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AN OPTIMIZED EPITHERMAL NEUTRON BEAM FOR NEUTRON CAPTURE THERAPY (NCT) AT THE BROOKHAVEN MEDICAL RESEARCH REACTOR (BMRR)

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INTRODUCTION

The first clinical trials of NCT were initiated at Brookhaven in 1951, using the Brookhaven Graphite Research Reactor (BGRR). Subsequently, the Brookhaven Medical Research Reactor (BMRR) was built primarily for clinical applications of NCT, with an improved beam extraction facility providing flexibility for future development of filters/moderators for NCT. This flexibility was exploited to provide an optimized epithermal neutron beam which was recently installed and tested in the east irradiation facility (shutter) of the BMRR.

The new epithermal neutron beam was implemented using an Al_2O_3 moderator or "Spectrum Shifter" which was designed, installed and tested in collaboration with associates at Idaho National Engineering Laboratory (INEL). The resultant beam is "optimized" in that the fast neutron and γ contaminations have been reduced to acceptable values (less than a few % of maximum normal tissue dose), while the epithermal neutron flux density of 1.8×10^9 n/cm^2-sec allows NCT to be carried out in 30 min in a single application (1). It is, however, anticipated that clinical application of NCT will be carried out in ~4 fractions (~15 min each, with bilateral irradiations), as recommended by an international committee convened to recommend the best approach to clinical trials (2). Biological parameters have been determined for the above beam, as described below. It is expected that sufficient data will be accumulated in ongoing phase I clinical trials with BSH and BPA, to allow a decision to be made about the advisability of initiating therapy trials in humans, in ~12-24 months.

BMRR EPITHERMAL BEAM

Facility and Beam Parameters. The new Al_2O_3 moderated "optimized" epithermal beam installed at the BMRR is shown in Fig. 1; the point of irradiation is 169 cm from the core center, with 65.4 cm of Al_2O_3 and 11.4 cm of Bi plus 2 thin sheets of Cd forming the filter/moderator in the movable shutter assembly. Beam parameters are summarized in Table 1 (1). The components of the biologically effective dose from the mixed field in a tissue equivalent cylinder (16.6 x 23 cm) and the dose to tissues containing 3 to 30 μg ^{10}B/g are given in Ref. 1 and 3. From these data it is possible to derive a dose distribution for bilateral irradiations, as in Fig. 2. From the above figures, conclusions can be drawn:

1. As has been prescribed by advisory panels on NCT, bilateral irradiations provide a uniform dose distribution throughout a human head, and should be used for treatment of deep seated tumors.
2. The current beam is "optimized" in that further reduction in the fast neutron or γ contamination in the incident beam would not significantly increase therapeutic gain (TG) (1,3).

Whole Body Dose. Measurements of absorbed dose to tissue were made along the wall (biological shield) at the center, and at 10, 35, 50 and 60 cm from the center of the epithermal neutron beam facility. Values for "no shielding" were obtained at the same location. Additional measurements were made in

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Table 1. Summary of Beam Parameters for Current Optimized Epithermal-Neutron Beam (65.4 cm Al_2O_3 and Al plus 11.4 cm Bi)

Power	3 MW
Epithermal-neutron flux density* (n/cm^2-s)	1.8×10^9
Fast-neutron flux density (n/cm^2-s)**	$\sim 1 \times 10^8$
Thermal-neutron flux density (peak at ~2-cm depth in phantom; n/cm^2-s)	2.8×10^9 (no added filtration) 2.5×10^9 (0.5-mm Cd added) 1.9×10^9 (1.0-mm ^{6}Li added)
Absorbed dose from fast neutrons free in air	4.5 rad/min
Absorbed dose from gammas, free in air	1.2 rad/min
Fast-neutron dose per epithermal neutron	4.2×10^{-11} rad/(n-cm^2)
Gamma dose per epithermal neutron	1.12×10^{-11} rad/(n-cm^2)
Fast-neutron dose per thermal neutron (no added filtration)	2.7×10^{-11} rad/(n-cm^2)

