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INSTALLATION AND TESTING OF AN OPTIMIZED EPITHERMAL NEUTRON BEAM AT THE BROOKHAVEN MEDICAL RESEARCH REACTOR (BMRR)

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INTRODUCTION

Initial clinical trials of Neutron Capture Therapy (NCT) in the U.S. were unsuccessful. Lack of success has been attributed to two causes: (1) absence of selective localization of boron in tumor cells, and (2) poor penetration in tissue of the thermal neutron beams used. Since then, improved compounds have been developed which can be selectively targeted to tumor^{11,12,13}. In addition, improvements have been made in neutron delivery. At a workshop on neutron sources for NCT held in 1986, it was recommended that current technology be utilized to produce pure epithermal neutron beams for NCT, which would provide the increased penetration in tissue required for improved therapy. The study group on neutron beams recommended that these beams should have an epithermal neutron flux density of $\sim 1 \times 10^8$ n/cm²-sec (or more), to enable application of therapy within ~ 1 hour (or less)³.

While the possibility exists that various filter configurations can be designed which would produce monoenergetic neutron beams at various energies, such beams tend to have intensities which are insufficient for therapeutic application. In an effort to maximize intensity, we have chosen to utilize the entire reactor core as a source of neutrons (i.e., the complete core as viewed from the point of irradiation), and to use the broad epithermal energy region (1 to 10,000 eV) for the production of thermal neutrons at depth in tissue for NCT. Concomitantly, appropriate moderators are used to selectively suppress the undesirable fast neutrons ($E > 10$ keV).

Various calculations indicate that an optimized epithermal neutron beam can be produced by moderating fission neutrons either with a combination of Al and D₂O, or with Al₂O₃. We have designed, installed and tested an Al₂O₃ moderated epithermal neutron beam at the Brookhaven Medical Research Reactor (BMRR). The epithermal neutron fluence rate of 1.8×10^9 n/cm²-sec produces a peak thermal neutron fluence rate of 1.9 to 2.8×10^9 n/cm²-sec in a tissue equivalent (TE) phantom head, depending on the configuration. Thus a single therapy treatment of 5×10^{12} n/cm² can be delivered in 30-45 minutes. All irradiation times are given for a BMRR power of 3 MW, which is the highest power which can be delivered continuously.

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MATERIALS AND METHODS

The design, construction, installation and testing of this epithermal neutron beam was done in a collaborative project between Brookhaven National Laboratory (BNL) and Idaho National Engineering Laboratory (INEL). Installation and testing of the Al_2O_3 filter arrangement was done at the east irradiation facility of the BMRR (see Fig. 1). The 5 MW (3 MW continuous power) reactor was designed and built in 1959 primarily for use as a neutron source for medical and biological experiments⁸. A cross-section of the irradiation facility is shown in Fig. 2; regions A and B are housed in a 20 ton shutter which was designed so that it could be easily removed for the installation and testing of various filters and/or moderators. Removal of the shutter (in 2 parts) is accomplished with an overhead crane, in ~1 hour. This flexibility has been fully utilized in these experiments, as a number of permutations have been evaluated in arriving at the "final" configuration^{4,6}. Region C has 2 empty aluminum tanks, which can be filled with liquids (such as D_2O), or solid "microspheres" (such as Al_2O_3), with a combined thickness of 12 cm.

An effort has been made to compare calculated values of beam parameters with experimental measurements of the same parameters at each step in the filter installation. Calculations were made at INEL with one-dimensional (cylindrical) models for the SCAMP and the ANISN discrete ordinate codes. This combination of codes couples the cross section library of SCAMP (ENDF/B-V) with the high order scattering and secondary gamma production of the ANISN model. In addition, final design and "as-built" analyses were carried out with a 2 dimensional model using the DOT 4.3 code and the Bugle-80 ENDF/B-IV cross section library. Cylindrical (r-z) geometry was used, with the z axis coinciding with the beam axis¹⁸.

