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WORKSHOP
on
NEUTRON CAPTURE THERAPY

January 22-23, 1986

R.G. Fairchild and V.P. Bond, Editors

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Brookhaven National Laboratory

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PREFACE

Since clinical trials of Neutron Capture Therapy (NCT) terminated in the U.S. in 1961, definite improvements have been brought about in the delivery of both boron and neutrons to tumors. Furthermore, potentially optimal conditions for NCT may soon be in hand due to the anticipated development of band-pass filtered beams relatively free of fast neutron contaminations, and of broadly applicable biomolecules for boron transport such as porphyrins and monoclonal antibodies. Consequently, a number of groups in the U.S. are now devoting their efforts to exploring NCT for clinical application. The purpose of this Workshop was to bring these groups together to exchange views on significant problems of mutual interest, and to assure a unified and effective approach to the solutions. The following list of questions was distributed prior to the Workshop, and serves to summarize the major problems for which solutions are being sought. Following the scientific program (Part I), small working groups met in an effort to obtain a consensus regarding problems and approaches; their deliberations and recommendations are summarized in Parts II and III.

Questions to be Considered

It can be assumed that, if enough ^{10}B and thermal neutrons can be delivered to a tumor, for example an intracranial malignant glioma, the tumor can be controlled. For instance, with a ^{10}B concentration of 40 μg/g tumor tissue and a thermal fluence of $\sim 5 \times 10^{12}$, with a resulting effective dose of ~5000 rads x RBE, remission might be obtained with a single treatment session. The basic question then is -- in view of the major recent developments in neutron beam generation, control of neutron energy distribution, compound selectivity for the tumor, biological and radiobiological understanding, and clinical application that have occurred since the early unsuccessful trials in patients -- can such a dose be delivered to the tumor with sparing of normal tissues sufficient to ensure success of the overall procedure? The answer lies in a thorough knowledge of requirements and capabilities in the areas of medicine, pharmacology, biology, radiobiology, and physics, with consideration of the compromises that can be made to optimize each step and factor in the overall procedure in order to obtain the best chances for success.

More specifically, a number of questions must be considered, and either answered or addressed in terms of what must be done to obtain the answers. Some principal, interrelated questions are listed below.

1. Is a compound now available that localizes in the tumor selectively, uniformly, in adequate amounts, and for a sufficient time period, with clearance from the blood and normal tissues?

2. Assuming that the answer to the first question is affirmative, is it better to complete the entire treatment in a single session, or to distribute it in several sessions over a period of days to weeks? The answer to this depends on a number of factors, included in separate questions below.

3. From accumulated radiotherapeutic and radiobiological knowledge and experience, is it more desirable to treat in a single session or over a long period? Considering the predominantly high-LET radiation at the tumor and the lower-LET radiations delivered to intervening normal tissues, how much advantage can be expected from fractionation?

4. Are "hypoxic cells" in the tumor a serious consideration, in terms of the "oxygen enhancement ratio"? Before debulking? After debulking?

5. What anatomical and physiological factors resulting from the presence of the tumor may affect the uniform uptake of a ^{10}B-containing compound? Hypoxic areas resulting from poor blood supply? With or without debulking? With a single treatment? With multiple treatments?

6. Do anaplastic and more differentiated tumors, or regions of tumors, take up the boron compound equally well?

7. Is it more advantageous to perform a craniotomy and direct a thermal (or "soft" epithermal?) beam at the surface of the previously debulked brain volumes? Or is it equally efficacious to use tailored "epithermal" beams applied externally without surgical procedures beyond the reflection of intervening skin? In either case, is the optimal duration of a single treatment of the order of minutes or several hours?

8. Do repeated craniotomies for protracted exposure carry little additional hazard to the patient, and if so, how many might be tolerated?

9. Is fractionated therapy advantageous or necessary to minimize postoperative brain edema? With debulking? Without it?

10. What is the extent of medical facilities, and their nearness to the neutron source, required if craniotomies are to be performed? If they are not performed?

11. How rapidly can capillary growth or reconstitution occur in an irradiated tumor bed?

12. Does sudden destruction of a large tumor mass in the brain present serious dangers? Gross hemorrhage? Unsatisfactory resolution in the residual mass? Is this an argument for fractionation?

13. What role does the blood-brain barrier play in the overall procedure? To what degree is it compromised by irradiation, and how soon is it reconstituted, as a function of dose?

14. Protons with energies of about 500 eV or less are evidently incapable of producing ionizations. Do such protons cause detectable biological effects?

15. Certainly with use of an external neutron beam, an "epithermal" beam is superior to a thermal beam. Is this also true if a craniotomy is performed?

16. An ideal beam would be one that delivered the needed fluence of thermal neutrons to the treatment volume, with the higher-energy neutrons concentrated as much as possible below the knock-on proton cutoff, where the biological effect would be minimal or absent. The relative number at higher energies should be curtailed drastically. To what degree is it possible to approach such an ideal by controlling the energy of the incident neutrons, by the use of a band-pass filter, or by combinations thereof?

17. Almost any procedure to "clean up" a fast or epithermal neutron beam to bring it closer to the ideal results in a loss of neutrons. What is the fractional neutron loss, in approaching as nearly as possible the ideal

neutron energy distribution? How does this translate into the size of the neutron source (reactor power) needed for a given fluence of thermal neutrons delivered to the tumor volume? On the basis of the number of fractions desirable or tolerable, to be determined by clinical and radiobiological considerations, what must the reactor power rating be to permit satisfactory therapy?

18. From recent clinical trials and perhaps other information, how strong a case can be made now that BNCT, with currently available compounds, is in fact beneficial to patients with malignant gliomas?

19. What compounds (e.g., porphyrins, monoclonal antibodies) or procedures are under study and development? How much promise do these "third-generation" approaches appear to have?

20. If one glioblastoma is controlled by BNCT or other means, what is the probability that a similar tumor will appear soon in another region of the brain?

21. Are enough data available to define which form of $Na_2B_{12}H_{11}SH$ is "optimal" (i.e., monomer, dimer, or dimer monoxide)?

22. Which filter arrangement should be evaluated: Fe, Sc, Al-S, or a combination thereof?

23. Is it clear that the proton-recoil dose from a 24-keV beam reduces its attractiveness for use with BNCT?

24. Does the ^{10}B compound go to every cell in the tumor in non-necrotic areas? How uniformly?

Even though some of the above questions must be addressed by physicians and others by physicists, radiobiologists, or pharmacologists, they are provided in one listing because of the high degree of interdependence among the various factors. The gamut of factors must be kept in mind when any question is addressed, particularly from the standpoint that the evaluation of one question may bear on or even provide definitive input data necessary for a quantitative evaluation of other factors.

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Dr. André Wambersie (Catholic University of Louvain, Medical Faculty, Brussels, Belgium) performed invaluable functions by chairing the joint working group, and by presenting an independent overall evaluation of NCT.

This Workshop was sponsored by the United States Department of Energy, with additional support from the Callery Chemical Co., Callery, PA, and Associated Universities Inc., Upton, NY.

The proceedings were prepared for publication with the most able assistance of Ms. Margaret Dienes, Technical Editor, BNL.

Workshop Cochairmen

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Local Organization Committee

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CONTENTS

Preface iii

I. SCIENTIFIC PROGRAM:

Introductory Remarks .....M. Goldhaber 1
Medical Aspects of Boron-Slow Neutron Capture Therapy .....W.H. Sweet 3
The Radiobiology of Boron Neutron Capture Therapy .....V.P. Bond 22
Intermediate-Energy Neutron Beams from Reactors
for NCT .....R.M. Brugger, T.J. Less, and G.G. Passmore 32
Research Related to Boron Neutron Capture Therapy at
The Ohio State University .....R.F. Barth et al. 42
Studies at MIT on the Biodistribution of B-10 Compounds and
Production of Epithermal Neutrons .....G.L. Brownell and C. Carney 49
A Clinical Trial of Neutron Capture Therapy for Brain
Tumors at New England Medical Center and the Massachusetts
Institute of Technology .....R.G.A. Zamenhof et al. 55
The NCT Program at Nuclear Medicine, Inc. .....D.J. Noonan 77
An Intermediate-Energy Neutron Beam for NCT
at MURR .....R.M. Brugger, T.J. Less, and G.G. Passmore 83
The Power Burst Reactor Facility as an Epithermal Neutron
Source for Brain Cancer Therapy .....F.J. Wheeler 92
Neutron Capture Therapy at Brookhaven National
Laboratory .....R.G. Fairchild et al. 106
The Design of Filtered Epithermal Neutron Beams for BNCT..R.C. Greenwood 123
A Plan for Neutron Capture Therapy Studies with a 2.5-MeV
Proton Beam on ^{7}Li .....J.W. Blue et al. 143
Aspects of Implementation of NCT .....J.L. Russell, Jr. 155
Future Boronated Molecules for Neutron Capture
Therapy .....A.H. Soloway, F. Alam, and R.F. Barth 162
Distribution of Sulfyhydryl Boranes in Mice and Rats.D.N. Slatkin et al. 173
Medical and Biological Requirements for Boron Neutron Capture
Therapy .....R. Gahbauer et al. 178
Clinical Aspects of Boron Neutron Capture Therapy ...J.H. Goodman et al. 184

II. COMMITTEE PRESENTATIONS AND DISCUSSIONS 188

III. COMMITTEE RECOMMENDATIONS 205

Author Index 207
Participants in the Workshop 208

INTRODUCTORY REMARKS

M. Goldhaber
Brookhaven National Laboratory

Disintegration of boron-10 by slow neutrons was observed more than 50 years ago. In the first experiments, with Chadwick, we observed the disintegration with an ionization chamber (see Figure 1). Because of a discrepancy with the nuclear masses as known at that time, we thought that boron-10 bombarded with slow neutrons would disintegrate into three particles, because the energy seemed too low for a two-body disintegration. Fermi and collaborators found the same reaction a short time later and, not worrying about masses, suggested that only two particles are emitted. Later, with H.J. Taylor, we used photographic emulsions to decide whether two or three particles are emitted. We found only two particles, confirming Fermi's guess (see Figure 2). It needed fast neutrons to produce three particles. The energy missing in this reaction gave us an important hint, leading to a revision of the nuclear mass scale.

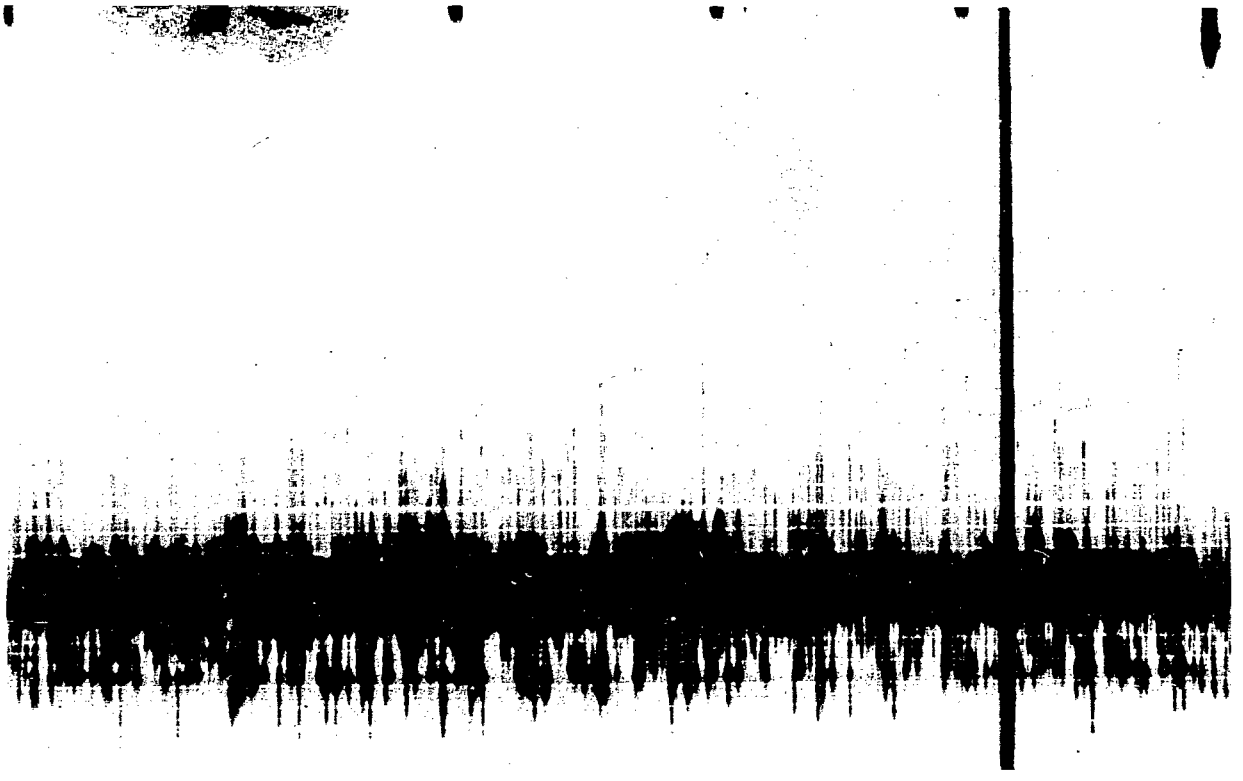
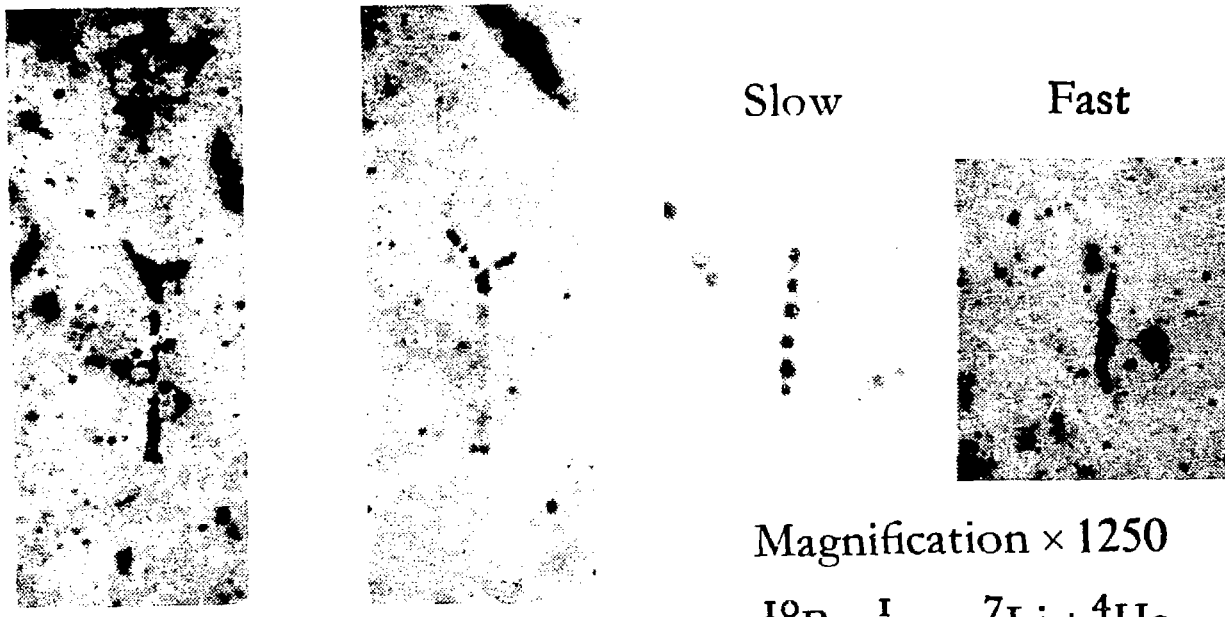


Figure 1. First observation of disintegration of boron by slow neutrons (December 10, 1934). Oscillograph traces (about one-half minute) from ion chamber coated with boron.



(*Photographed by* H. J. TAYLOR *and* M. GOLDHABER.)

Figure 2. Tracks in photographic emulsion. A photographic plate, impregnated with boron, was exposed to the action of slow and fast neutrons. Disintegration of boron according to the equations given produces tracks of developable grains in the emulsion. (From Rutherford's last book, "The New Alchemy", Cambridge University Press, 1936).

When I came to the University of Illinois in 1938, it seemed that the disintegration of boron by slow neutrons could be of some value in cancer treatment, provided one could get the boron into a tumor. As a demonstration experiment, Kruger and Hall studied the development of tumors in mice by transplanting tumors from one mouse to another, with or without soaking the tumors in a boric acid solution. The tumors that were soaked in boric acid solution before transplantation did not develop further when the mouse was treated by slow neutrons, whereas the control tumors did. Since then, many people have taken up this study. Right from the beginning the crucial question was: Can you get the boron to go preferably to the tumor cells? And this is the point of this workshop, which I'm sure you will discuss sufficiently to go back with a feeling for the important next steps.