*Measured at center of irradiation port face; 0.4 to 10,000 eV
**Measured at center of irradiation port face; E>10 keV

these same locations. Additional measurements, with 2.54 cm for added shielding (LiOH, lithiated polyethylene or boronated polyethylene, were made in these same positions) to evaluate the effects of such shielding. The measured values of absorbed dose in air at the facility wall surface indicate that whole body doses will be significantly reduced. It is clear that whole body dose for therapeutic irradiations will be less than 20 rads, and thus not constitute a health hazard. This was verified by dog irradiations carried out by INEL and associates (both for tumor therapy of spontaneous brain tumors and for normal tissue tolerance studies) where the (normal) CNS was identified as the critical (limiting) tissue in these studies (4,5). The above is in contradiction to statements made by others, suggesting that "...neutron leakage through the present Brookhaven reactor biological shielding could be lethal to the patient from whole body dose before the tumor is destroyed" (6).

Subsequent to the above studies, 2.54 cm of lithiated polyethylene were added to the facility wall surrounding the 10 x 10 in. port, so that lower values should now obtain.

COMPARISON OF EPITHERMAL NEUTRON BEAMS

A comparison of the various epithermal neutron beams proposed for NCT and available in the literature, is shown in Table 2, on the basis of "in air" parameters. It is evident that the D_2O moderated beam developed at the BMRR in 1965, and the Fe filtered beam recently studied at Harwell are unfit for human use due to the high fast neutron dose (1). It should be noted that the University of Missouri Reactor at Columbia (MURR II), is as good as any reactor proposed to date, with respect to high intensity and purity; in addition, it can be easily modified for clinical applications at minimal cost (16).

RADIOBIOLOGICAL PARAMETERS MEASURED AT THE BMRR

$^{10}B(n,\alpha)^7Li$ and $^{14}N(n,p)^{14}C$ Reaction. The RBE of the $^{10}B(n,\alpha)^7Li$ reaction were determined to be ~2.5 for uniformly distributed boron in the form of H_3BO_3 (7). Further calculations and studies showed that the "RBE" of any boron compound will be strongly dependent upon intra (or extra) cellular distribution (8); an experimental technique was devised to evaluate the intracellular distribution of "unknown" compounds (9). The RBE for the $^{14}N(n,p)^{14}C$ reaction was determined to be ~2.0 (7).

Fast neutrons. The RBE of fast (and epithermal) neutrons was measured with hamster V-79 cells irradiated in air at the "point of irradiation" (center of the bare port face) in Fig. 1. The RBE of ~2.2 was determined by comparison of D_0s obtained with the neutrons, and 250 kVp x-rays as shown in Fig. 3 (10). It is of interest to note that while ~95% of the neutrons are in the epithermal range (0.5 eV to 10 keV) only ~15% of the H recoil dose comes from these neutrons, while the bulk of the dose comes from neutrons with energies of a few hundred keV. Thus, there are no untoward biological effects resulting from utilization of predominantly epithermal neutron beams.

Normal Tissue Tolerance. Dog irradiation being carried out by P. Gavin and associates at the BMRR epithermal neutron beam are designed to determine the limiting or "critical" tissue for head irradiations, in anticipation of treating brain tumors with BSH. Following irradiations of normal dogs with

Table 2. Beam Parameters Measured or Calculated "In Air" for Various Epithermal Neutron Beams

Beam	Measurement or calculation	Epithermal neutron flux density (n/cm^2-sec)	Rad in Air/epithermal neutron (10^{-11} rad/neutron/cm^2) Neutrons	Gammas	Reference
BMRR (Al_2O_3 moderator)	M	1.8×10^9	4.2	1.1	
Harwell/Pluto (Fe filter)	M	2×10^7	29.0	4.2	1
BMRR* (D_2O moderator)	M	1.1×10^{10}	27.0	3.2	1
Georgia Tech* Research Reactor (Al-S filter)	M	6.9×10^7	14.8	27.0	1
MITR (Al-S moderator)	M	2.6×10^8	~24	?	23
HFR, Petten (Al-S moderator)	C	1.1×10^9	7.8	1.7	13
PBF (20 MW) (Al-D_2O)	C	10×10^9	2	1	14,15
MURR II (10 MW) (Al_2O_3)	C	7.9×10^9	2.8	0.3	16

a 5 x 10 cm field, post administration of BSH, it was found (4,5) that:

a. The highest physical dose occurred at ~3 cm;

b. Severe neurological disease was observed at doses (to blood) exceeding 38 Gy;