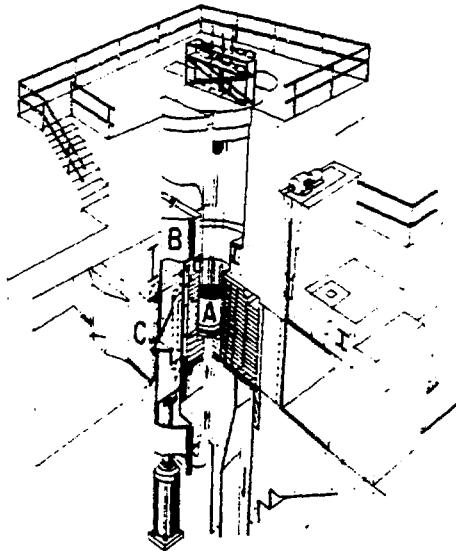


Fig. 1. Cross sectional view of the Brookhaven Medical Research Reactor, showing the core (A), removable shutter (B), and one of two identical patient irradiation facilities (C). The current configuration has an epithermal neutron beam in the east irradiation facility, and a thermal beam in the west facility. Maximum reactor power is 3 MW.

As-Built Al_2O_3 Filter Installed in BMRR

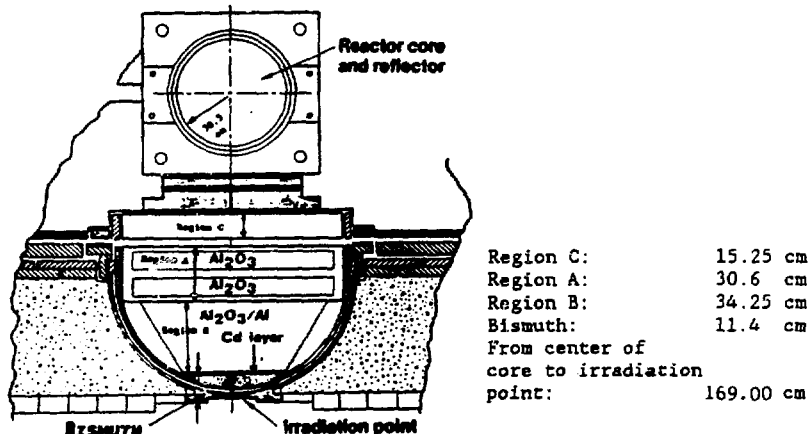


Fig. 2. Cross section of epithermal neutron beam facility showing reactor core and filter/moderator arrangement in beam shutter for the "current" configuration in Table I.

Various shutter configurations were evaluated, from a completely empty shutter, to the reference case "R" in which 18 cm D_2O served as the moderator, as had been installed in 1965 to produce a Cd filtered epithermal neutron beam^{1,2}, to the "final" configuration of 45.7 cm Al_2O_3 , 19.7 cm Al, 11.4 cm Bi and 0.051 cm Cd (see also Ref. 18).

Measurements of total dose to tissue, fast neutron dose, γ dose, and thermal, epithermal and fast neutron fluence rates, have been made at each stage in the filter installation, and compared to calculated values. Paired ionization chamber measurements (tissue equivalent [TE] and graphite- CO_2 chambers) were used to evaluate the total dose, and fast neutron and γ components of the mixed radiation fields. Threshold and fission foils were also used to evaluate the fast neutron dose, and ^7LiF thermoluminescent dosimeters were used to verify γ -dose measurements. Gold, sodium and copper foils were used to measure thermal and resonance neutrons. Thermal neutron depth-flux curves were measured in a 16.6 x 23 cm cylinder filled with TE fluid^{1,2}. Details of the dosimetric techniques are given in Ref. 14. Fast neutron dose distributions in the phantom were obtained from the measured Kerma dose, and attenuated as a function of depth as calculated¹⁸. The γ dose values in the phantom were obtained from values measured previously with similar thermal neutron distributions². Measured values (used in this paper) were ~30% higher than theoretical calculations values¹⁸.