Since it seems desirable to bombard a patient with neutrons, it might be worth while to use resonance scatterers such as Mn, Co, etc., which would enhance the neutron spectrum at a few hundred electron volts.

Medical Aspects of Boron-Slow Neutron Capture Therapy

W.H. Sweet, M.D., D.Sc., D.H.C.
Massachusetts General Hospital
Neurosurgical Service
Boston, MA 02114

ABSTRACT

Earlier radiations of patients with cerebral tumors disclosed the need: 1) to find a carrier of the boron compound which would leave the blood and concentrate in the tumor, 2) to use a more penetrating neutron beam, and 3) to develop a much faster method for assaying boron in blood and tissue. To some extent #1 has been accomplished in the form of $Na_2 B_{12} H_{11} SH$, #2 has yet to be achieved, and #3 has been solved by the measurement of the 478-keV gamma ray when the ^{10}B atom disintegrates following its capture of a slow neutron. The hitherto unreported data in this paper describe through the courtesy of Professor Hiroshi Hatanaka his studies on the pharmacokinetics and quality control of $Na_2 B_{12} H_{11} SH$ based on 96 boron infusions in 86 patients. Simultaneous blood and tumor data are plotted here for 30 patients with glioblastomas (Grade III-IV gliomas), illustrating remarkable variability. Detailed autopsy findings on 18 patients with BNCT showed radiation injury in only 1. Clinical results in 12 of the most favorably situated glioblastomas reveal that 5 are still alive with a 5-year survival rate of 58% and the excellent Karnofsky performance rating of 87%. For the first time evidence is presented that slow-growing astrocytomas may benefit from BNCT.

1. INTRODUCTORY STUDIES

Treatment at the MIT nuclear reactor from 1959 to 1961 of 16 patients with malignant brain tumors after i.v. administration of p-carboxybenzene boronic acid and of 2 more after intracarotid injection of sodium perhydrodecaborate was followed by death of all 18 from 10 days to 12 months. Post-mortem examination in 14 of these patients revealed varying amounts of residual tumor in all but two, in whom none could be found. (1) There was the additional striking unexpected finding in 10 of the 14 patients of radiation damage to the blood vessels of the normal brain. This ranged from swelling of the endothelial nuclei with perivascular lymphocytic cuffs to eosinophilic hyalinization of all layers, disappearance of cellular elements in the blood vessels, and occlusion of their lumens.

This radiation produced a destructive form of semi-solid coagulation necrosis of all parenchymal and vascular elements which increased with the passage of time following radiation. The type of change differs markedly from the liquefactive events characteristic of necrosis from a purely vascular infarct. These changes were worst in the 2 patients receiving sodium perhydrodecaborate, which was given via the internal carotid route, with associated higher blood and tissue levels at the time of irradiation. The paracarboxybenzene boronic acid was given i.v. The vascular occlusions led to fatal ischemic necrosis of the normal brain. In the 4 patients not showing such extensive vascular radiation injury, death was due to recurrent tumor in 2 of them, bacterial meningitis in one, and massive hemorrhage following on staphylococcal meningitis in the 4th. Fig. 1 is from our case 8, who lived usefully for 10 of the 11-1/2 months she survived after her BNCT. These 2

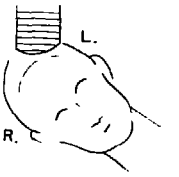
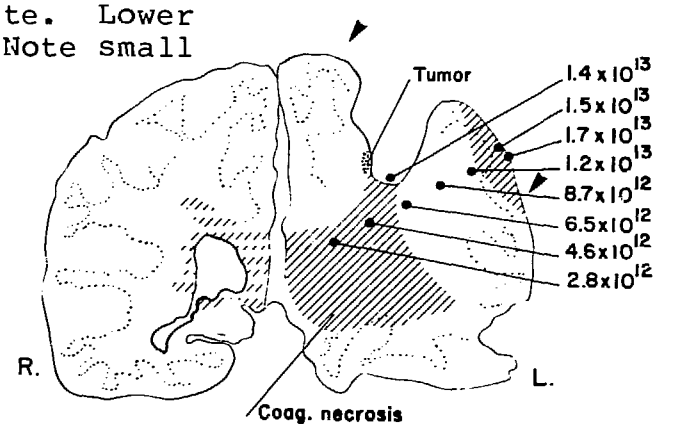
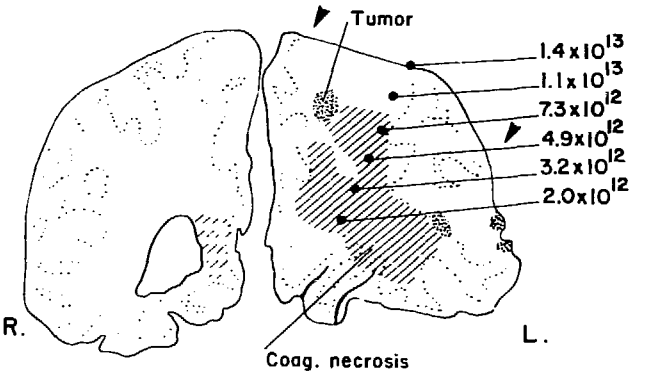


Fig. 1
Line diagram of 2 coronal sections. Post-mortem Case #8. Position of collimator indicated at top. Hatched area: complete radiation necrosis. Semi-hatched area: incomplete necrosis. Arrows at brain surface mark edges of collimator. Upper section through operative site. Lower section: 1.5 cm posterior. Note small zones of residual tumor.





coronal sections show the type of slow neutron flux data obtained by Brownell and colleagues from gold wires inserted into the brain. These were removed after the radiation, and the flux was measured in each 1 cm length. We were especially unhappy to see small nests of tumor cells in the part of the field with a high neutron flux. These observations had pointed to 3 crucial needs: 1) A boron compound that would remain incorporated in the brain tumor yet leave the blood so that a high tumor:blood ratio of boron levels would develop. Knowledge of the pharmacokinetics of changes in concentration over time in blood, normal brain, and neoplasm would be essential to selection of the best time for radiation of the favorable compound. 2) Deeper penetration of the neutron beam, necessitating a portal design to provide a major epithermal component thereof. This was so obvious from the first that my original request to the Atomic Energy Commission in 1950 specified development of a method using epithermal plus thermal neutrons - much easier said than done. 3) A much faster method for assay of boron in blood. The maximum permissible neutron flux appears to be determined by the concentration of boron in the blood stream at the time of irradiation, since the dose to the vessel walls in normal brain appears to be the limiting factor.

Important also but not as crucial are detailed microscopic studies of origins of alpha-particle tracks after neutron radiation of histologic sections of tissue loaded with boron to determine distribution of the boron atoms in extracellular spaces and intracellular organelles.

2. SUBSEQUENT STUDIES

Major progress has been made on all of these scores. Albert Soloway and colleagues, suspecting that addition of the bioactive sulfhydryl moiety to the boron cage might lead to firmer binding to tumor, synthesized $Na_2\ B_{12}H_{11}SH$. (2) Comparing the anions $B_{12}H_{12}^{2-}$ and $B_{12}H_{11}SH^{2-}$ with respect to their attachment to bovine serum albumin (BSA) they found binding under physiologic conditions to be strong enough to prevent extensive dialysis from breaking the linkage. Even precipitation by trichloroacetic acid did not break this boron-protein linkage. However, an ion exchange chromatographic column with an anion-type resin totally removed the $B_{12}H_{12}^{2-}$ anion from the protein, whereas the $B_{12}H_{11}SH^{2-}$ anion continued to migrate with its protein component. These findings point to a salt bond type of linkage for $B_{12}H_{12}^{2-}$ and a covalent linkage for the attachment of the $B_{12}H_{11}SH^{2-}$ to the protein molecule. Toxicity studies in rabbits showed that slow intravenous

injections at intervals spread over 5 days of 200 mg ^{10}B/kg in 12 animals and 300 mg/kg in 1 animal were well tolerated. The rabbits were sacrificed at 30 days and no abnormalities were found in any organ. In C3H mice bearing subcutaneously transplanted ependymoblastomas the tumor/blood ratios varied from 1.7 to about 20, averaging 8, following doses of $Na_2 B_{12}H_{11}SH$ from 140-175 μg ^{10}B per g of mouse. The tumor/normal brain ratios varied from 10 to 50 in 12 mice, were 5 and 8 in 2 mice.

Such gross differentials between tumor and normal brain depend upon an intact blood-brain barrier, and we thought it important to determine how soon this is reconstituted after the cerebral insult of the first craniotomy. Soloway et al. found after partial lobectomies in normal dogs that the barrier to tri-isopropanolamine borate is reestablished in 3 weeks. (3) Now with CT scanning after injections of contrast agents a more precise timing of the optimal day to perform the radiation is possible.

The less than perfect knowledge of boron chemistry was responsible for a protracted period of inconsistent results in efforts to purify and stabilize the compound. However, it did become clear that the pure compound concentrates in glioblastoma and other intracranial tumors and to some extent remains there as it leaves the blood. The most complete data we had obtained by 1968 on this score came from a young physician (Dr. W.P.) stricken by glioblastoma. Fig. 2 shows that his initial craniotomy was performed 2 days after the last of 3 daily i.v. doses of boron totalling 11 mg/kg of body weight. Only 3 of his 5 tumor samples showed boron levels above that in blood; the highest tumor level was 1.5 times that in blood. With the earlier explicit urging by him and his wife we carried out a second craniotomy shortly before he seemed likely to die of his bilateral frontal lesion, taking many blood, tumor, and normal tissue samples following 5 daily injections totalling 77mg/kg of ^{10}B as $Na_2 B_{12}H_{11}SH$, the last injection 3 days before the operation. The doctor died 9 days later and further such samples were again taken at autopsy. At the second operation the B level in the 11 tumor samples ranged from about 1.5 to about 3 times that in blood. At post-mortem 12 days after the last B injection the concentrations in 12 of the 18 tumor specimens were still in the range of those tumor specimens taken 9 days earlier whereas the blood level now was 1/10th that at the earlier time.

In 1972 Amano in our laboratories, working with the rat glioblastoma model developed by Benda et al. the year earlier (4), demonstrated the site of uptake of the B atoms in $Na_2 B_{12}H_{11}SH$. Sections of the rat glioblastoma at varying intervals after injection of 150 μg ^{10}B/g rat were

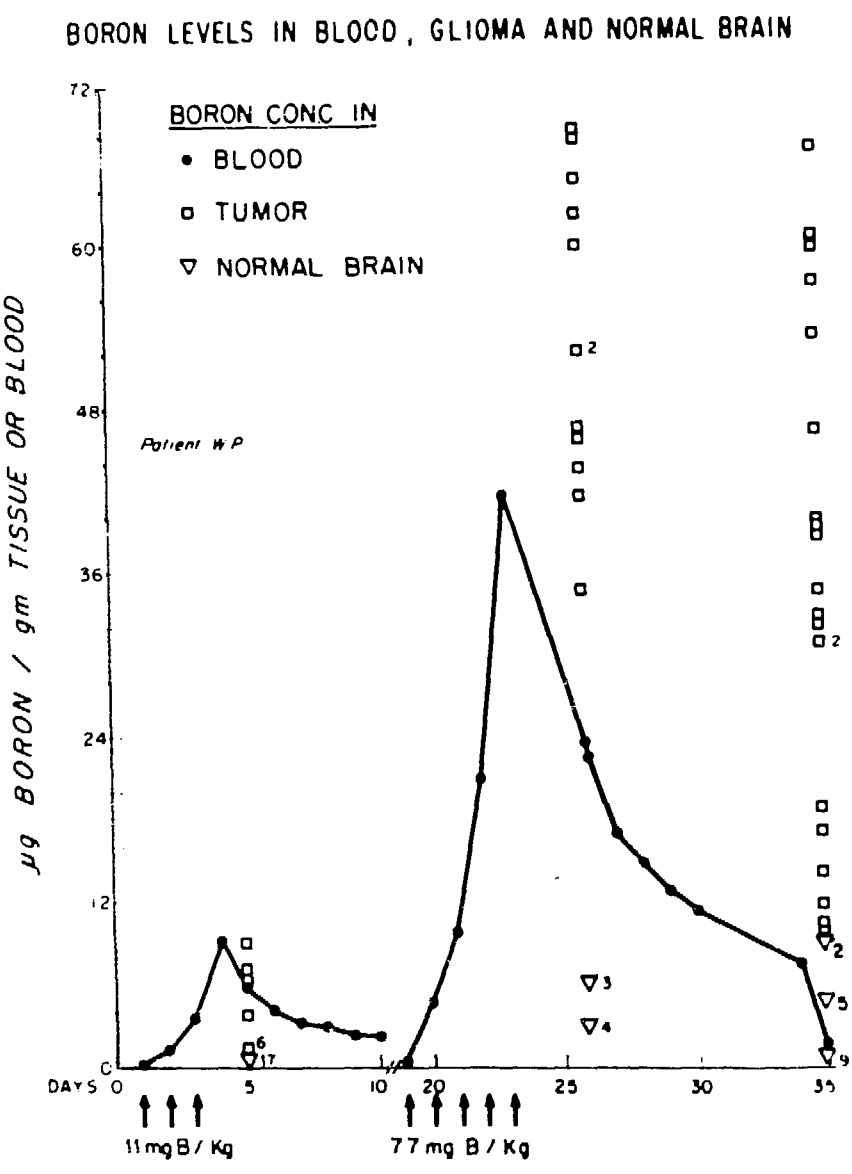


Fig. 2

Bilateral frontal glioblastoma patient Dr. W.P. Craniotomies 1/4 and 1/11/68. Post-mortem 1/22/68.

radiated with slow neutrons. Three and more hours later the alpha-particle tracks are almost all intracellular and most of the cells in some sections show at least 1 such track. There was a gratifying absence of such tracks in endothelial cells by 24 hours after injection. However, these studies were never pursued to the point of obtaining statistically significant data as to percentages of unlabelled neoplastic cells and endothelial cells present at various time intervals.

Hatanaka's collaborating chemists at the Shionogi Corporation have provided him with the consistently pure ^{10}B-labelled $^{10}B_{12}H_{11}SH$. His persuasive capabilities, inexhaustable energy, and thoughtfully comprehensive studies have enabled him to carry out 96 boron infusions in 86 patients mostly since he returned to Japan in 1968 after 3 years of work on our neurosurgical service. There were 68 patients with glioma and 9 with other types of tumors treated by BNCT. Nowhere else in the world have others of us been able to persuade our relevant committees to endorse continuation of human radiations of this type.

However, important long continued work by Fairchild and colleagues at Brookhaven and by Brownell and colleagues at MIT has improved many of the physical parameters of the radiation including increasing the epithermal components of the beam, decreasing its unwanted core gamma and fast neutron elements, and improving the dosimetry, as they have described. Of special importance is the perfection by Fairchild and colleagues of the rapid method of assaying samples for ^{10}B content by measuring the prompt 478-keV gamma ray which accompanies each disintegration of a boron atom upon capture of a thermal neutron. (6) The previous colorimetric method involving tissue digestion required hours. All of these and their other related efforts will be described here by those who have carried them out.

3. STUDIES OF HATANAKA AND COLLEAGUES

Many of you were in Tokyo in October 1985 at the 2nd Boron Slow Neutron Capture Symposium organized and financed by Professor Hiroshi Hatanaka and made worth attending largely by virtue of the work reported by him and his colleagues. However, he devoted a major effort to doing such things as arrange financial travel assistance for attendees of that symposium and editorial work on the volume Boron Neutron Capture Therapy for Tumors with more than 75 contributors. Hence he wasn't able by mid-October to present a complete report of his own work. In the 3 months since then he has marshalled and written up many data not presented in Tokyo and has graciously sent me the typescript of 3 of the more important chapters under his own authorship in that forthcoming book - one chapter on boron uptake by human brain tumors and quality control of boron compounds, another chapter describing the autopsy studies in 18 of his cases of malignant brain tumors treated by BNCT between 1968 and 1985, and a third chapter describing his clinical experience with his entire series of 77 tumors treated by BNCT in that time.

The data I shall describe from this point onward in this presentation are virtually all the work of Hatanaka and

colleagues in which I have had almost no part and am bringing to you as a consequence of his courtesy. There is time only for an abbreviated summary.

A. $B_{12}H_{11}SH$ Levels in Brain Tumor, Blood, and Urine and Quality Control of Boron Compounds

This compound was infused by a motorized pump into the carotid or vertebral artery as an isotonic aqueous solution diluted with an equal volume of normal saline. The infusion was usually started at 7PM on the night before radiation and took 1-2 hours. In all but 8 patients the BNCT was carried out within 4 weeks of the partial or subtotal tumor excision at craniotomy. Of the 86 occasions in which patients received boron injections no clearcut tumor tissue was still present at radiation in 29 re-operations so that tumor:blood ratios are available in only 57 instances. Hatanaka's complete table gives the patient's age, type of tumor, dose in mg ^{10}B/kg, vessel infused, number of hours after infusion til specimens were taken and treatment started, concentration in μg ^{10}B/g sample for tumor and blood, and correction for average blood level of boron during radiation because of greater decline of level in blood than in tumor.

