3
2
1
TUMOR
NORMAL TISSUES
TG ≈ 2
14 cm
-6
-4
-2
0
2
4
6
cm

FIGURE 1

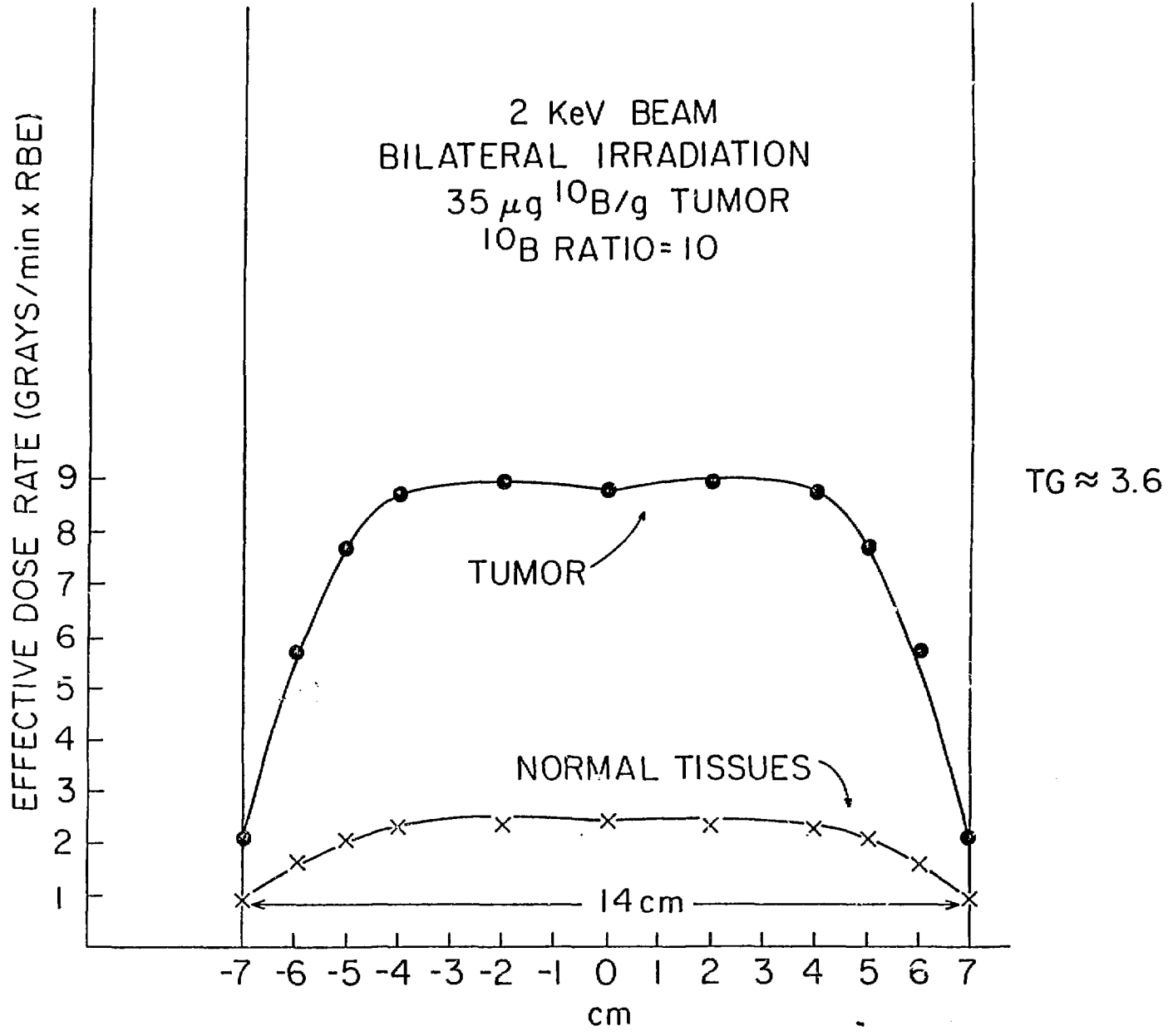
2 KeV BEAM
BILATERAL IRRADIATION
35 μg ^{10}B/g TUMOR
^{10}B RATIO = 10
EFFECTIVE DOSE RATE (GRAYS/min x RBE)
1
2
3
4
5
6
7
8
9
TUMOR
NORMAL TISSUES
14 cm
-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7
cm
TG ≈ 3.6