RESULTS

The results of 8 shutter configurations are summarized in Table I, varying from a completely empty shutter (configuration 1) to the "current" geometry in which a total of 65.4 cm of Al_2O_3 and Al was used to moderate the beam. The relative fast neutron and γ contaminations in the new beam have been reduced to ~10% of the contaminations present in the old Cd filtered epithermal neutron beam developed in 1965 (configuration "R").

The various beam parameters for the current configuration are summarized in Table II*. Assuming a 1-to-1 correspondence between incident epithermal neutrons, and thermal neutrons generated at depth in tissue (a conservative assumption), 45 min would be needed to deliver a therapeutic fluence of 5×10^{12} thermal neutrons/cm², which is within the suggested time limit of 60 min as recommended by the Physics Committee at the 1986 Workshop on NCT³.

Three different configurations were evaluated for irradiating a TE phantom head in the epithermal beam (irradiation point, Fig. 3). These were: (1) no added filtration at the phantom, (2) 0.5 mm Cd filter added, and (3) 1 mm ⁶Li added. Results of the thermal fluence rate measurements are given in Fig. 3 for a reactor power of 1 MW. It can be seen that by increasing the filtration at the point of irradiation, the peak/surface ratio increases from 2.8 to 4.2 to 4.9 for the 3 geometries respectively, while at the same time the peak intensity is reduced from 2.8 to 1.9 $\times 10^8$ n/cm²-sec. Depending on experimental conditions, increased peak/surface ratios may be useful for providing increased skin sparing for situations in which it is desirable to leave the skin and skull intact. As described in the discussion, it is anticipated that these flux densities will restrict irradiation times to ≤ 30 min.

For the purpose of this symposium, effective dose rate (rad \times RBE) curves have been plotted on semi-log scales for the ¹⁴N(n,p)¹⁴C, and ¹⁰B(n, α)⁷Li reactions, as well as for the fast neutron (N recoil) and γ -dose (from the reactor, and H(n, γ)D reactions). As prescribed by the symposium organizers, RBEs of 1.6 have been used for the nitrogen and fast neutron (N and H) dose, and 2.3 for the ¹⁰B dose; also, a nitrogen concentration of 1.84% was assumed for brain, as opposed to the value of 2.6% reported for "standard man".

Results are given in Fig. 4 for the current filter configuration shown in Table I and summarized in Table II (65.4 cm Al_2O_3 and Al). for the case where 0.5 mm Cd was used to filter the epithermal beam incident upon the 16.6 \times 23 cm head phantom. As noted by the increased peak/surface (P/S) flux ratio, some degree of filtration at the point of irradiation is probably desirable, for increased skin-sparing. In addition, the same parameters have been graphed for the depth-flux curves obtained with 1 mm ⁶Li filtration (Fig. 5). Here the large P/S value of 4.9 and the peak flux density at 2.0 cm depth may prove useful under certain situations. Parameters requested for comparison at this workshop (advantage depth, etc.) are summarized in Table III for the two beams.

*Parameters are given in Table II for a reactor power of 1 MW, as measured. Results can be extrapolated linearly to the maximum power of 3 MW.