Fig. 3 is my summary in graphic form of his data for 30 of the glioblastomas grade III or IV in the series. From this one can see poorer correlations in levels in tumor and blood with the injected dose than one might expect. Thus of the 5 patients receiving the biggest doses of 61 to 81 mg ^{10}B/kg these included not only the 2 highest total tumor levels with some of the highest tumor: blood ratios but also 2 of the lowest absolute levels in blood and tumor of the entire series. The neoplastic cystic fluid also had a high B content in the 5 cases in which such fluid was found. In Fig. 4 Hatanaka plots the B levels in blood in a patient in whom only cystic fluid was available as a sample of glioblastoma at the time of BNCT. Table 1 indicates that such cystic fluid may be representative of levels in solid tumor.

Fig. 5 is a similar example for one of the astrocytomas, case 56. It is clear that a determination of the blood level at the time of radiation will permit a more precise calculation of the advisable dose. Marked variations in ^{10}B concentration in different portions of the same tumor as illustrated in our patient Dr. W.P. are also apparent in Fig. 5; these variations also point to the wisdom of giving the highest dose permissible. Similar data are given for the 17 treatment episodes in the lower-grade astrocytomas. Table 2 illustrates 4 of these.

HUMAN GLIOBLASTOMA μg ^{10}B/g IN TUMOR, BLOOD AND TUMOR CYST AT NEUTRON RADIATION

(All radiations but one ... 11 to 16 hours after B Infusion)

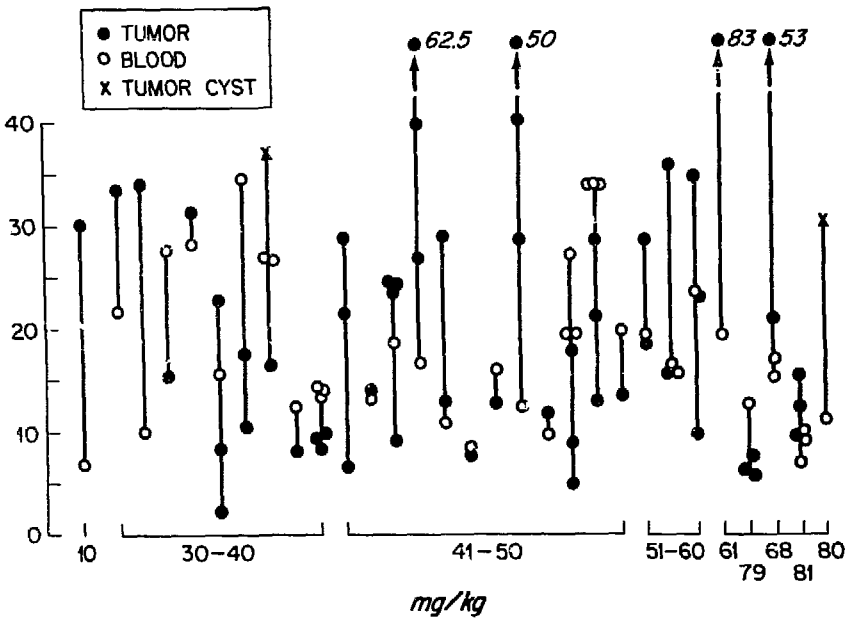


Fig. 3

Data of H. Hatanaka's on 30 glioblastomas given BNCT in whom tumor or tumor cyst data were available at craniotomy for radiation to compare with blood.

Table 1. Boron Content in Cerebral Glioma Cyst Fluid

Dose	Hours after injection	Boron in tumor	Boron in blood	Boron in cyst fluid
36	20	-	10.0	37.0
46	14	17.7	27.0	14.2
61	15	83.1	19.0	32.9
80	14.5	-	11.1	30.5
40	14	16.2	24.4	36.9

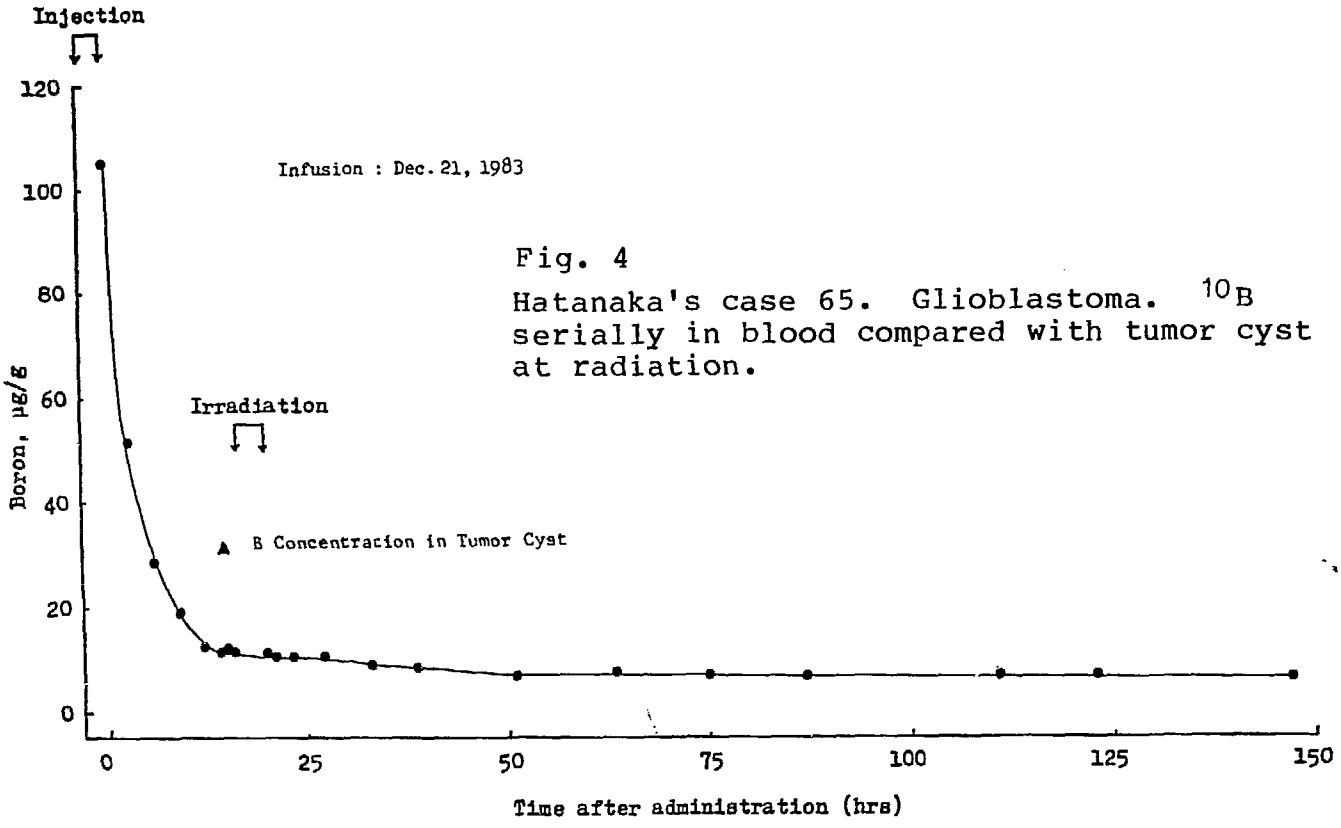


Fig. 4

Hatanaka's case 65. Glioblastoma. ^{10}B serially in blood compared with tumor cyst at radiation.

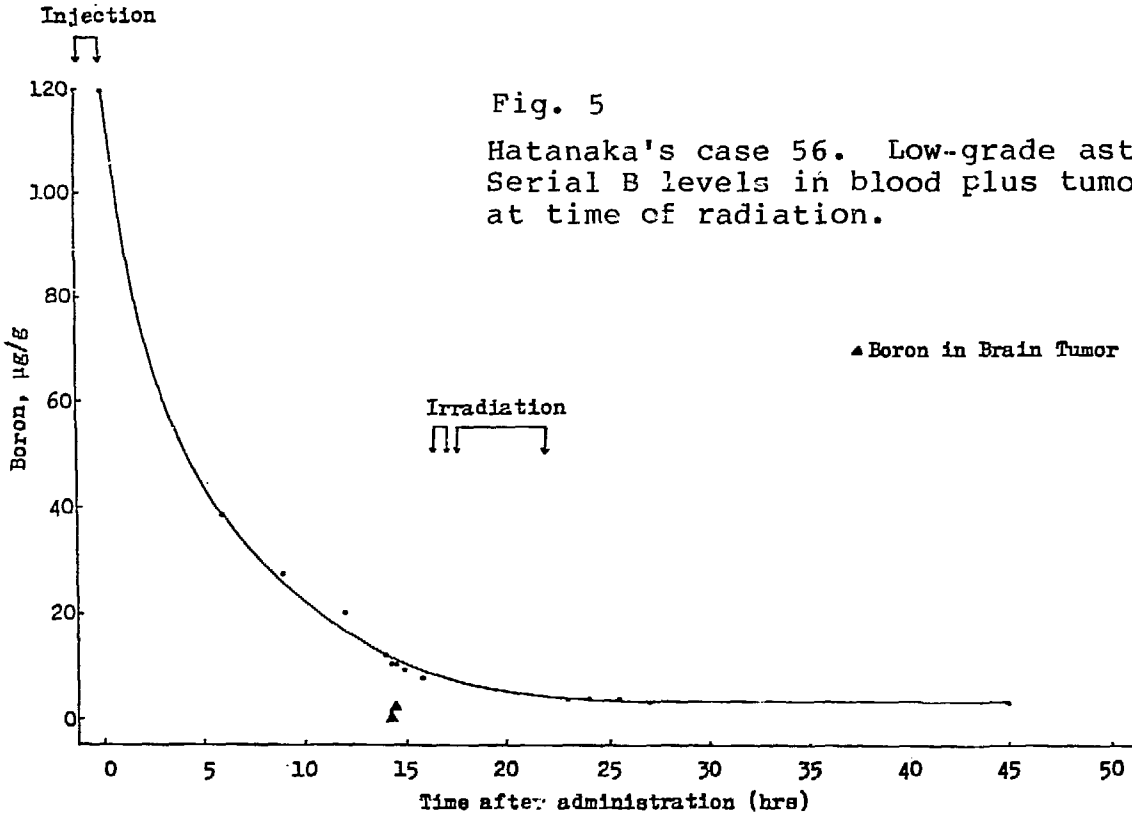


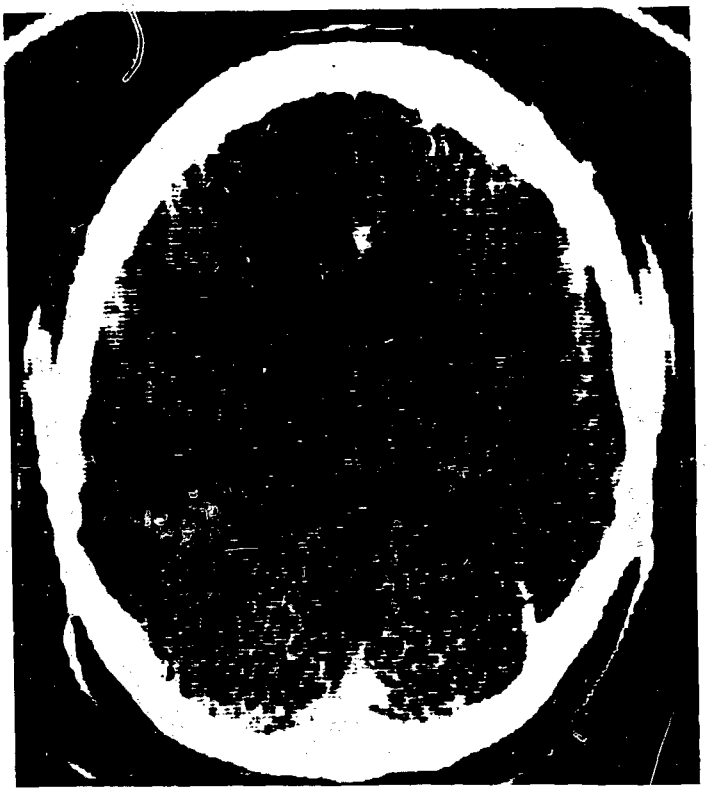
Fig. 5

Hatanaka's case 56. Low-grade astrocytoma. Serial B levels in blood plus tumor level at time of radiation.

Table 2. Hatanaka,B Levels in Tumor and Blood at Radiation in 4 of his 15 Low-Grade Astrocytomas (Grades I-II)

No.	Interval (hours)	Boron in Tumor ($\mu g^{10}B/g$)	Boron in Blood ($\mu g^{10}B/g$)	T/B
54	13.7	8.6	15.9	0.548
	(15.5)		(10.7)	(0.80)
56	14.4	1.45	10.5	0.14
	(16.0)		(5.7)	(0.25)
70	14.3	3.6	15.1	0.24
	(17.0)		(11.7)	(0.31)
73	15.4	11.1	21.2	0.537
	(19.5)		(13.9)	(0.82)

It is striking that 21 of a total of 54 of these tumor samples showed concentrations of more than 20 $\mu g^{10}B/g$ tumor; 23 astrocytoma tumor samples were between 10 and 20 and 10 were below 10 $\mu g^{10}B/g$. Hatanaka points out that the individual astrocytoma cells may represent a small part of the tumor tissue block but probably have a much higher B content than the matrix in which they lie. On this basis (as well as in those tumors with a relatively high B content in the entire tumor sample) he has given BNCT to 15 patients with low-grade astrocytomas. Thus in his case 70 he calculated from the histologic sections a tumor cell to total specimen ratio of less than 3.5%. There was only 3 $\mu g^{10}B/g$ of tumor specimen. In this patient, a 40-year-old woman, CT scans 10 months after BNCT are strongly suggestive that tumor has been fruitfully destroyed (Figs. 6a & b). The patient carries on as a housewife. A similar sequence of events characterizes his case 71, a 46-year-old man with a left hemiparesis from a right-sided tumor. The tumor cell to total specimen ratio was 2.7%. The CT scan 9 months after BNCT shows return of the displaced midline structures back to the midline and replacement of the neoplastic area by a clearly demarcated low-density area without a cyst wall, pointing again to the probability of selective destruction of neoplasm (Figs. 7a & b). The patient works as a printer. Hatanaka's longest followup after BNCT of a patient with a Grade I-II astrocytoma of a cerebral hemisphere is of a 39-year-old woman, his case 56, who 3 years later shows by CT scan no evidence of tumor regrowth. This patient's ratio of tumor cell to specimen was a minuscule less than 0.5% and her 2 neoplastic tissue samples at irradiation had contained only 0.7 and 2.2 $\mu g\ ^{10}B/g$. I have described these 3 cases in some detail because they