It was concluded that:

c. "... it is clear that the radiation changes (in normal brain) are from direct endothelial damage." and that

d. "The dose distribution for the various components is driven mainly by the tissue boron concentration.

e. Endothelium (in normal brain) was identified as the "critical tissue" (4).

From the above, it can be concluded that CNS should be the critical tissue for NCT irradiation with a 5 x 10 cm field, or larger, as the relative contribution from the $^{10}B(n,\alpha)^7Li$ reaction will increase as field size increases. It is anticipated that a 10 x 10 cm field (or larger) will be employed in clinical trials. It is important to note that, since a single acute exposure of ~2000 rads from photons would be expected to produce necrosis in nornal brain, it is evident that at least with BSH, there is a significant geometrical protection factor as predicted by Rydin et al., resulting from irradiation of endothelial cells from within the blood vessel only (11). Using numbers provided above, i.e., tolerance ≈2000 rads, blood dose from boron ~3800 rads, RBE (for uniform ^{10}B distribution) ~2.5, this protection factor would be ~4. While further refinement of the data is required, it is evident that such a geometrical protection exists, and is no doubt in part responsible for the efficacy reported by Joel et al. in the treatment of an intracranial rat tumor with BSSB (12).

Fractionation and the Blood Brain Barrier (BBB). There has been considerable concern on the part of some investigators regarding the possibility of breakdown of the BBB following fractionated irradiations in BNCT. Review papers have indicated that this possibility is somewhat remote with respect to the parameters encountered in BNCT (17). Experiments were recently performed in our laboratory in which possible breakdown of the BBB was evaluated in mice following delivery of 2.1×10^{13} n/cm^2, or 2100 rads (5250 rads x RBE) to the blood from the $^{10}B(n,\alpha)^7Li$ reaction produced by BSH (18). This dose was obtained by irradiating mice ~70 min after administration of BSH, such that the blood concentration at the time of irradiation was ~12 μg ^{10}B/g. It is anticipated that BNCT will be carried out with a maximum fluence of $\sim 5 \times 10^{12}$ n/cm^2, and surely no more than 10^{13} n/cm^2 (1). With 4 fractions, the maximum fluence per fraction would be $\leq 2.5 \times 10^{12}$; thus, the current experiment involved the delivery of ~10x more thermal neutron fluence than would be encountered clinically (in a single fraction). Assessment of the BBB integrity was made by measuring ^{10}B concentration in normal brain at 24 hours following irradiation and the second application of BSH. Neutron autoradiographic techniques were used for this evaluation, with a sensitivity of 0.1 μg. ^{10}B/g (22). Results are shown in Table 3.

Clearly there was no leakage of ^{10}B across the BBB of normal (irradiated) brain, indicating that in BNCT the integrity of the BBB would be retained in fractionated regimens (18).

Table 3. Evaluation of BBB Integrity Following BNCT

Treatment	Group I	Group II	Group III
BSH	+	+	+
BMRR (2.1×10^{13} n/cm^2)	+	-	-
BSH	+	+	-
^{10}B in blood	12.2 ± 1.8 (10)	8.8 ± 1.0 (10)	12.1 ± 0.7 (11)
^{10}B in brain	0.1 ± 0.0 (9)	0.1 ± 0.1 (8)	0.2 ± 0.1 (8)

TREATMENT PLANNING AND ISODOSE CHARTS

Given the availability of an optimized epithermal neutron beam, whose radiobiological parameters have been documented, it is necessary to develop a treatment planning capability. Upon successful completion of phase I clinical trials (distribution studies) with a boronated compound showing promising pharmaco kinetic characteristics, therapy trials can then be initiated.