TABLE I. Calculated and Experimental Values for beam parameters for various shutter configurations; BMRR, 1 MW.								
Configuration Region	1	2	3	4	R	8	BNL-Inter. config.	Final config.
C	0	0	0	12 cm D ₂ O	12 cm D ₂ O	12 cm D ₂ O	0 cm D ₂ O	0 cm D ₂ O
A	0	16.5cm Al	17.8cm Al	16.5cm Al	2.5cm Al	17.8cm Al	17.8cm Al	8.25cm Al
	0	0	9.6cm D ₂ O	0	6 cm D ₂ O	9.6cm D ₂ O	9.6cm D ₂ O	22.86cm Al ₂ O ₃
B	0	0	0	0	0	0	11.42cm Al	11.42cm Al
	7.6cm Bi	7.6cm Bi	7.6cm Bi	7.6cm Bi	15.6cm Bi	7.6cm Bi	22.86cm Al ₂ O ₃	22.86cm Al ₂ O ₃
							11.4 cmBi	11.4cm in Bi
							0.051cm cd	0.051cm cd
Fast n-KERMA rads/min								
SF-ANISN	3272	1166	98.8	86.1	48.9	10.4	1.03	0.600
FW-ANISN	1410	553	59	-	45	-		
FW-DOT			55.1					1.032
J K-E(exp)	1070	360	54	51	27	10.1		-
SARAF (exp)					26	8.25	2.26	1.75
INEL (exp)								1.68
Gamma-KERMA rads/min								
SF-ANISN	30.12	28	24.3	26.7	7.76	20.2	0.733	0.463
FW-ANFW-DOT			19.9					0.122
J K-E(exp)	40.8	40.8	28.7	27.5	9	24		-
SARAF (exp)					8.3	20.8	0.81	0.4 (continued)

TABLE I. (cont.)

[illegible]

TABLE I. (cont.)

Configuration Region	1	2	3	4	R	8	BNL-Inter. config.	Final config.
C		0	0	12 cm D ₂ O	12 D ₂ O	12cm D ₂ O	0 cm D ₂ O	0 cm D ₂ O
A	0	16.5cm Al	17.8cm Al	16.5cm Al	2.5cm Al	17.8cm Al	17.8cm Al	8.25cm Al
	0	0	9.6cm D ₂ O	0	6 cm D ₂ O	9.6cm D ₂ O	9.6cm D ₂ O	22.86cm Al ₂ O ₃
B	0	0	0	0		0	11.42cm Al	11.42cm Al
	7.6cm Bi	7.6cm Bi	7.6cm Bi	7.6cm Bi	15.6cm Bi	7.6cm Bi	22.86cm Al ₂ O ₃	22.86cm Al ₂ O ₃
							11.4cm in Bi	11.4 cm in Bi
							0.051cm cd	0.051cm cd
Gamma-Kerma/ epi flux cGy/(n-cm ⁻²) (XE-11)								
SF-ANISN	1.82	2.78	3.86	5.11	2.57	12.75	1.48	0.99
FW-ANISN								
FW-DOT								0.492
J K-E(exp)	14.35	26.15	34.16	39.53	11.9			
SARAF (exp)					11.0	28.5	2.056	1.123

*FW-DOT calculations are for 6 inch Bi, DOT 17 of INEL report.

SF : S. Fiarman

FW : F. Wheeler

J K-E: J. Kalef-Ezra

Saraf: S.K. Saraf

INEL : Idaho National Engineering Laboratory

TABLE II. Summary of beam parameters for current "optimized" epithermal beam

Power	3 MW
Epithermal neutron flux density* (n/cm ² -sec)	1.8×10^9
Thermal neutron flux density (peak flux at ~2 cm depth in phantom; n/cm ² -sec)	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)
Fast neutron dose in air (Kerma)*	5.3 rads/min.
γ -dose in air (Kerma)*	1.2 rads/min.
Fast neutron Kerma/epithermal neutron	4.87×10^{-11} rad/(n-cm ²)
γ -Kerma/epithermal neutron	1.12×10^{-11} rads/(n-cm ²)
Fast neutron Kerma/thermal neutron (no added filtration)	3.15×10^{-11} rads/(n-cm ²)