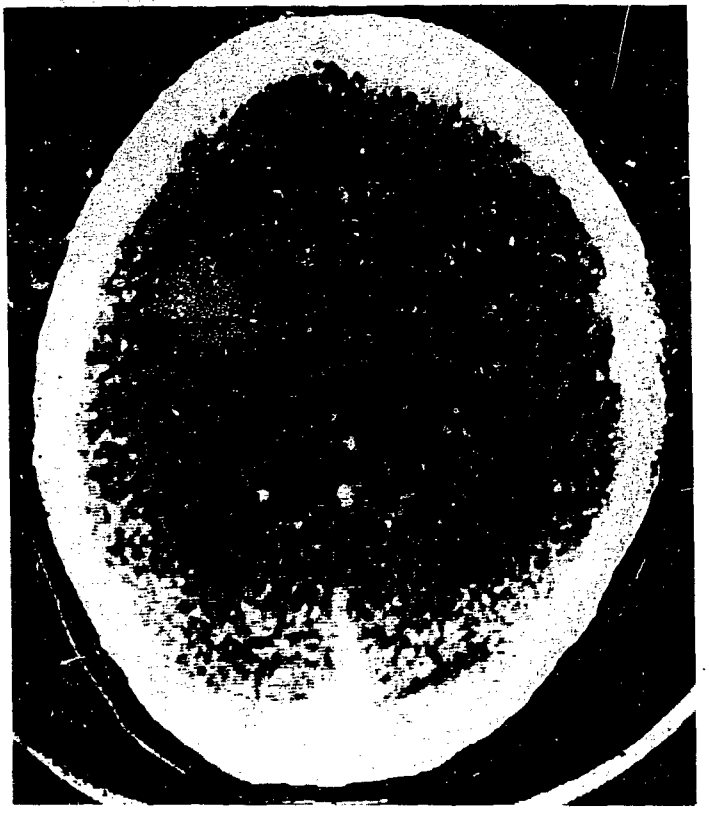
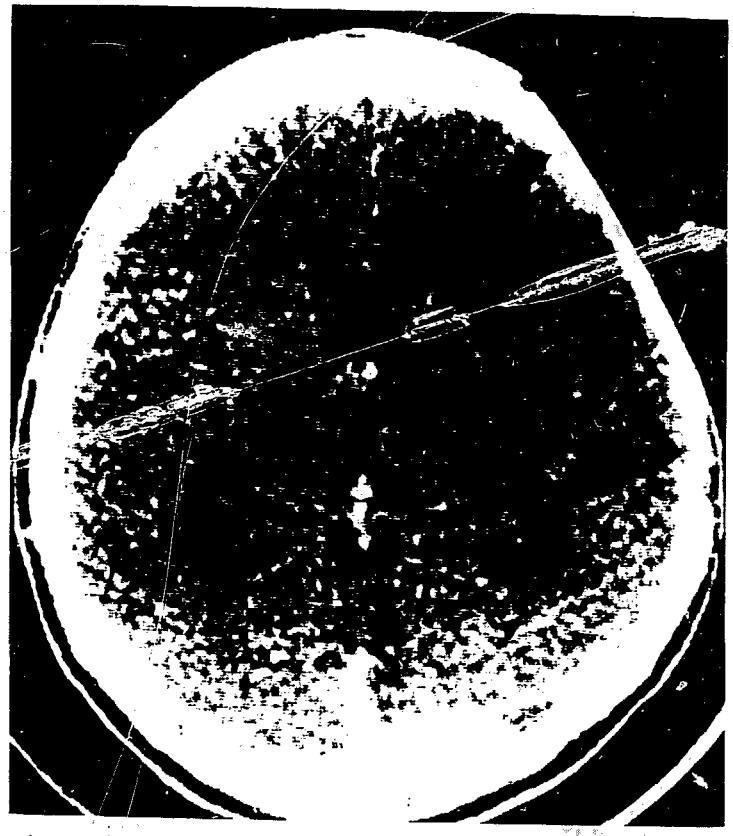


Fig. 6 40-year old woman - Grade I-II astrocytoma.

a. CT scan Jan. 2, 1984, before biopsy of small left frontal tumor, shows low-density area (mottled darkness) compressing anterior part of left lateral ventricle.

b. CT scan with contrast, Jan. 23, 1985, 10 months after BNCT. The diffuse low-density area replaced by a sharply marginated "hole" which does not show the contrast-enhanced ring typical of a gliomatous cyst. Left anterior horn a little larger than its right-side counterpart - probably due to decreased size of tumor. Patient continues her work as housewife.



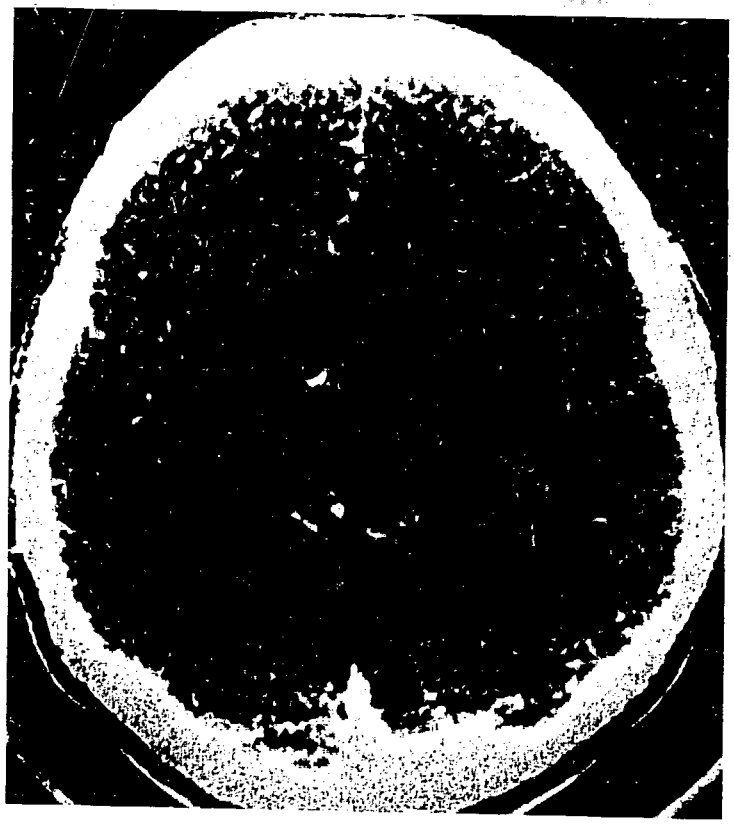


Fig. 7 46-year-old man - Grade I-II astrocytoma.

a. CT scan April 26, 1984. Right basal frontotemporal tumor does not take up i.v. contrast medium; it appears as a diffuse low-density dark area with a marked shift of midline structures to contralateral side with compression of right lateral ventricle.

b. CT scan Feb. 21, 1985, 9 months after BNCT on May 30, 1984. Neoplastic area has been replaced by a sharply demarcated low-density area with no ring of enhancement. Midline structures have returned to midline, and the 2 lateral ventricals are of equal size. No neurological deterioration; working as a printer.

represent the first intimations of evidence that even these slow-growing astrocytomas with minimal boron uptake in "tumor" tissue samples may benefit from BNCT. Alpha-particle radiography of histologic sections will be an important step to analyze the validity of this form of treatment.

The simultaneous levels of ^{10}B in blood and csf are shown in graphic form in Fig. 8. In 3 of the patients with tumor dissemination via csf this fluid showed much higher ^{10}B levels than were seen in the 10 patients without such dissemination.

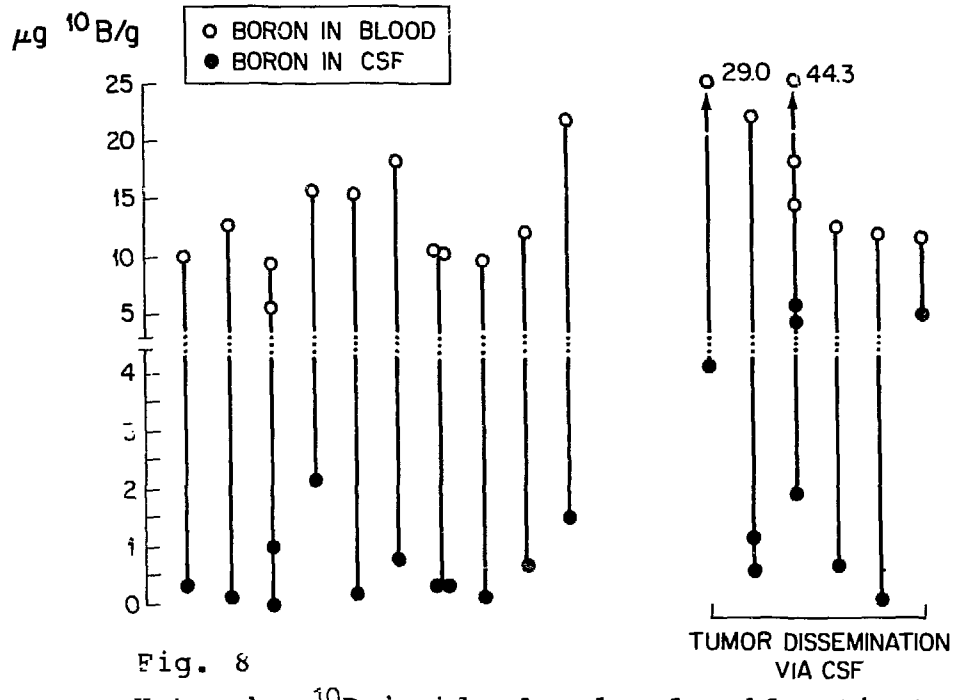


Fig. 8

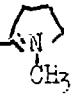
Hatanaka. ^{10}B in blood and csf. 16 patients with glioblastoma.

An additional practical tactic of Hatanaka was to recover the expensive ^{10}B secreted in the urine. In the 26 patients in whom he did this the recovery varied from a high of "106%" in 1 day to a low of 16% in 3 days. He continued the collection of urine for a maximum of 4 days -usually only 2 or 3 days - but recovered an average of 70% of the administered dose in the 26 cases. Our data for recovery of boron from urine after $Na_2 B_{12} H_{11} SH$ show similar variability from patient to patient. Of the 4 patients with i.v. injections one continued to excrete steadily to reach 63% by 8 days. The other 3 excreted 60-80% of the agent in the first 2 days with very little/day thereafter. (5) The last 2 of our patients received intracarotid injections via an infusion pump at the rate of 2 ml/min for a total of 90 and 70 min respectively. The first patient, given 34.1 mg ^{10}B/kg,

had a urinary excretion of 57% in 12 hours and only an additional 1% by 171 hours. The second patient, given 26.3 mg ^{10}B/kg, excreted in the urine 79% of the B in 20 hours and only an additional 4% by 71 days.

Table 3 illustrates an additional useful study of Hatanaka to demonstrate the importance of eliminating common impurities of $Na_2B_{12}H_{11}SH$ in order to maintain low toxicity. The intracarotid injection speed in man is always kept at a rate far below the 33mg/kg/min described in the mice.

Table 3. LD_{50} of $Na_2{}^{10}B_{12}{}^{11}SH$ and its Impurities

Compound		Injection Speed mg/kg/min	LD_{50} i.v., Mouse mg/kg
$Na_2{}^{10}B_{12}H_{11}SH$	1a	33	1000
		200	300
		1200	215
$Na_4{}^{10}B_{12}H_{11}SS{}^{10}B_{12}H_{11}$	2a	240	62
$Na{}^{10}B_{12}H_{11}$-S- 	3a	120	14
$Na_4{}^{10}B_{12}H_{11}SSO{}^{10}B_{12}H_{11}$	4a	240	53

B. Clinical and Autopsy Studies in 18 Patients Treated in Japan

Hatanaka's chapter 36 describes with many illustrations the neurological, operative, and post-mortem features of these 18 cases. The causes of death were: 1) wide dissemination of tumor in 4; 2) tumor regrowth adjacent to the original radiation field in 2; 3) pneumonia in 7; 4) wound infection complicating second-look surgery in 2; and 1 each from hemorrhage in the digestive tract or unrelated late cerebral stroke or damage to the CNS by antibiotics. Of the deaths related to pneumonia 3 occurred within 3 months - too short a period for the full radiation effect to occur. The radionecrosis observed in 70% of our patients was seen in only one of these; that patient's tumor, 8-10 cm deep, was treated by an unusually large dose of neutrons.

Within what Hatanaka describes as an "Adequately Radiated Site" - i.e. a total thermal neutron dose of 2.5 x 10^{12} neutrons/sq cm - there were only 2 cases in whom residual tumor cells were recognized at post-mortem in that

site. They both died of their glioblastomas within 3 months of BNCT, and as Hatanaka points out this may be a "premature" time to determine whether or not the tumor cells would have died later. I note also that the tumor specimens obtained at BNCT in these 2 patients contained only 18 and 10 μg ^{10}B/g in one and 15, 12, and 9 in the other. As Fig. 3 shows, 18 of the 30 glioblastomas plotted contained more ^{10}B than these 2 at the time of radiation.

Beyond the "Adequately Radiated Site" tumor cells were seen in 11 of the 18 cases, although 4 of these 11 were classified by Hatanaka as having died too soon to assess tumor cell death from radiation. In 4 other cases, 3 with astrocytoma and 1 with rhabdomyosarcoma, no tumor was found at the primary site which was given BNCT - a further intimation that the method may have a place in treatment of such tumors. In 7 cases remote dissemination of tumor cells far from the original site, probably via the cerebrospinal fluid, was seen; 5 of these were glioblastomas. This in my view points to the need for meticulous surgical technique during excision of the tumor with an effort to stay out of frank tumor as a general surgeon would do, as well as emphasizing the obvious urgency of achieving diagnosis and operation. Invasion via the corpus callosum of the opposite hemisphere is another feature of these tumors mandating expeditious treatment.

Hatanaka concludes from his post-mortem studies that over 1000 rads of ^{10}B radiation (or circa 3000 rem) is required to destroy viability of tumor cells and that delivery of this dose requires a minimum of about 2.5 x 10^{12} neutrons/sq cm to the deepest part of the tumor.

The first series of animal studies at the lower powered version of the MIT reactor measured the dose of mixed type radiations at that reactor portal. In these a number of us including Hatanaka and Brownell found that the level tolerated by normal brain in an asymptomatic dog was 4500 rads. (7) Of this dose 1275 rads were due to ^{10}B disintegrations. This healthy animal, dog 7, was sacrificed at 25 months after radiation of cerebrum for 17 min through a 2.5-cm bony trephine opening in the skull. At post-mortem the brain showed only a few entirely acceptable lesions - small in the white matter and smaller in the grey matter. Lesser doses in 4 other dogs produced no discernible changes. Tables 4a and b indicate the relevant parameters in 3 of the 7 dogs studied; these 3 indicate well tolerated, unacceptable, and barely tolerable doses. The Tables in the chapter cited give all of our data in all 7 dogs. Zamenhof and colleagues have later radiated a group of adult beagle dogs at the upgraded 5-megawatt MIT reactor using over 2000 rads due to ^{10}B distintegrations. (See their chapter, this volume.)

Table 4.
Mixed Field Dosimetry Data for Normal Mongrel Dog Irradiations

a. Dog #	Fast Neutron (Rads)	Incident Gamma (Rads)	Total Background (Rads)	$^{10}B(n,\alpha)\ ^{7}Li$ Dose (Rads)	Total Dose to Blood (Rads)
R1	273	587	2059	708	2767
R6	505	1140	3134	2880	6014
R7	505	1140	3243	1274	4517

b. Dog #	Boron Administered (mg ^{10}B/kg)	Rx ^{10}B Concentration (mg ^{10}B/kg)	Rx Duration (min)	(10^{10} Flux n/cm^2-s)
R1	47.24	6.65	11.1	1.85
R6	27.48	21.80	17.0	1.50
R7	19.31	8.9	17.0	1.61

C. Clinical Experience of Boron Neutron Capture Therapy for Gliomas

Since 1968 Hatanaka has treated 68 patients with gliomas by BNCT. Nearly all were treated at one of two 100-kilowatt reactors. The Musashi Institute of Technology reactor used since 1974 delivers at its medical portal 1.5 x 10^9 n/cm^2/sec. Cerebral gliomas grades III and IV comprised 48 patients. These have a poor prognosis, even with the standard improved current methods of treatment. The survival rates at 2 years were only 8-17% in one comprehensive study involving 14 different centers. (8) I shall present Hatanaka's BNCT results mainly in this group since the results despite the small numbers are still persuasive because of the lethality of the disorder. The low power of the available reactor has not only precluded the use of an epithermal beam, but also its construction has prevented direct radiation of the side of the head, as for example would be optimal for a temporal-lobe tumor. For treatment the upper half of the patient's head must be placed in a space hollowed out of the graphite layer of the thermal column. Consequently it was reasonable for Hatanaka to consider as a separate and more favorable group those patients whose tumors nearer the vertex of the head permitted direct access of the neutron beam to the bed of tumor removal. He has also set arbitrarily the maximum distance of 6 cm from the cerebral surface as the "reachable" depth of his beam. Even at this relatively shallow depth the thermal neutron flux is down to about one-tenth the original level, since it is decreased by 50% for every 1.8 cm it travels in tissue. (9) He has then studied as a separate group those with tumor not deeper than 6 cm. As a subgroup thereof

he describes those tumors accessible to the direct beam. He has also come to realize the importance of a large craniotomy of diameter more than 10 cm and describes the results of this third subgroup. Table 5 summarizes his results in these 3 favorable subgroups as compared with the whole group. His 5- and 10-year survival rates are calculated by the method of Kaplan and Meier. (10)

Table 5. BNCT Grades III-IV Gliomas

	All BNCT Cases	Tumor not deeper than 6 cm: All Cases	Vertical Location	Craniotomy over 10 cm
# of pts	38	12	6	5
Age	50.2	49.8	41.5	45.4
Mean Survival Days	613	1320	2183	2574
5-yr survival rate	19%	58%	83%	100%
10-yr survival rate	9.6%	29%	42%	50%
Now alive	8/38	5/12	3/6	3/5
Karnofsky rating	73%	87%	95%	100%

His most dramatic case is a man 50 years old when diagnosed and operated on in 1972. He presented almost all of the most unfavorable prognostic features (8), namely, major neurologic symptoms and signs, short duration of symptoms, absence of seizures, a tumor invading the motor speech area so that at Hatanaka's first operation he had to leave much of it behind, histopathologic classification of glioblastoma grade IV with necrotic areas typical of this degree of malignancy, absence of the favorable feature of cystic fluid, and no lymphocytic infiltrates in the tumor, suggesting development by the patient of some immunity to his tumor. I have found not a single other case report of survival as long as 5 years in this gloomy congeries of findings. The BNCT was on his 9th post-craniotomy day, 14 hours after the end of a 2-hour infusion of 40 mg ^{10}B/kg body weight into his left carotid artery. There was 15.3 μg ^{10}B/g of tumor in the sample removed 13.5 hours after the infusion ended. A blood sample at 14.5 hours after the end of the infusion contained 27.5 μg ^{10}B/g. The radiation required 7 hours. This man has no neurological deficit 13-1/2 years later and is an active industrious farmer. The last CT scans of January 30, 1981, show no sign of recurrent tumor. One notes the excellent result despite a tumor:blood ratio of only 0.56. This intimates that favorable factors such as B uptake by vulnerable parts of tumor cells may

override the radiation from the blood. Hatanaka has several other long-term survivors without significant deficits. These include one woman now 68 years old and 8 years after BNCT of an astrocytoma grade II-III also with no CT scan evidence of recurrence.