The consensus is that MCNP calculations are best suited for such evaluations. The distribution of the various beam components down the central axis of a TE cylindrical phantom have been calculated for an incident 2 keV beam. Such a standard geometry can be used for intercomparison between laboratories. Similar distributions were calculated for the BMRR epithermal beam (19). Isodose charts for each beam component were constructed from these data, using a program developed by two of us (RMB and AS). For example, an isodose chart for thermal neutrons is shown in Fig. 4. Similar charts are available for each component, with and without RBE, as desired. Additionally, 3-D plots are also available as is indicated in Fig. 5, for thermal neutrons.

COMPOUND DEVELOPMENT

As documented in papers presented at this Symposium, biological efficacy has been demonstrated for BSSB and BPA in an intracranial rat glioma. It is somewhat troubling that, although BSSB and BPA as well as boronated porphyrins demonstrate significantly greater biological efficacy than does BSH, both *in vitro* and *in vivo* (9,20), the latter compound is nevertheless being prepared for clinical trials both in the US and Europe.

It is our opinion that the full potential of NCT will be realized upon the exploitation of boronated biomolecules showing selective and long term binding to tumor cells. Such characteristics will enable normal tissue to clear, and permit the superposition of boron concentration and distribution, following compound administration, to be of benefit in fractionated therapy.

While BSH, BSSB and BPA all demonstrated transient association with tumor, compounds are available which demonstrate high uptake and long term binding to tumor cells. In Fig. 6 the *in vitro* response to thermal neutrons of cells incubated in the presence of a boronated porphyrin (BOPP), and a boronated low density lipoprotein (B-LDL) is compared to BSH (cells washed before irradiation in boron-free medium, to reveal the effects of bound boron only). Figure 6 illustrates that the porphyrin (BOPP) is ~10x more effect than BSH, and that the B-LDL is ~10x more effective than BOPP (20,21). Clearly, significant increases in therapeutic gain will be best accomplished through the exploitation of such compounds.

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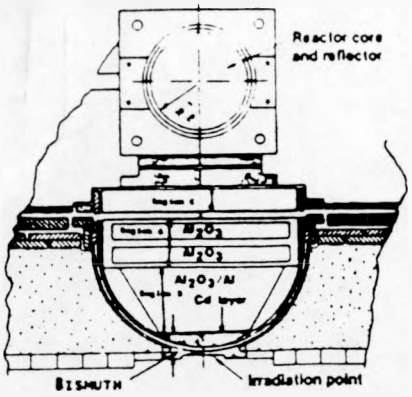