*measured at center of irradiation port face

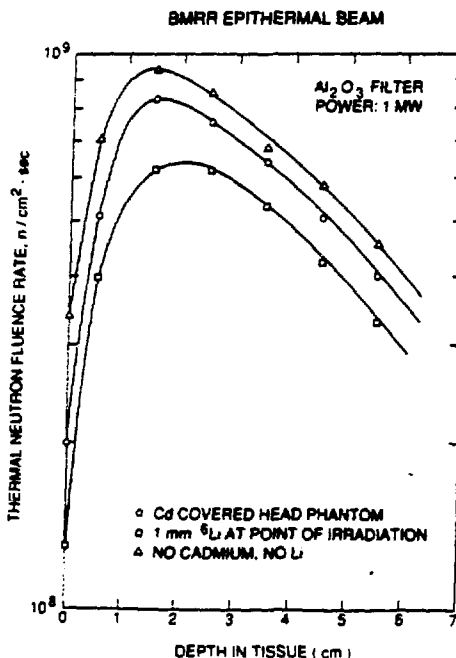


Fig. 3. Thermal neutron flux densities generated in tissue equivalent head phantom (16.6 x 23 cm cylinder) using an incident epithermal beam (current configuration; BMRR power 1 MW).

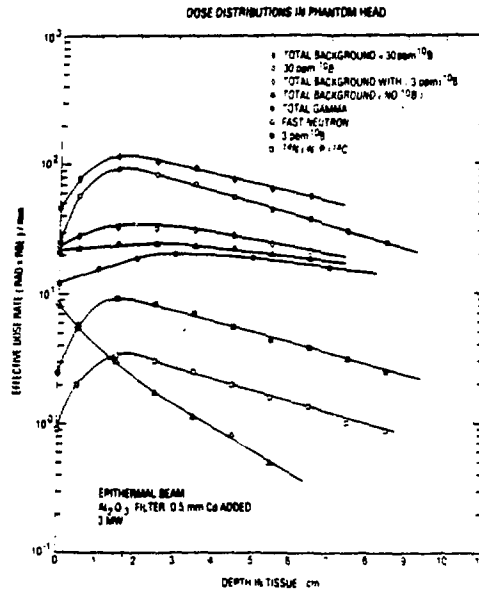


Fig. 4. Effective dose rate for the "current" epithermal neutron beam configuration at the BMRR (Power = 3 MW). A Cd filter 0.5 mm thick was added at the point of irradiation. Values for RBE, ^{14}N and ^{10}B content were as prescribed for this symposium.

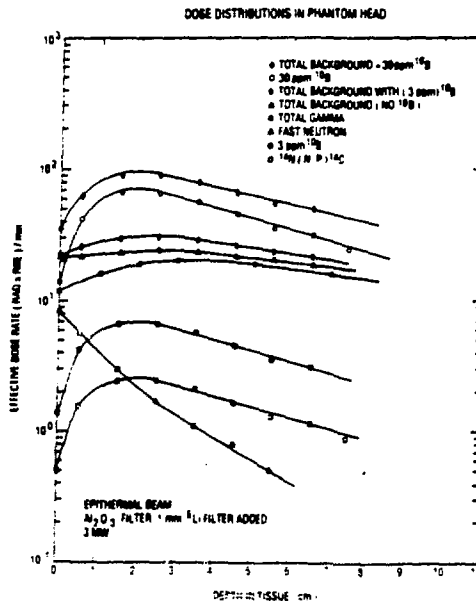


Fig. 5. Same as figure 4, but with a 1 mm thick ^6Li filter added at the point of irradiation.

TABLE III

Beam parameters for the 65.4 cm ($\text{Al}_2\text{O}_3 + \text{Al}$) moderated beam, for comparison at this Workshop (maximum and minimum advantage Depth and Dose Rate).