Serial studies with this modality have demonstrated that contrast enhancement of tumors may disappear only slowly after BNCT. This required a year in one 11-year-old girl with an oligoastrocytoma Grade II or III. Her scans, mentation, and physical growth remain normal 4 years after BNCT.

Aspects worthy of further investigation include, in addition to increasing the depth of penetration, the acquisition of more data re the maximal dose and timing of BNCT for whatever B carrier proves best. Thus the findings in Dr. W.P. suggest that a longer period between infusion and radiation may be better, and the variability of Dr. Hatanaka's blood and tumor data indicate that we must maximize the safe dose in every way we can. This will involve, among other tactics, governing the duration of radiation by the B levels in blood at that time.

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THE RADIOBIOLOGY OF BORON NEUTRON CAPTURE THERAPY

V. P. Bond
Brookhaven National Laboratory, Upton, NY 11973

1. INTRODUCTION

One of the major concerns of this workshop is the size and configuration of neutron sources, principally reactors, that may be desired or necessary for Boron Neutron Capture Therapy (BNCT), especially of brain cancers. This is a concern particularly when band-pass filters are used to achieve a more suitable incident so-called "epithermal" beam.[2,3] The reactor power required under these conditions depends principally on two factors, the band-pass width and the length of the treatment sessions to be used in therapy. Obviously, the narrower the band width required to obtain a suitable neutron energy distribution, and the larger the dose required per session, the greater must be the reactor power required for effective therapy. The second factor depends in turn on the total number of treatment sessions to be used to deliver the total therapeutic dose.*

Others here will speak to the questions of different and optimal band-pass filters or moderators, and fluence-rate losses with each. I shall speak principally to the questions of single-session vs. protracted therapy. That is to say, is it most desirable, with BNCT, to give the entire tumor control dose in a single short session, or in a single session lasting several hours, or in a fractionated pattern extending perhaps over several days?

In order to address these questions adequately, it is first necessary to discuss briefly the reasons why fractionated therapy is currently always used with "conventional" low-LET radiations, i.e., x rays, gamma rays, or electron beams. With this background, we can then address the question of how this "conventional" situation may be altered by the use of the high-LET radiations obtainable with BNCT, and what this may mean with respect to the desirability of single-session vs. protracted exposure in clinical applications of the BNCT approach.

2. DOSE PROTRACTION WITH CONVENTIONAL RADIOTHERAPY

It is useful, in understanding the reasons for dose protraction, to deal briefly with the history of radiation therapy. X rays were first used for cancer therapy (of the breast) within a couple of months of their discovery by Roentgen, in late 1895. Single-dose sessions were used. It was demonstrated by Kroening and Friedrich[7] as early as 1915, that fractionation in 13 sessions, compared with one, required a substantial increase in the dose necessary for skin erythema. The intepretation, however, was the inverse of that made today. It was judged from the relative ineffectiveness of

*Only "epithermal" beams applied externally are considered here, to the exclusion of the other option of directing a thermal beam to the tumor area in conjuction with craniotomy.

fractionated therapy that the maximum chance of tumor control depended on the entire dose being given in one short session. This inference was translated to practice.

Control of some tumors must have been obtained, as evidenced by the fact that such single-session therapy continued until well into the 1920s when, in classic experiments, Regaud[9,10] showed that fractionation should be interpreted in the reverse manner. Rams' testicles were used as a model for a tumor, with histological sterilization as evidence of conrol. The normal tissue observed was the skin of the overlying scrotum. The results of single session vs. protracted exposure are shown in Table I.

Table I. Efficacy of Fractionation; First Demonstration ("tumor" and normal-tissue dose equal)

Single dose			Five fractions		
Dose (R)	Sterili-zation	Necrosis	Dose (R)	Sterili-zation	Necrosis
<4100	0/2	0/2	<4500	0/3	0/3
4500	2/3	3/3	5000	3/5	0/5
>5000	1/2	2/2	6000	3/4	0/4

Note that with single sessions "tumor" control could be obtained only with the infliction of unacceptable scrotal skin destruction, but control could be obtained without such damage if the total dose was protracted in time.

Rarely does a single experiment revolutionize an entire discipline almost literally overnight, but, following this demonstration, conventional therapy was given only in fractionated patterns, which are now the hallmark of such therapy. In fact, the limiting factor in conventional radiotherapy is unacceptable damage to normal tissues. Fractionation is adjusted to yield the maximum tumor dose without unacceptable damage to normal tissues, which automatically fixes the maximum dose that the tumor will receive. Although the reasons why fractionation was more efficacious than was the single session were poorly understood at the time, an enormous amount of work has been done in an effort to understand the radiobiology involved. The difference clearly cannot be due to differential dose deposition in the tumor, since, with conventional radiations, at least part of the tumor and some normal tissue must receive the identical amount of radiation exposure.

The results of these mechanistic studies are now commonly summarized in the form of the "four R's" of conventional radiotherapy (see Table II):

1. Repair of sublethal intracellular damage. Both normal and tumor cells can repair sublethal damage. It was shown[13,14] relatively recently,

Table II

The "Four R's" of Fractionated Radiotherapy

1. Repair of sublethal damage
2. Regeneration (repopulation)
3. Redistribution of cell ages
4. Reoxygenation of hypoxic foci

The "Four R's" of BNCT

1. Restriction, physiologically, of ^{10}B and thus of high-LET radiation, to tumor.
2. RBE of high-LET radiation
3. Reduction in unavoidable dose to normal tissue
4. Resistance of cells, with high-LET radiation, to the influence of dose rate (repair), O_2 tension, and phase of cell cycle

however, that in general the repair rate for tumors is not greater than, and is usually less than, that for normal tissues.

2. Regeneration, or the restitution of depleted cell populations. Here, because normal tissues have feedback mechanisms that accelerate regeneration and tumors do not, a selective advantage would accrue to the normal tissue.

3. Redistribution of cell ages, or the redistribution of cells in a population with respect to location in the cell cycle. An initial dose fraction will induce partial synchrony by selective killing of cells in the more sensitive phases. With time, the remaining cells that were in a resistent stage will "redistribute" (be "recruited") into more sensitive stages.

4. Reoxygenation of hypoxic foci. Many but not all tumors, for whatever reasons, develop foci of hypoxic cells, which are more resistant (by a factor as much as 3) than are well-oxygenated tissues.

Each of the four R's would apply to tumor tissue. Only the first three would apply to normal tissues, since these are normally oxygenated to near the maximum and thus the use of even hyperberic oxygen does not appreciably increase their sensitivity.

It is useful to review briefly the relative importance of the four R's, particularly in view of the extensive study and evaluation that have taken place. There is no disagreement that repair is important, and therefore that, on this basis, fractionation works in favor of the normal tissues in nearly all if not all cases. Regeneration is also generally considered to be more active in the normal tissues, which would favor fractionation. However, regeneration occurs in the tumor as well. Clearly, if there were no other considerations, one would attempt to eradicate a tumor with a single large exposure. This might better eliminate regeneration from foci of viable cells that would be left with smaller, protracted doses. There is disagreement

with respect to how large a role this factor may play. However, Maciejewski et al. have shown, according to Trott,[13] for at least one human tumor, tumor of the larynx, that tumor regeneration during fractionated therapy may be the limiting factor in tumor control.

Redistribution is considered to be of importance in principle. With low-LET radiation, however, it is extremely difficult to make use of this phenomenon, mainly because of inadequate knowledge of the proliferative cycle in all or parts of the tumor, particularly after an initial irradiation. Reoxygenation was thought to be of substantial importance in perhaps all tumors, which led to a plethora of hyperberic oxygen chambers for use with radiation therapy. This also led to the revival of fast neutron therapy, on the basis that high-LET radiation, such as the knock-on protons from fast neutrons, "don't care" so to speak, whether a given cell is hypoxic or fully oxygenated. The initial promise of neither hyperic oxygen nor fast neutron beams has been realized, however, although it is frequently conceded that in some tumors the problem exists and merits the use of these approaches.

A substantial advance in understanding the advantages of fractionation has occurred in recent years [e.g. 14] with the realization that normal tissues can be divided into "early-responding" and "late-responding." The former are responsible for early effects such as reversible skin and mucous membrane damage; the latter are responsible for the serious irreversible late effects that are limiting. In general, the early-responding tissues are rapidly turning over and benefit relatively little from fractionation. The late-responding tissues (connective tissue, spinal cord) benefit more from fractionation. This phenomenon is shown in Figure 1, in which the dotted and full lines are for early- and late-responding tissues respectively. Note that the slopes of the curves are steeper for the late-responding tissues than for the early responders, indicating a greater efficacy of fractionation.

A great deal of discussion has ensued as to how best to make practical use of this finding. "Conventional" radiotherapy may be characterized, for instance, as administration of 2 Grays per fraction, five days per week, for as many weeks as necessary to deliver the desired total dose for a given tumor.

Proposed alterations in this schedule include "hyperfractionation" (dividing the treatment into smaller than conventional doses per fraction, without change in the overall treatment duration), "accelerated fractionation" (shortening the overall duration of a treatment regimen using conventional dose fractions), and "accelerated hyperfractionation" (combining both a decrease in dose per fraction and a shortening of the overall treatment duration). Accelerated hyperfractionation appears to have a number of prominent adherents.[1,5,6,11-14] This could be the most appropriate combination for taking maximal advantage of the enhanced repair of late-responding tissues while reducing the total therapy time for the given tumor to minimize tumor regeneration. Clinical trials of this approach are being mounted or are underway.

Clearly, in conventional irradiation with fractionation, several important variables must be considered. Tumors vary markedly with respect to the importance of each of the four R's in their control, and tumors can vary in this respect from location to location within the neoplastic growth.

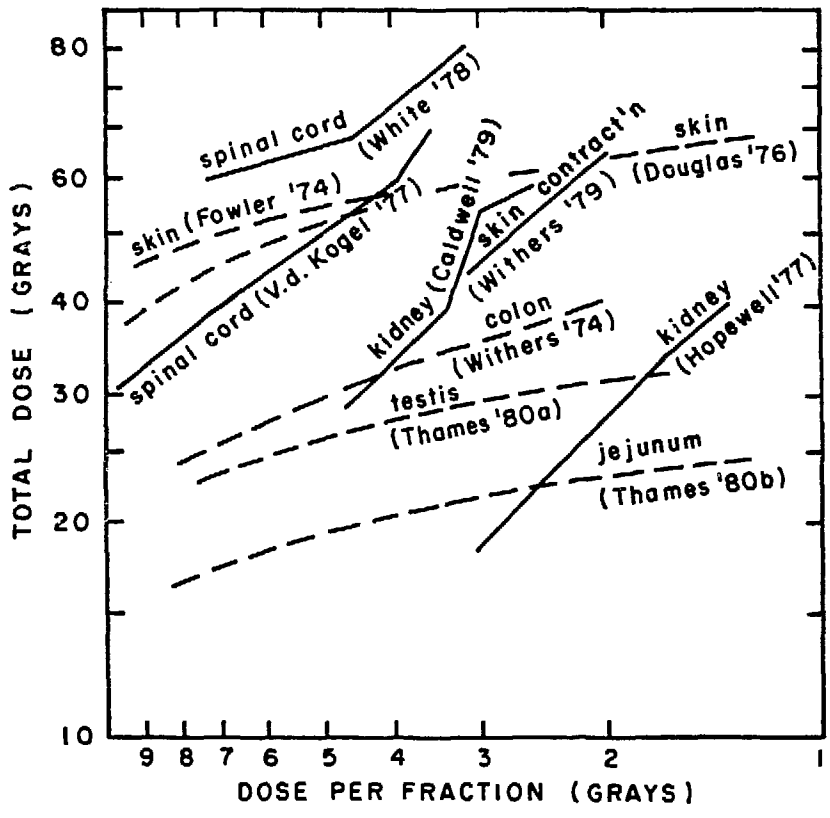

Figure 1. The increase of total isoeffective dose with decrease in size of each fraction, from multifractionation animal experiments. Dotted lines are for early-responding tissues and full lines for late-responding tissues. (From Fowler.[5])

Thus, to take advantage of the radiobiology now known, it would be necessary to have reached an as yet unattained goal, that of being able to determine these properties for each specific tumor, both initially and as a function of time during the overall therapy time period.

3. DOSE DELIVERY WITH HIGH-LET RADIATION; BNCT

In order to appreciate how the conventional radiotherapy approach might be modified with the use of high-LET radiations, it is convenient to consider first what might be termed the four R's of high-LET irradiation obtained with the BNCT approach (see Table II):

1. Restriction, physiologically, of ^{10}B, and thus of high-LET radiation, to tumor. This is accomplished physiologically, in order to confine the high-LET radiation from the neutron interaction principally to the tumor, provided that essentially all cells, hypoxic or otherwise, take up the boron-containing compound.

2. RBE of high-LET radiation. The RBE associated with the boron-10 neutron interaction is about 2.5 for several endpoints. This provides a larger

"effective dose" (absorbed dose times RBE) in the tumor than in the boron-poor surrounding normal structures.

3. Reduction in unavoidable dose to normal tissue. This effect, due to relative absence of ^{10}B, should lead to an appreciably higher tumor/normal-tissue effective dose ratio. Some dose from the radiations associated with the incident neutron beam, namely, the proton from nitrogen and the gamma ray from hydrogen, is unavoidable.

4. Refractoriness of (tumor) cells, with high-LET radiation only, to the influences of dose rate, hypoxia, and position in the cell cycle. The net effect may be a distinct advantage to normal tissues that may be irradiated with radiations having a mean LET lower than that delivered to the tumor by the BNCT reaction.

For the above-stated reasons, a closer look must be taken at the quantity and quality of radiation unavoidably delivered to intervening tissues. Clearly there will be a low-LET component from the hydrogen gamma and a high-LET component from a nitrogen proton. Also present will be some component of high-LET radiation from knock-on protons if any form of "epithermal" beam is used. The larger the contribution from this source, the higher, of course, will be the effective LET of the radiations interacting with normal tissue. It is therefore important to examine these components critically to see quantitatively the contribution from each type of radiation. It is also necessary to do radiobiology, in order to determine the net effectiveness of the overall beam.

Clearly of major importance are the knock-on protons from an epithermal beam, particularly since this component is generated within the tissue itself and cannot be avoided. The objective, then, is to obtain the lowest-energy "epithermal" beam that will deliver the necessary thermal fluence rate at tumor depth. With use of a band-pass filter such as iron, which yields a 24-keV fast neutron beam, a substantial dose, and an "effective dose" because the RBE of such neutrons is 2 or more, would have to be tolerated.

Figure 2 shows what may be close to an ideal beam, obtained with a scandium band-pass filter, yielding a neutron energy of about 2 keV (a higher-energy component has been scattered out of the beam). Note that no contribution from the 2-keV knock-on protons is shown. This is because, in terms of absorbed dose, the amount contributed is negligible compared with that from the nitrogen proton and the hydrogen gamma. Although scandium band-pass filters are now impractical because of the price of scandium, other moderators or filters to be discussed later in the workshop are cheaper and probably can produce almost equivalent results.

With the use of such filters, depending on the amount of boron-10 that can be taken up selectively by the tumor cells, and assuming that all cells take up some boron, the effective dose ratio, tumor to normal tissue, can exceed 6 and could be as much as perhaps 10.

With this effective dose ratio, one can begin to think in terms of the possibility of delivering the entire therapeutic dose to the tumor in a single short session, simply because the accompanying dose to the normal tissues, particularly the brain, may be so low that the resulting damage is acceptable.