FIGURE 2

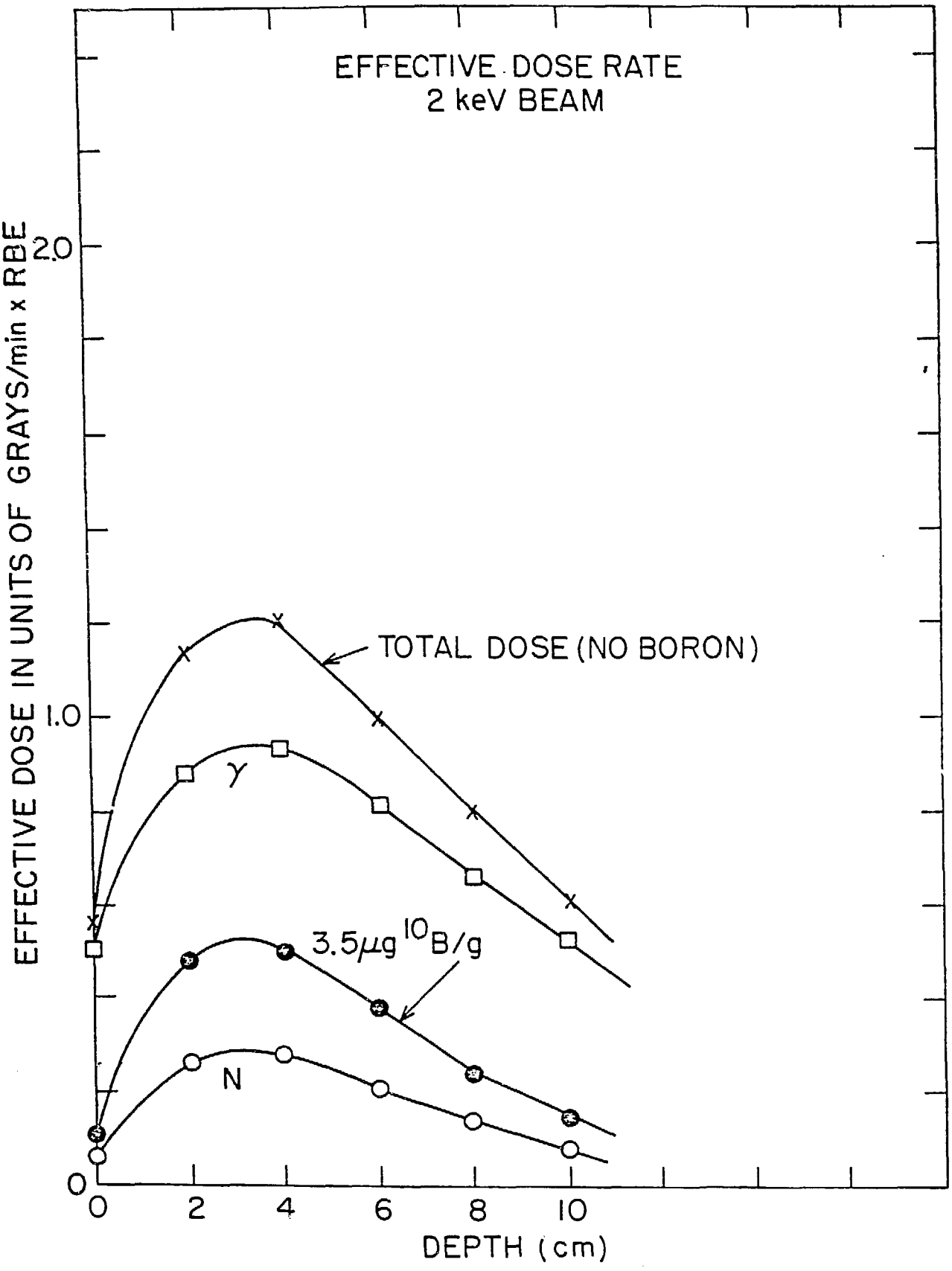
EFFECTIVE DOSE RATE
2 keV BEAM
EFFECTIVE DOSE IN UNITS OF GRAYS/min x RBE
2.0
1.0
0
TOTAL DOSE (NO BORON)
γ
3.5μg 10B/g
N
0
2
4
6
8
10
DEPTH (cm)

FIGURE 3