0.5 mm Cd added Filtration	
min. advantage depth	9.2 cm
max. advantage depth	11.1 cm
Advantage Depth Dose Rate	3.6 (radxRBE)/min
1.0 mm ⁶ Li added Filtration	
min. advantage depth	9.4 cm
max. advantage depth	11.0 cm
Advantage Depth Dose Rate	3.1 (radxRBE)/min

DISCUSSION

For the purpose of beam comparison for this symposium, it was requested that plots of beam components be made on semi-log scales as in Figs. 4 and 5. However, biological response is more readily conceptualized with a linear scale than with a logarithmic ordinate scale of physical radiation dose. Thus for the purpose of evaluating the significance of depth-dose curves in this discussion, data have been developed on a linear scale. This has been done for the case of 1 mm⁶Li added filtration, in Fig. 6. Here the adventitious radiation components (N, H, and γ) are plotted along with the total (N+H+ γ) as well as the distribution from 3 ppm ¹⁰B. From Table II it can be seen that the reactor-produced γ is negligible compared to that from the H(n, γ)D reaction, so that the N and γ curves represent unavoidable contributions to normal tissue dose produced by the thermal neutron distribution. The contribution from fast neutron dose (H) could be reduced by further moderation, but at the cost of reduced beam intensity. Calculations indicate that the fast dose H could be reduced relative to epithermal neutrons by ~ 4 (to $\sim 2.4 \times 10^{-11}$ rad/epithermal neutron) by utilization of the now empty "C" region, with a concomitant reduction of epithermal neutron fluence rate by ~ 4 . Such a reduction in H dose is graphed in Fig. 6, where it can be seen that the peak dose to normal (boron free) tissue (at ~ 2 cm) would then be reduced by $\sim 5\%$. The net reduction in total normal tissue dose due to the 50% reduction in fast neutron dose is insignificantly small, and becomes increasingly so as the presence of boron is introduced in normal tissues.

Fig. 7 illustrates the situation in which boron is present in tissue. Total-dose curves are shown for 30, 15, 6 and 3 ppm ¹⁰B. If it is assumed that 30 ppm is in tumor and 3 ppm is in normal tissue (i.e., a tumor-to-normal tissue or "T/N" concentration ratio = 10), reducing the fast neutron dose component by a factor of 2 (to 2.4×10^{-11} rad/epithermal neutron) would reduce the maximum dose to normal tissue by less than 4%. The effect of reducing the fast neutron dose is included in the 3 ppm curve where such effect would be maximum, but has been ignored for the higher B concentrations, as the significance is minimal. Since a change in Therapeutic Gain (tumor dose/maximum normal tissue

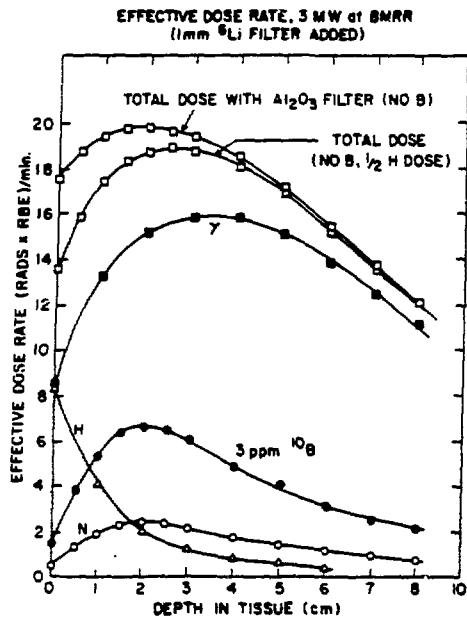


Fig. 6. Same parameters as Fig. 5, but plotted on a linear scale. In addition, the effects of reducing the fast neutron dose (H) by a factor of 2, to 2.4×10^{-11} rad/epithermal neutron, is shown in the "total dose" curves.