However, if ratios that high cannot be obtained, or even if they can, the radiation to the normal tissue must be considered in terms of the

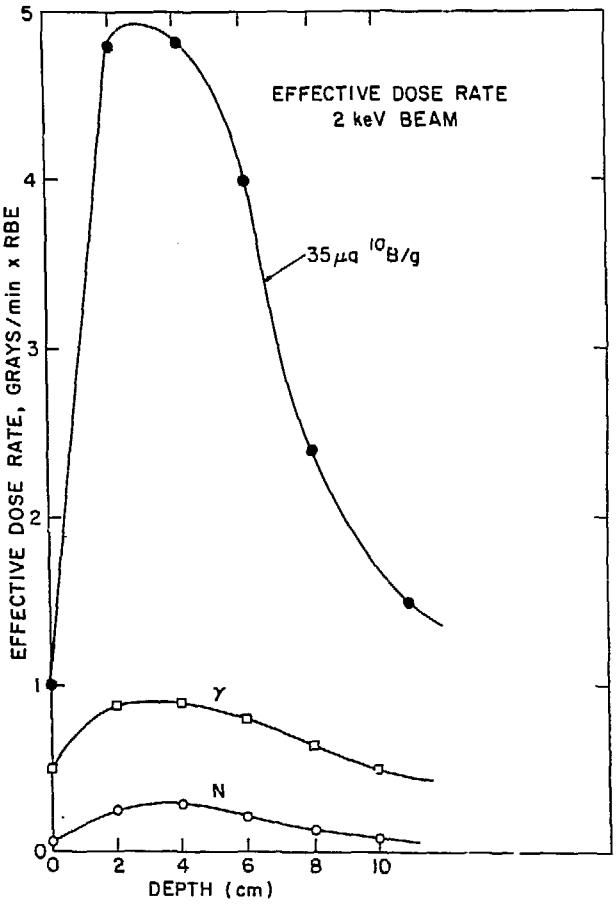

Figure 2.
"Effective dose rate" obtainable with a scandium band-pass filter, yielding a 2-keV "epithermal" neutron beam. With selective tumor uptake of ^{10}B, the tumor/normal tissue ratio could be about 6.

effective LET and the sparing that one might hope to obtain by some form of dose protraction. One would expect some gain in favor of the normal tissues from protraction simply because of the unavoidable gamma component from hydrogen. Thus, if sparing of normal tissues is thought to be required, protraction can be resorted to. One could simply extend the single-session treatment from a few minutes to several hours. Alternatively, the total dose could be given in smaller increments, perhaps at the rate of two or more sessions per day, or one per day. The greater the protraction, the greater the chance of tumor regeneration.

However, the possibility of completing the therapy in a single session should not be taken lightly. Trott[13] indicates that the limiting factor in the cure of at least one tumor, cancer of the larynx, is regeneration during fractionation with conventional therapy. This might be avoided by the use of a larger dose in a single session. The deciding factor will of course be the absolute effective doses deliverable to both the tumor and normal tissue. The latter is extremely dependent on the exact composition or quality of the "epithermal" beam.

If single-session therapy is tried, then many of the concepts deeply ingrained in conventional therapy might have to be reversed. That is to say, the limiting factor would be how much one can give to a tumor, particularly to a large one, in a short space of time. Consideration must be given to

such potential problems as cerebral edema, serious hemorrhage from vessels destroyed in the heavily irradiated tumor, the possibility of release of toxic substances during dissolution of the dead tumor mass, and the effect of the continued presence of the non-viable tumor mass.

Many of the potential problems might be avoided by debulking the tumor, perhaps two weeks before anticipated radiotherapy, to allow reconstitution of the blood-brain barrier. It must be made clear, however, that, although debulking is desirable from a number of standpoints, the resulting decrease in the number of cells does not appreciably lower the dose of radiation required for control. The curability, of course, depends not only on the type of radiation and the dose but also on the total number of tumor cells (the size of the tumor). It has been shown experimentally, by removing half of a sizable experimental tumor before irradiation, that very little or nothing is gained in terms of the dose required for control.[4] The reasons for this can be seen in Figure 3, which shows an exponential curve for the number of surviving (tumor) cells vs. dose (curve a). Curve b, for a tumor having one tenth the number of cells, has the same shape as curve a. Note that the dose (on the abscissa) required to reduce the absolute number of cells to some level (indicated by dotted line c), and thus presumably the "curative" dose, would be reduced by only a few percent by debulking. One would have to remove well over 95% of the total viable tumor cells to obtain

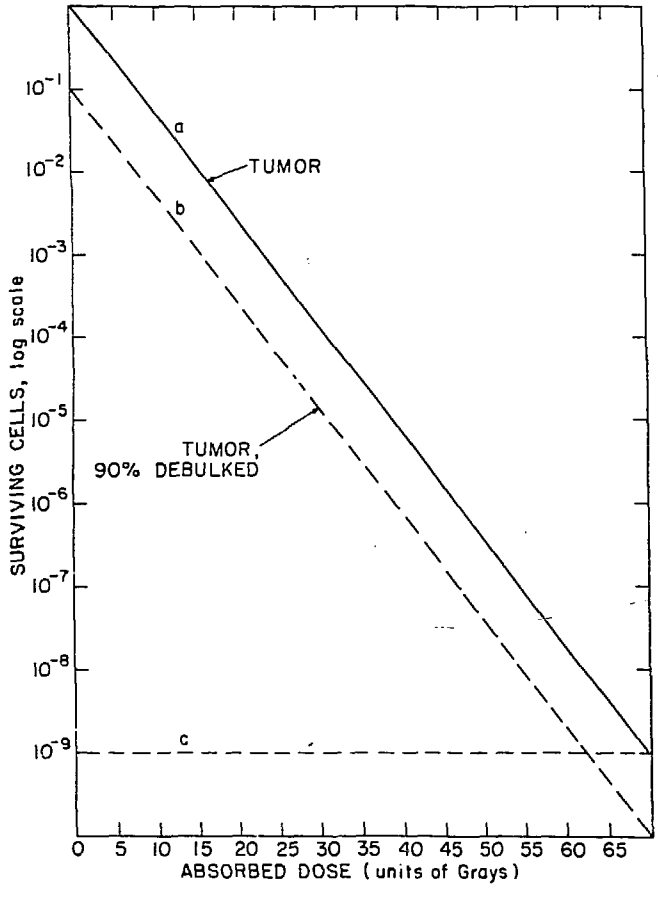

Figure 3.
Schematic to show that debulking of a tumor by as much as 90% would not decrease appreciably a "tumor-control" dose. If curve c represents a level of cell survival necessary for tumor control, then doses for the intact vs. debulked tumor are not appreciably different.

any significant advantage, in terms of the dose required for tumor control, from the debulking procedure.

Reasons for fractionation with BNCT may well emerge. For instance, it is possible that the boron compound may not enter or remain in the tumor cells, as has been noted for some sensitizing agents. If this turns out to be the case, then fractionation might have to be tried with the hope that later injections of the boron compound would go to the cells that previously were non-receptive (perhaps because they were hypoxic).

Clearly it is critical to determine, with autoradiographic or similar techniques, the micro-distribution of the boron compound within the tumor, both in the unirradiated tumor mass and after various doses of radiation. Also required are further studies on the effects of radiation on the blood-brain barrier to determine more accurately what dose impairs blood-brain barrier function as well as the time needed for recovery.

Although it is not possible to predict without further physical, dosimetric, and radiobiological studies whether a single session or protracted therapy would be the more efficacious with BNCT, it seems likely that modest fractionation might be optimum. Important in making this decision would be a determination, for the particular tumor, of the rate of regeneration of tumor foci following single sessions at different dose levels. Also important would be knowledge of the absolute effective doses received by tumor and normal tissues, to ensure that single-session therapy of the tumor would not result in a dose to normal tissues leading to unacceptably severe complications.

This information is critical with respect to the power of the reactor required for therapy. Obviously a much larger reactor would be needed if the total dose were to be given in single short sessions, particularly with use of a narrow band-pass filter, than if extended protraction were deemed necessary.

CONCLUSIONS

BNCT offers many new and exciting possibilities for cancer therapy which, if they can be realized, could strongly impact the present approaches to therapy. However, adequate data -- physical, biological, or medical --are not yet available for proper evaluation. Some of the biological data can be obtained largely from animal models, but the final test for almost all of them must come from experience with cancer patients. Although more work must be done, this need not be either overly time-consuming or excessive in terms of overall program and cost. With close coordination of the various interested groups working on the physical, dosimetric, and radiobiological aspects, it should be possible to collect the necessary information within a year or two.

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Intermediate-Energy Neutron Beams from Reactors for NCT*

R. M. Brugger, T. J. Less and G. G. Passmore
Research Reactor, Nuclear Engineering and Physics Departments
University of Missouri
Columbia, Missouri 65211

ABSTRACT

This paper discusses ways that a beam of intermediate-energy neutrons might be extracted from a nuclear reactor. The challenge is to suppress the fast-neutron component and the gamma-ray component of the flux while leaving enough of the intermediate-energy neutrons in the beam to be able to perform neutron capture therapy in less than an hour exposure time. Moderators, filters, and reflectors are considered.

1. INTRODUCTION

The trend in the development of neutron capture therapy (NCT) is toward using a beam of intermediate-energy neutrons.[1] These neutrons will penetrate into patients and be moderated into thermal neutrons in the vicinity of the tumors. These thermal neutrons will then be captured by the boron in the tumor, delivering a lethal dose to the tumor. Since only a few intermediate-energy neutrons will be captured by boron near the surface of the patient, the ratio of dose-to-tumor to dose-to-healthy tissue will be improved and the viability of NCT will be enhanced. This paper outlines ways that such beams might be obtained when a nuclear reactor is the prime source of neutrons.

2. TARGET

The target of development is to produce a beam of neutrons that peak the flux of thermal neutrons at the location of the tumor. Figure 1 shows the depth in tissue at which the thermal neutron flux is a maximum when the neutrons hitting the surface of the phantom have an energy "Neutron Energy". It is noted that when the neutrons are thermal, the maximum is at the surface, but the depth of the thermal peak increases rapidly as the neutrons' energy increases toward 1 eV. Neutrons of 1 eV will penetrate

*Work partially supported by a grant from NSF

several centimeters before reaching a thermal peak. To peak at 4 cm requires neutrons of 35 eV, while neutrons with hundreds of keV of energy peak the thermal flux only a few centimeters further in the phantom. Thus neutrons from about 1 eV to several hundred keV should be effective in peaking the thermal flux near a tumor two to six centimeters deep in a patient. To achieve an effective intermediate-energy neutron beam, thermal neutrons should be removed because they do not penetrate deep enough.

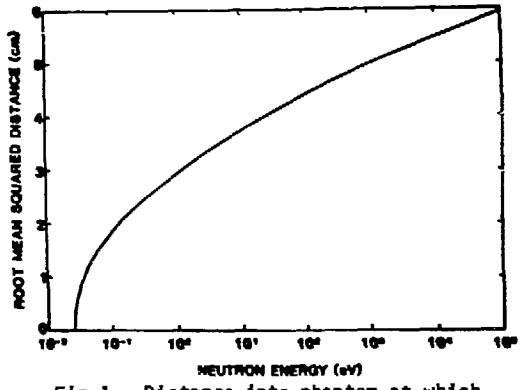

Fig 1. Distance into phantom at which thermal neutron flux is a maximum when neutrons of given energy illuminate a phantom.

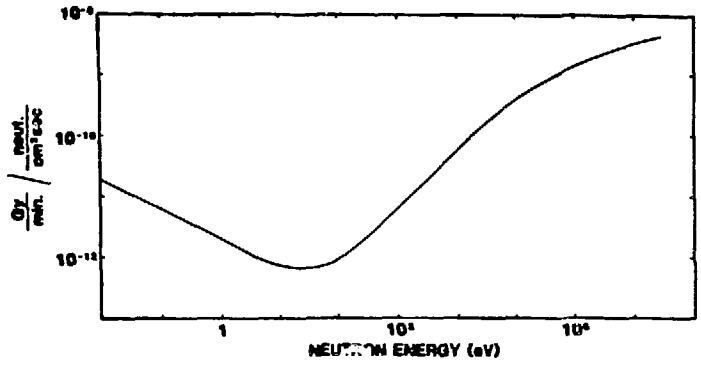

Fig 2. Dose per unit neutron flux as a function of neutron energy.

Figure 2 shows the Kerma rate per unit neutron flux (KR/NF) for neutrons as a function of their energy. The lowest value is about 10^{-12} Gy/min per n/cm^{2}sec and the values go up rapidly for neutrons with energies above a few tens of keV. To keep the dose to the patients as low as possible from the neutrons that are not absorbed by boron, neutrons above a few tens of keV should be excluded from the beam.

Considering the conditions mentioned in the preceding paragraphs, an intermediate-energy neutron beam for NCT should have neutrons with energies between about 1 eV and several keV. Thus the flux of thermal neutrons should be suppressed as well as that of fast neutrons. In addition the flux of gamma rays must be reduced to an acceptable level.

The beam of neutrons filtered by a scandium filter comes close to satisfying these conditions. Figure 3 shows the distribution of thermal neutrons in a phantom head when it is illuminated with neutrons from a scandium beam.[2] The data show that the thermalized flux does peak 4 cm inside the head. A similar set of data for a thermal beam is shown in contrast. With this thermal beam the thermal flux is peaked at the surface and is lower everywhere inside the phantom.

To specify the magnitude of the intermediate flux that must be accessible from the beam from the reactor, several facts must be

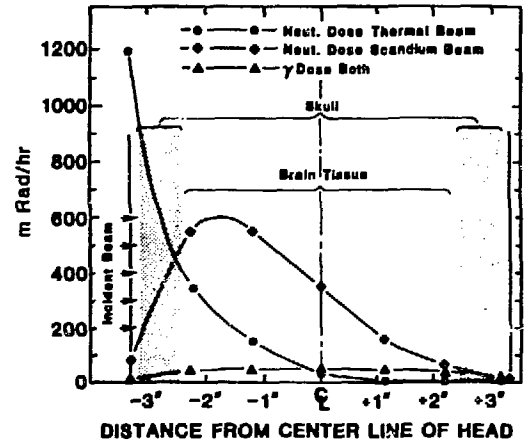

Fig 3. Measured thermal neutron fluxes across a phantom when the phantom is illuminated with a scandium filtered beam or a thermal neutron beam.

determined. The conversion factor from an intermediate current illuminating the patient to the thermal flux at the tumor must be selected. Calculations and measurements of this conversion factor have been made, but they are dependent on the energy of the neutrons, the size of the beam, and the depth of the tumor. A factor less than one can be calculated for a small-diameter beam, while a factor of two or three can be calculated for an infinite plane source. Numbers close to one seem to be representative and on the conservative side, so a conversion factor of one is what is used in this evaluation of ways to produce intermediate beams.

Another number that must be selected is the dose to the tumor from the radiation produced from the thermal neutron capture by the boron. Doses often used are several Gy, and for this evaluation a dose of 20 Gy will be used with a boron concentration in the tumor of 50 μgm/gm. With this dose, about the lowest dose that can be realized to tissue from the neutrons not interacting with boron is 0.2 Gy. The delivery time will be selected to be 30 minutes. The other two conditions that will be set are a total dose from gamma rays of less than 0.5 Gy, and a dose to the skin from thermal neutrons captured in boron of less than 0.3 Gy. Table 1 lists the Kerma and the neutron fluxes that would produce these doses.

TABLE 1. Target Doses and Fluxes for NCT Beams

Irradiation time	30 minutes
Kerma to tumor from capture of thermal neutrons in boron (50 μgm/gm)	20 Gy
Thermal neutron flux at tumor to produce 20 Gy/30 min	2.6×10^9 n/cm^{2}sec
Intermediate neutron current at surface to produce 2.6×10^9 n_{th}/cm^{2}sec at tumor	2.6×10^9 n/cm^{2}sec
Kerma in 30 minutes from intermediate flux with no boron capture	0.2 Gy
Thermal neutron flux to give 0.36 Gy in 30 minutes to skin from boron capture (50 μgm/gm)	3.9×10^7 n/cm^{2}sec
Kerma in 30 minutes to skin (no boron) from 3.9×10^7 m/cm^{2}sec thermal neutrons	0.01 Gy
Fast-neutron flux to give 0.3 Gy in 30 minutes	3.9×10^6 n/cm^{2}sec
Gamma Kerma Rate to give 0.5 Gy in 30 minutes	1.7×10^{-2} Gy/min

3. BEAMS FROM REACTORS

There are thirty-four research reactors in the USA with operating power levels of one MW and above.[3] These are listed in Table 2 even though not all of them are adaptable to NCT.

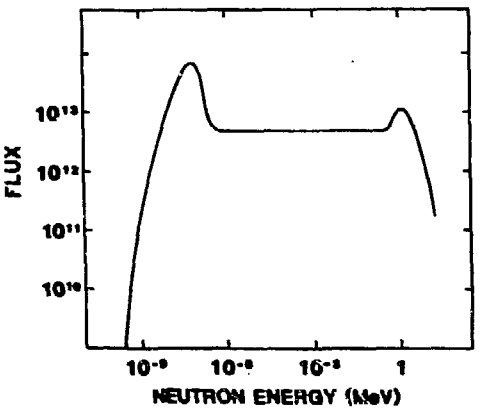

Fig 4. Example of the neutron flux spectrum near the core of a moderated fission reactor.