Fig. 1

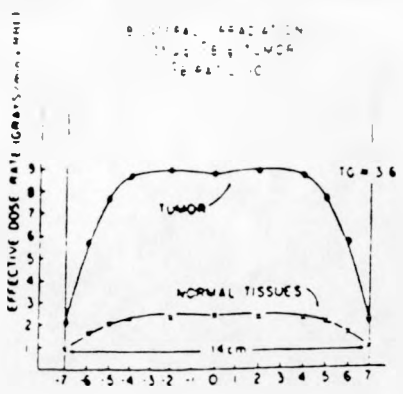

Fig. 2

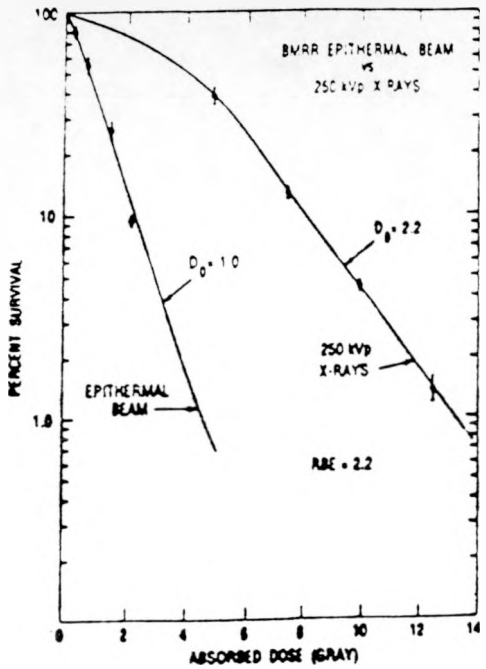

Fig. 3

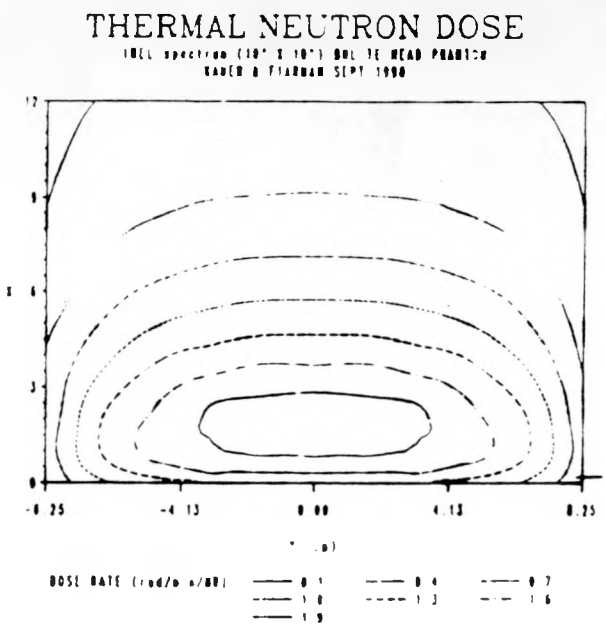

Fig. 4

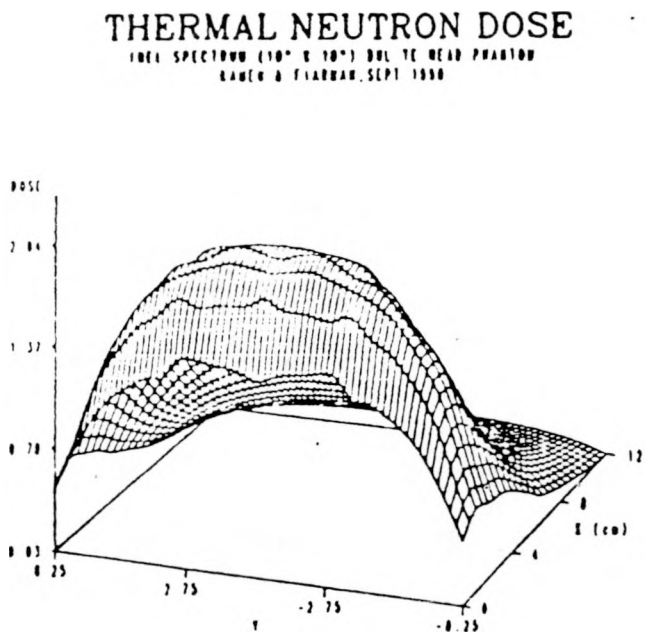

Fig. 5

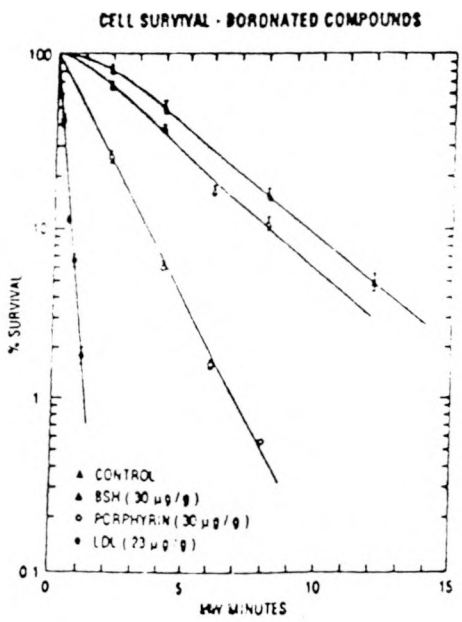

Fig. 6