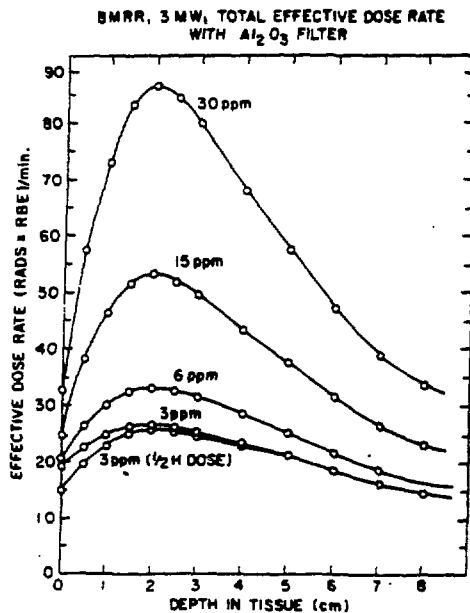


Fig. 7. Total Effective Dose Rate curves are shown for the same parameters as Fig. 5 and 6 but with 30, 15, 6 and 3 ppm ^{10}B added to tissue.

dose) of at least 10% is necessary to produce demonstrable changes in local control, a reduction of 4% or less in the maximum dose to normal tissue would not be worthwhile, and would have even less significance for T/N ratios <10. With present compounds, T/N ratios in excess of 5 are not expected.

It should be emphasized here that we believe the parameter of importance is the Therapeutic Gain (TG). The consensus is that for the treatment of brain tumors, a tumor dose 50% in excess of normal tissue dose is needed to approach curative levels (i.e., $TG = 1.5$). Since TGs in excess of 1 are not available with conventional therapy (as tumor dose is limited to the tolerance of normal tissues supporting the tumor) the potential ability of NCT to deliver TGs of from 2 to 3 as indicated in Fig. 7 becomes important.

Radiation therapy is based on the thesis that the dose to normal tissue will be raised to the tolerance levels, in the hope of achieving toxic levels in tumor. The dose to normal tissue, as well as therapeutic gain, can be evaluated from Fig. 7, where tumor and normal tissue dose can be evaluated based on depth in tissue and boron content. It appears unlikely that radiation oncologists would deliver whole-brain irradiation in a single effective dose exceeding 1000 (rad x RBE). Assuming 30 ppm in tumor, and T/N = 5, therapy in a single dose would take ~30 min. as evaluated from Fig. 7. With fractionated therapy, effects of edema would be reduced and total dose could be increased. A point of major importance in NCT is that the ability to target ^{10}B selectively to tumor potentially provides beam localization on a cellular level. In view of the local recurrence characteristic of malignant brain tumors, it is anticipated that large irradiation fields will be used (i.e., ≥ 10 cm diameter fields), in order to include areas of potential recurrence in the treatment volume. Protection of normal tissue should come from clearance or restriction of ^{10}B from these tissues (i.e. T/N ratios ≥ 5).

It has been suggested that 24 keV neutrons could be useful for clinical applications of NCT¹⁰. The dose per incident neutron would be $\sim 24 \times 10^{-11}$ rads/incident neutron, as opposed to the value of 4.9×10^{-11} rads/incident neutron for an Al_2O_3 moderated beam with a 1/E spectral distribution. Given the dose distribution shown in Fig. 6, it is clear that if the fast neutron (H) dose is increased by a factor of ~5 (as it would be for the 24 keV beam), the dose to surface tissue would be ~50 (rad x RBE)/min. This would reduce the therapeutic gain by a factor of 1.5, for the situation in which tumor has 30 ppm ^{10}B and T/N = 5. Such a reduction in TG is significant and may be unwarranted, as intense beams of 1/E neutrons are now available, as described in this paper. Further, the distribution of thermal neutrons generated by 1/E, 2 keV and 24 keV neutrons in water has been reported to be similar, in that the location of peak thermal flux density and depth of penetration does not vary significantly; thus the increased surface dose from 24 keV neutrons may not be offset by increased depth of penetration⁹. The above analysis is based on the assumption of a 1 to 1 correspondence between incident neutron intensity and thermal neutrons generated at depth in a head phantom. Table IV shows that this assumption is expected to be valid, for 24 keV neutrons.