All these fission reactors produce neutrons by the fission process, and the primary neutrons have a fission neutron energy spectrum that is peaked near one MeV. All these reactors moderate the neutrons to lower energies to control the neutrons, and to use the neutrons to maintain the fission process. Thus the primary source of neutrons is some mixture of fast fission neutrons, 1/E slowing-down neutrons and thermal neutrons. Figure 4 displays an example of such a flux distribution. In some way the flux of intermediate-energy neutrons must be enhanced while the fast neutrons and thermal neutrons are strongly suppressed. The thermal neutrons can be relatively easily suppressed by Cd or Li.

There are several handles that are available to manipulate the fast and intermediate fluxes. These are selective moderation, selective filtering and selective reflection, and these can be coupled to a greater or lesser extent. Additional controls will have to be added to reduce the gamma-ray flux and the thermal neutron flux.

Moderators Moderators reduce the energy of the faster neutrons by elastic scattering, in which the struck atoms carry off some of the energy from the neutrons, or by inelastic scattering, in which the neutrons excite states in the struck atoms and transfer some of their energy to excited states of the atoms. To produce a flux of intermediate-energy neutrons, a moderator is needed that quickly moderates neutrons out of the fast groups into the intermediate groups, but does not quickly moderate the intermediate neutrons on down into the thermal groups. For example, hydrogen quickly moderates the fast neutrons out of the fast groups, but it also quickly moderates the intermediate neutrons into the thermal groups. On the other hand, moderation by lead or bismuth changes the energy of the fast and intermediate neutrons very little.

Using the MURR as a standard geometry and the diffusion code DISNEL to calculate neutron moderation, the effectiveness of a number of possible moderators has been tested. Figure 5 shows the flux variation as a function of radius out from the center of the core for an Al_2O_3 moderator. One notes that the intermediate flux (0.15 eV-9.1 keV) decreases less rapidly than the fast flux (9.1 keV-10 MeV). Figure 6 shows the flux distribution at a radius of 80 cm, and it is clear that the fast flux has been suppressed compared to the intermediate flux.

Table 2. Research and Test Reactors in the USA (January, 1986)

NAME AND/OR OWNER	DESIGNATION	LOCATION	TYPE	POWER, kW
Advanced Test Reactor (DOE)	ATR	INEL, ID	Tank	250,000
Fast Flux Test Facility (DOE)	FFTF	Richland, WA	Sodium cooled	400,000
Brookhaven High Flux Beam Research Reactor (DOE)	HFBR	Upton, NY	Heavy water	60,000
Brookhaven Medical Research Reactor (DOE)	BMRR	Upton, NY	Tank	5,000
High Flux Isotope Reactor (DOE)	HFIR	Oak Ridge, TN	Tank flux trap	100,000
National Bureau of Standards Reactor	NBSR	Gaithersburg, MD	Heavy water	10,000
Oak Ridge Research Reactor (DOE)	ORR	Oak Ridge, TN	Tank	30,000
Omega West Reactor (DOE)	OWR	Los Alamos,NM	Tank	8,000
Union Carbide Corporation Reactor	UCNR	Sterling Forest, NY	Pool	5,000
Power-Burst Facility (DOE)	PBF	INEL, ID	Open tank	Transient
Annular Core Research Reactor (DOE)	ACRR	Kirtland AFB, East, NM	UO_2BeO & transient	2,000
Bulk Shielding Reactor (DOE)	BSR	Oak Ridge, TN	Pool	2,000
General Atomic Company, Advanced TRIGA-Mk F Prototype Reactor	TRIGA-Mk F	La Jolla, CA	U-Zr hydride	1,500
Northrop Corporate Laboratories (Space Radiation Laboratory)	TRIGA-Mk F	Hawthorne, CA	U-Zr hydride	1,000
Rhode Island Nuclear Science Center		Fort Kearney, RI	Pool	2,000
Tower Shielding Reactor No. 2 (DOE)	TSR-2	Oak Ridge, TN	Light water	1,000
US Geological Survey Laboratory (Department of the Interior)	TRIGA-Mk I	Denver, CO	U-Zr hydride	1,000
Neutron Radiography Facility (DOE)	TRIGA-Mk I	FMEF-Richland, WA	U-Zr hydride	1,000
University of California-Berkeley	TRIGA-Mk III	Berkeley, CA	U-Zr hydride	1,000
Georgia Tech Research Reactor	GTRR	Atlanta, GA	Heavy water	5,000
University of Illinois	TRIGA-Mk II	Urbana-Champaign, IL	U-Zr hydride	1,500
University of Lowell		Lowell, MA	Pool	1,000
Massachusetts Insitute of Technology	MITR	Cambridge, MA	Heavy-water reflected	5,000
University of Michigan (Ford Nuclear Reactor)		Ann Arbor, MI	Pool	2,000
University of Missouri	MURR	Columbia, MO	Tank	10,000
North Carolina State University	PULSTAR	Raleigh, NC	Pool	1,000
Oregon State University	TRIGA-Mk II	Corvallis, OR	U-Zr hydride	1,000
Penn State TRIGA Reactor (Pennsylvania State University)	PSTR	University Park, PA	Pool-TRIGA core	1,000
State University of New York (Western New York Nuclear Research Center, Inc.)	PULSTAR	Buffalo, NY	Pool	2,000
Texas A&M University (Nuclear Science Center Reactor)	NSCR	College Station, TX	U-Zr hydride	1,000
University of Virginia	UVAR	Charlottesville, VA	Pool	2,000
Washington State University	WSTR	Pullman, WA	Pool-TRIGA core	1,000
University of Wisconsin	TRIGA	Madison, WI	Pool-TRIGA core	1,000
Armed Forces Radiobiology Research Institute (DNA, DOD)	AFRRI	Bethesda, MD	TRIGA-Mk F	1,000

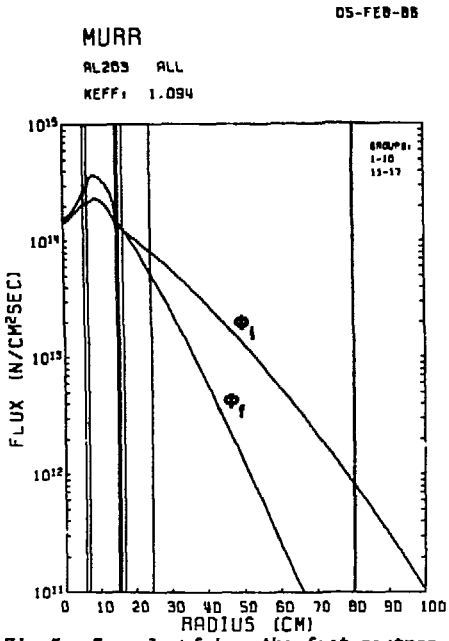

Fig 5. Example of how the fast-neutron flux (9.1 keV-10 MeV) and the intermediate-neutron flux (0.15 eV-9.1 keV) change as the neutrons diffuse out into the moderator, in this case a moderator of Al_2O_3.

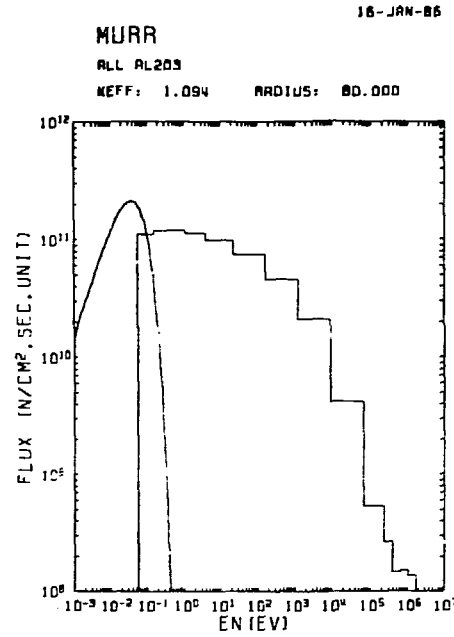

Fig 6. The neutron spectrum at a distance of 80 cm from the centerline of the reactor when the reactor is moderated with Al_2O_3.

Figure 7 shows the ratio of the intermediate flux to the fast flux at several levels of the intermediate flux for a number of elements and compounds used as moderators. From these data and other calculations it appears that it is important to have some aluminum as moderator. This is probably because aluminum has a higher cross section for fast neutrons than for intermediate neutrons, thus causing more interactions by the fast neutrons. It appears that an element of mass near oxygen needs to be mixed with the aluminum to produce some moderation and reduction of energy,[4] but not as rapid moderation as from hydrogen or some other light elements. An Al-metal-plus-15%-D_2O moderator has been built and tested by a group at the University of Tokyo,[5] and shows a good ratio of intermediate to fast neutrons. Calculations for an Al_2O_3 moderator for the MURR have been made, and will be reported on in more detail in a later session of this meeting.[6]

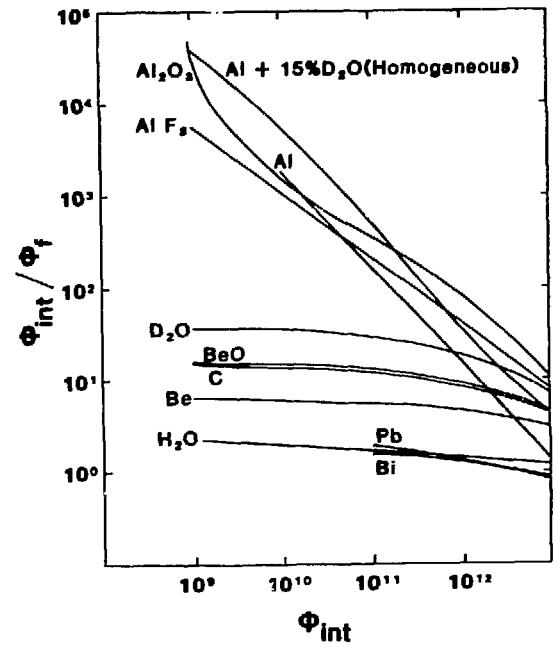

Fig 7. A comparision of the magnitudes of the intermediate fluxes to the fast fluxes for several different moderating materials.

These calculations and measurements indicate that an intermediate-energy neutron beam can be produced at a fission reactor by the proper design of the moderator.

Filters A second method to produce beams of intermediate neutrons starting with the prime flux from a reactor is to use filters that preferentially pass intermediate neutrons while stopping fast neutrons, thermal neutrons and gamma rays.[7] Several elements have windows in their cross sections that produce such filtering. Table 3 lists some of the filters that have been identified as passing intermediate-energy neutrons, ones for which materials are plentiful enough that a filter for NCT is practical. In these filters the primary material has a window at the desired energy, but also windows at higher, undesirable energies. The secondary materials are added because these shade the higher-energy windows. The amount of each material is usually a compromise based on the maximum flux desired compared to the degree of suppression of faster neutrons and gamma rays.

Table 3. Neutron Filters for Reactor Beams

Filter Material		Beam Energy	Relative	
Primary	Secondary	(keV)	Flux	Gamma Discrimination
U-238	Se,Mn,Ge	0.186 ± 0.001	1	Good
U-238	none	0.186 to Several		Good
Sc	^{60}Ni, ^{64}Zn	2 ± 0.35	6	Okay
Fe	Al, S	24 ± 1	4	Okay
Al/S	Ar	<30	30	Help Needed

The flux obtainable with filters depends on a number of parameters. With a prime flux as high as from the MURR it is estimated that a beam of 1 X 10^9n/cm^{2}sec can be realized if the source area is large--about 2000 cm^2 --and the path from source to patient is short--less than 2 m. A specific number can not be given because the flux depends on several parameters that are reactor specific, such as the magnitude of the 1/E flux, the maximum source size that is usable, the source-to-patient distance, and the amount of filtering material that is used.

The uranium and scandium filters have primary windows at neutron energies that are near the minimum for the KR/NF. The higher-energy windows in uranium probably do not extend above a few keV and neutrons passing through all the windows can be used for NCT. This concept is discussed in more detail in a later paper.[6] There are higher-energy windows in the scandium cross section, and it has been difficult to find secondary materials to shade these windows. In addition pure scandium metal is expensive, and a large enough amount to make a filter with a large area may be too expensive to be practical.

The energy of the iron filter is beginning to creep up the KR/NF curve. It has been reported that the KR/NF for 24-keV neutrons is twice that for lesser energies.[8] The Al/S filter may have the same problem since some of the neutrons passed by this filter are near 30 keV. However, the Al/S filter does appear to transmit the largest fraction of intermediate-energy neutrons.

There can be some coupling between the filter and the moderation of the source. Starting with the highest intermediate flux will increase the beam current. Moderators that seem to be better are Be, C, Fe, Pb, D_2O, BeO, Al_2O_3, Al + D_2O, PbO, and AlF_3. There is about a factor of two in magnitude of intermediate flux from the best to least of these. Also it has been suggested that choosing the moderator/reflector so that it has a window to match the window in the filter can increase the effective depth of the source and thus increase the source strength.[4] This has been demonstrated in the DENIS beam at Harwell.[8]

Reflectors Selective reflection or scattering of neutrons is another possible way to produce a flux of intermediate-energy neutrons.[9,10] The source-to-patient path is shielded from direct line-of-sight to the source and a reflector changes the energy and redirects neutrons from the source toward the patient. Reflector materials are selected that preferentially scatter intermediate-energy neutrons toward the patient. To be efficent, the reflector must be close to either the source or the patient. One disadvantage of this arrangement when the reflector is near the patient is that the full beam is brought out into the room and is hard to control. Such a reflector by hydrogenous material placed outside the biological shield near the patient has been tried at the GTR with some success.[11] At other reactors, selective reflectors have been placed in tangential beam tubes close to the core and have been used with filters. A magnesium scatterer coupled with a scandium filter helps to suppress the fraction of faster neutrons. At the present time, the use of reflectors to produce an intermediate-energy beam for NCT is not promising.

Several general comments can be made about achieving an intense intermediate-energy neutron beam. First, the reactor that is the primary source of neutrons must be relatively high flux, since a penalty of at least a factor of 100 is paid in intermediate flux to suppress the fast flux significantly below the intermediate flux. This is true whether one uses moderators, filters or reflectors. Second, even with relatively high fluxes, a large source area and a short source-to-patient distance are required to have enough intermediate flux illuminating the patient.

4. Thermal Neutron and Gamma-Ray Suppression

Besides suppressing the fast neutrons, it is also necessary to suppress the thermal neutrons and the gamma rays. The thermal neutrons can be suppressed with a strong thermal neutron absorber, such as Li-6 or Cd. The Li-6 is a 1/v absorber, and when enough is used to suppress the thermal neutrons, some of the neutrons near 1 eV, which are acceptable for NCT, are lost. One advantage of Li-6 is that it emits no gamma rays when absorbing neutrons. In contrast, Cd has a high absorption cross section near thermal which drops sharply above 0.3 eV. With a Cd absorber, the thermal neutrons can be absorbed, while the higher energy neutrons are not. However, when Cd absorbs neutrons, gamma rays are emitted and these must be controlled.

If the moderating, filtering, or reflecting materials are not sufficient to suppress the gamma rays coming from the reactor and the gamma rays coming from neutron capture in moderator, filter, or reflector

materials, then some additional gamma shielding must be added. Bismuth is the best such shielding because it causes very little change in the energy of the neutrons, and its capture cross section is small. The bismuth must be quite pure to reduce capture gamma rays from trace impurities. Lead is another good gamma shielding material, but with about five times the capture cross section. Lead has a higher thermal conductivity than bismuth, which can be important when the shield is placed close to the core of a reactor.

While bismuth and lead do not change the energy or absorb many of the neutrons, they do change the directions that the neutrons are traveling. Thus to be used as gamma shields, the shielding needs to be placed close to the source or close to the patient, where the loss of neutrons directed away from the patient will be compensated by other neutrons being redirected toward the patient.

5. Other Considerations About Neutron Sources

Besides the beam, several other conditions are important to have an effective therapy facility for NCT. At the patient position there should be enough room so that the patient can be moved and oriented so that the tumor is illuminated effectively while the dose to the rest of the patient's body is minimized. There should be a therapy room with adequate shielding to protect the staff, and with windows and diagnostic devices so that the patient can be observed. The room and reactor floor area should be clean, attractive and bright to provide a positive environment for the patient. The therapy area should be close and accessible to patient care facilities and an active cancer therapy program. Close proximity to a veterinary medicine department or animal care facility is also useful.