Three important points should be noted from the above discussion:

1. The maximum dose to normal tissue occurs at 2 cm depth for all conditions (i.e., with or without boron). Thus one would expect brain tissues at ~2 cm depth to be the "critical" organ.

TABLE IV. Peak and depth at peak thermal flux density for mono-directional neutron beams with 1.0 n/cm^3 (from ref. 17)

Source Energy	Beam Diameter (cm)	Medium	Depth at Peak (cm)	Thermal Flux at Peak (n/cm^3)
29 keV	16.6	Tissue Eq.	3.4	1.94
1.4 eV			1.9	3.29
1/E			2.6	2.56
29 keV	10.0	Tissue Eq.	3.4	1.11
1.4 eV			1.9	2.26
1/E			2.4	1.74

2. The biological half-life for BSH in humans has been found to be from 6-10 hours⁷ to a few days¹⁸, when administered slowly. These data are supported by those obtained following i.v. infusion in rodents¹⁵. Therefore it is unlikely that tumor boron concentrations will be reduced during therapy by amounts in excess of ~5%. In addition, the dimer form of BSH (BSSB) has been shown to have a longer biological half-life, and to produce tumor-boron concentrations of about twice that found with BSH¹⁵. Thus it is quite likely that BSSB will be found advantageous for new US clinical trials on BNCT for malignant gliomas. In any case, since it is anticipated that therapy will be delivered in multiple fractions, as recommended by the recent International Workshop on Clinical Aspects of NCT¹³, time per fraction should be <30 min.

3. For tumors within 1-2 cm of the midline of the head (~7 cm depth), it is expected that bilateral (opposed port) irradiations will be used. Previous studies have shown that with an optimized epithermal beam, 35 ppm ^{10}B and T/N = 10, Therapeutic Gain (TG) is equal to 3.6 over the central 10 cm of a phantom head². With the current example in which 30 ppm is assumed in tumor and T/N = 5, the use of bilateral irradiations would raise the TG at the midline (7 cm) from ~1.2 to 2. At the BMRR, bilateral irradiations would be carried out with a 2.5 cm thick collimator at the point of irradiation. The fall-off in air of the beam intensity at 2.5 cm from the port face is shown in Fig. 8 to be about 10%.

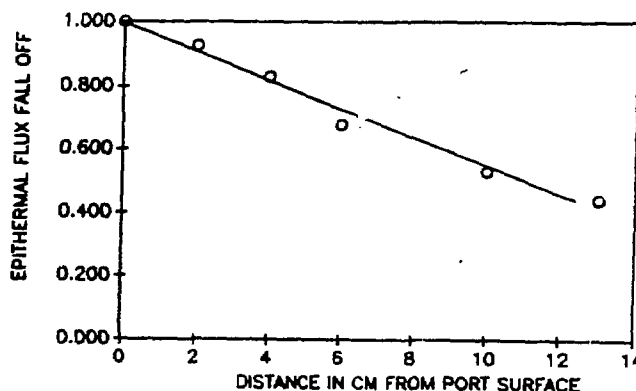


Fig. 8. Fall off in air of the epithermal neutron flux density along the beam axis.

SUMMARY

NCT is a binary system, in which ^{10}B is physiologically targeted to tumor, and then allowed to interact with thermal neutrons generated in the treatment volume by an externally applied neutron beam. Consequently, an unusually large number of parameters obtain, which bear on the resultant Therapeutic Gain (TG). However, a perusal of these data, particularly Fig. 7, indicate that significant increases in TG will be obtained if the absolute amount of ^{10}B can be increased above 30 ppm. For example, increasing ^{10}B concentration in tumor to 45 ppm would increase TG by ~33% (with a T/N = 5). A similar increase in TG would follow an increase in T/N from 5 to 10. Those associated with the development of boron compounds for NCT feel that such developments are within reach.

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