6. Conclusions

There are several ways to produce a beam of intermediate-energy neutrons. The use of selective moderation or selective filtering appears to be more promising than selective reflection. Starting with a relatively high-power and high-flux nuclear reactor, it appears that a beam of sufficient intensity can be achieved that a patient could be treated in less than an hour. The quantity and the quality of each beam depends upon the specific design and the reactor source; more detailed calculations and measurements need to be made to confirm the quality and intensity in each case.

7. Acknowledgments

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Research Related to Boron Neutron Capture Therapy at The Ohio State University

Rolf F. Barth[1], Albert H. Soloway, Fazlul Alam, Dianne M. Adams, Nancy R. Clendenon, Joseph H. Goodman, Reinhard Gahbauer, Alfred E. Staubus, Thomas E. Blue, T. Courtney Roberts, Carl P. Boesel, Alan J. Yates, Naoki Mafune, Walter E. Carey, Joseph W. Talnagi, James R. Girvin, Ralph E. Stephens and Melvin J. Moeschberger

The Ohio State University
Columbus, Ohio 43210

ABSTRACT

Research in the area of boron neutron capture therapy (BNCT) at The Ohio State University is a highly multidisciplinary effort involving approximately twenty investigators in nine different departments. Major areas of interest include: 1. Boronation of monoclonal antibodies directed against tumor-associated antigens for the delivery of ^{10}B; 2. Synthesis of ^{10}B-containing derivatives of promazines and porphyrins that possess tumor-localizing properties; 3. Development of a rat model for the treatment of glioblastoma by BNCT; 4. Quantitation and microdistribution of ^{10}B in tissues by means of a solid state nuclear track detector. The ultimate goal of this research is to carry out the extensive preclinical studies that are required to bring BNCT to the point of a clinical trial.

I. BORONATION OF POLYCLONAL AND MONOCLONAL ANTIBODIES

Rolf F. Barth, Albert H. Soloway, Fazlul Alam, Dianne M. Adams and Naoki Mafune

Research in the area of boron neutron capture therapy at The Ohio State University began in 1980 when Drs. Soloway and Barth focused their attention on the possibility of using monoclonal antibodies for the delivery of boron-10. Prior to the development of hybridoma technology, attempts to produce polyclonal antibodies directed against tumor-associated antigens more

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often than not were unsuccessful. The picture changed radically with the introduction by Köhler and Milstein (1,2) of a method to immortalize antibody-producing cells by fusing them with myeloma cells. By 1980 it was amply demonstrated that monoclonal antibodies could be produced against antigens that had such restricted expression, that they could be regarded as operationally "tumor specific" (3). It was widely believed that monoclonal antibodies might be useful for the targeting of agents either for the diagnosis or treatment of cancer. Dr. Soloway's longstanding interest in the development of ^{10}B-containing compounds that had tumor-localizing properties and Dr. Barth's interests in tumor immunology led to a collaborative effort on the boronation of polyclonal and monoclonal antibodies. Dr. Soloway had been among the first to sugggest that antibodies directed against tumor-associated antigens might provide a means for selectively targeting ^{10}B (4). Initial studies carried out by him indicated that it was possible to incorporate 0.6 to 1.2% of ^{10}B per molecule of bovine gamma globulin without denaturing the protein (5). These data provided the impetus to proceed onward to develop the methodology for linking a large number of ^{10}B atoms per molecule of monoclonal antibody.

Initially our attention was focused on the direct linkage by thiol disulfide interchange of the polyhedral borane, $Na_2B_{12}H_{11}SH$, to a polyclonal antibody directed against human thymocytes (ATGAM™), which was kindly provided by the Upjohn Company, Kalamazoo, MI. In 1982 Dr. Fazlul Alam joined in these efforts to boronate antibody molecules. It quickly became apparent that this simple approach would not yield heavily boronated antibody molecules (6). Attention then turned to the use of a heterobifunctional reagent, N-succinimidyl 3-(2-pyridyldithio) propionate (SPDP) that could be used to conjugate a much larger number of boron cages per antibody molecule. The antibodies employed for this were either ATGAM™ or the monoclonal antibody 17-1A, which is directed against a human colorectal cancer-associated antigen (3). The latter has been kindly provided to us by Dr. Zenon Steplewski of the Wistar Institute, Philadelphia, PA. Using SPDP we succeeded in incorporating up to 130 atoms of ^{10}B per molecule of antibody (7). There was a significant loss in immuno-reactivity associated with this, however, which led to the development of an alternative approach. That was to heavily boronate poly-DL-lysine (BPL) with an isocyanate polyhedral borane derivative, $Me_3NB_{12}H_{11}NCO$-, and then to crosslink it to antibody molecules utilizing SPDP and m-maleimido-benzoyl N-hydroxysuccinimide ester (MBS) (8). This method has yielded highly boronated immunoreactive antibodies, but contained a mixture of products including unconjugated BPL, unconjugated and variably conjugated antibody molecules, and bridged oligomers. Current efforts are directed towards the separation of the monoconjugated antibody molecules from this complex mixture.

Another approach has focused on the attachment of BPL to Fab' fragments of MoAb 17-1A rather than the intact antibody. $F(ab')_2$ fragments were reduced with β-mercaptoethylamine and the resulting Fab' fragments have a single reactive sulfhydryl group that is far removed from the antigen-binding site. Maleimido groups then were inserted into BPL using MBS and the resulting BPL-MB conjugates were reacted with the Fab' fragments. Since only one BPL molecule can bind to a fragment, the covalent linkage occurs at the

identical site on all Fab' fragments, thereby providing a greater degree of control over the site of attachment than otherwise might be possible with intact antibody molecules. Immunoreactivity of the boronated Fab' fragments was similar to unboronated fragments, as determined by immunofluorescent endpoint titers. These preliminary results suggest that there may be significant advantantages in using immunoglobulin fragments rather than intact antibodies for the delivery of ^{10}B. Once the in vitro binding affinities of the ^{10}B-labeled MoAbs and their fragments have been determined, then their ability to sustain a lethal n,α reaction will be studied. If it can be demonstrated that the boronated immunoconjugates have a high degree of in vitro reactivity for colorectal cancer target cells, then in vivo distribution studies of the boronated antibodies will be carried out in nude mice carrying the human colorectal cancer cell line SW1116.

II. SYNTHESIS OF BORONATED PROMAZINES AND PORPHYRINS

Albert H. Soloway, Fazlul Alam and Rolf F. Barth

It has been reported that chlorpromazine (CPZ) preferentially localizes in malignant melanomas (9). Fairchild et al. (10) have shown that sulfur-35-labeled CPZ localized in melanoma with concentrations up to 100 μg per gram of tumor with excellent biological half-life and tumor to normal tissue ratios. If a boronated analogue, containing 10 boron atoms per molecule (i.e. one carborane cage), behaved similarly, then tumor concentrations of $\sim$30 μg ^{10}B/g might be attainable. Our efforts have been directed towards attaching polyhedral borane moieties to the phenyl rings of the promazine structure, at a distance from the S-N-N binding axis. Two compounds have been synthesized by reacting lithiocarborane with 2-acetylpromazine and 3,7-diacetyl promazine. In addition, we have carried out some preliminary studies on the synthesis of boron-containing porphyrins that potentially could be used for the selective delivery of ^{10}B. We have encountered a number of problems that have, for the present time, led us to defer further work on this and concentrate on the promazine derivatives. These studies will be discussed in detail by Dr. Soloway.

III. DEVELOPMENT OF A RAT MODEL FOR THE TREATMENT OF GLIOBLASTOMA BY BNCT

Rolf F. Barth, Nancy Clendenon, Joseph H. Goodman, James R. Girvin, Reinhard Gahbauer, Alfred E. Staubus, Fazlul Alam, Albert H. Soloway, Walter E. Carey, Carl P. Boesel, Alan J. Yates, Melvin J. Moeschberger and Ralph G. Fairchild (Brookhaven National Laboratory)

This segment of our work focuses on the development of an animal model for the treatment of glioblastoma by means of BNCT. It is based on Hatanaka's clinical studies on the treatment of grade IV gliomas by a combination of surgery and BNCT (11) Drs. Clendenon and Goodman have carried out previous

work with two ethyl nitrosourea-induced glioma cell lines. One, designated D74, is a differentiated tumor associated with a shorter survival time, and the other, F98, an undifferentiated tumor that is associated with a longer survival time. The biologic behavior of these tumors is similar to human glioblastoma in that they kill by forming an expanding intracranial mass, they are uniformly lethal, and they do not metastasize. The experimental plan briefly is as follows: 1. implant F98 or D74 tumor cells stereotactically into the brains of rats, 2. allow the tumors to grow intracerebrally for $\sim$ 2 weeks, 3. administer the polyhedral borane $Na_2B_{12}H_{11}SH$ intravenously, 4. allow sufficient time for the compound to distribute so as to achieve optimum tumor to brain and tumor to blood concentrations, and 5. irradiate with a collimated beam of thermal neutrons using the Medical Research Reactor at Brookhaven National Laboratory.

Two experiments have been carried out to date. $Na_2{}^{10}B_{12}H_{11}SH$, kindly provided by Dr. H. Hatanaka (Teikyo University, Tokyo, Japan) and Dr. M. Narisada (Shionogi Research Laboratories, Osaka, Japan) was administered intravenously at a dose of 50 mg/kg body wt. to rats that had been innoculated intracerebrally 14 days earlier with F98 cells. On the basis of preliminary pharmacokinetic data it was decided to irradiate them 24 hours following administration of the capture agent. In the first experiment animals received 2, 4 or 6 x 10^{12} n/cm^2 delivered "head on" through a 2.5-cm^2 opening. In the second experiment the neutron fluences were increased to 10^{13}, 2 or 4 x 10^{13} n/cm^2. Survival curves were estimated by means of the Cox proportional hazards model (12). Fluences of 2, 4 or 6 x 10^{12} n/cm^2, which corresponded to doses of 469 to 1407 cGy for ^{10}B-containing tissues (assuming a 10 µg/g concentration of tumor), showed no therapeutic effect compared to untreated controls (median survival time 17d, range 17-19 d). Enhanced survival was seen in rats irradiated with 10^{13} n/cm^2 (MST 25 d, range 19-26d), but this was not augmented by administration of $Na_2{}^{10}B_{12}H_{11}SH$, suggesting that an insufficient amount of ^{10}B had localized in the tumor. A thermal neutron fluence of 4 x 10^{13} n/cm^2, which corresponded to a dose of 9380 cGy for ^{10}B-containing tissue and 3040 cGy for non-boron-containing tissue, was associated with uniform lethality within 2-3 days of irradiation, thereby defining the upper limit of acute CNS tolerance. Although it was somewhat disappointing not to see differences between animals that had received $Na_2{}^{10}B_{12}H_{11}$ and those that had not, this was not surprising.

The two essential requirements for the success of BNCT are localization of requisite quantities of the capture agent at the site of the tumor and a sufficient fluence of thermal neutrons to sustain a lethal n,α reaction. Dr. Fairchild's calculations indicate that there was a sufficient dose of neutrons. Pharmacokinetic studies and tumor boron analyses, however, suggest that 24 hours was not an optimum time interval between administration of the capture agent and neutron irradiation. In parallel with the animal studies described above, <u>in vitro</u> studies with F98 cells were carried out at the same time and survival was determined by means of a clonogenic assay. These studies showed that with a fluence of 2 x 10^{13} n/cm^2 and a concentration of 50 µg/ml of $Na_2{}^{10}B_{12}H_{11}SH$ it was possible to reduce the surviving fraction to 4 x 10^{-4}. On the basis of calculations carried out by Dr. Fairchild (Personal

communication), a dose of 2×10^{13} n/cm^2 to the head should be tolerated by rats. Furthermore, a dose of 50 μg of $Na_2\,{}^{10}B_{12}H_{11}SH$ theoretically should be attainable on the basis of preliminary pharmacokinetic data. For these reasons we are optimistic that the tumor model that has been developed will prove to be useful for studying the potential therapeutic efficacy of BNCT for the treatment of glioblastomas. In addition, important information will be obtained on the normal-brain tolerance for neutron irradiation in the presence or absence of $Na_2\,{}^{10}B_{12}H_{11}SH$. This ultimately should help in the design of large animal studies.

IV. QUANTITATION AND MICRODISTRIBUTION OF BORON-10

Thomas E. Blue, T. Courtney Roberts, Rolf F. Barth and Joseph Talnagi

The final component of our research program on BNCT is directed towards developing methodology for the quantitation and microdistribution of ^{10}B in tissues by employing a Solid State Nuclear Track Detector (SSNTD). The ^{10}B concentrations of samples of tissue taken from brains, tumors, and from the blood of rats are being measured with the polycarbonate SSNTD CR-39, using an autoradiographic procedure and an image analysis system for automatic track counting (13).

The procedure is briefly described as follows. Homogenized samples of tissue and blood are placed within 1.0 cm x 1.0 x 0.02 cm wells on the surface of CR-39 detectors, and then irradiated in the thermal column of the OSU Research Reactor, with a fluence of 2×10^{11} neutrons/cm^2. The tissue and blood samples in the wells act as charged particle radiators for the CR-39 detectors. The fluence is monitored with a fission chamber that typically records $1.9 \pm 0.2 \times 10^7$ counts. Following irradiation, the track detectors are etched and counted. Then the detector response is determined by dividing the number of tracks that were counted per cm^2 of detector surface by the number of fission chamber monitor counts that were recorded during the detector irradiation. Finally, the ^{10}B concentration is determined by comparing the detector response of the sample with a calibration curve of the detector response versus ^{10}B concentration for detectors with radiators of known concentrations of ^{10}B.

Among the often cited virtues of CR-39 are optical quality, uniformity of response, and low threshold for charged-particle detection. For ^{10}B concentration measurements in tissue, however, the low threshold LET of CR-39 is a problem, since proton tracks from the (n,p) reaction of nitrogen may be recorded. In order to obtain a large percentage increase in detector response with increasing ^{10}B concentrations, the detector etch time has been optimized, so that the ratio of alpha and lithium-7 recoil tracks to proton tracks is a maximum. This optimum etch time has been measured to be 4 ± 0.5 hours for a 70°C, 6.25 M NaOH etchant by maximizing the ratio of the response of a detector with a boron radiator to the response of a detector with a TEL radiator.

Nevertheless, for this etch procedure, the calibration curves of detector response versus ^{10}B concentration have different intercepts for tissue equivalent liquid (TEL), blood, and brain, indicating that the nitrogen concentration in a sample is an interfering input for ^{10}B concentration measurements. This observation has been confirmed by measuring the detector response with urea, the nitrogen-containing component of TEL, as the sample.

It appears that ^{10}B concentrations of at least 2 μg ^{10}B per g blood can be measured with good accuracy using CR-39. However, for the measurement of smaller concentrations, the etch procedure for CR-39 will have to be be modified so that the detection efficiency for protons is reduced.

CONCLUSIONS

A multidisciplinary effort has been mounted by investigators at The Ohio State University to develop BNCT as a possible treatment modality for cancer. If BNCT is ever going to succeed, it will require the efforts of experts in fields as diverse as boron chemistry, nuclear engineering, immunology, reactor physics, radiation oncology, medicinal chemistry and neurosurgery, to, name but a few. Since no single institution either in the United States or abroad currently has all of the people or material resources required to carry out this task, the best chances for mounting a truly comprehensive research program rests in the development of a collaborative effort that will draw on the resources of various cooperating institutions. Recognizing this, the research group at The Ohio State University has developed collaborative ties with the Medical Department at Brookhaven National Laboratory, the Lewis Research Facility, National Aeronautics and Space Administration, in Cleveland, and the Research Institute, Churchill Hospital/University of Oxford in England. We would like to believe that ultimately this collaborative effort could lay the groundwork for a major national study on the efficacy of BNCT.

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Studies at MIT on Biodistribution of B-10 Compounds and Production of Epithermal Neutrons

Gordon L. Brownell and Charles Carney
Massachusetts Institute of Technology
Cambridge, MA 02139

ABSTRACT

The determination of the biodistribution of B-10 compounds in brain and the production of relatively pure epithermal neutron beams are two important tasks required for the widespread application of neutron capture therapy. At MIT, studies are underway to determine cellular and sub-cellular distributions of boron by means of track-etch autoradiography and by use of a wavelength dispersive scanning electron microprobe. Nuclear magnetic resonance and magnetic resonance imaging are also being explored for in vivo determination of macroscopic boron distributions.

A relatively pure beam of epithermal neutrons would be of great advantage in neutron capture therapy. In addition to offering improved depth-dose distributions, such beams demonstrate considerable dose build-up at the surface and result in significant skin sparing. This may offer the possibility of irradiating brain tumors through the intact scalp and skull and permit fractionated dose therapy. Such improvement would be enhanced with new boron compounds that exhibit greater retention in the tumor. The use of (p,n) reactions on low-Z nuclei such as ^{7}Li produce copious quantities of relatively low-energy neutrons. There have been a number of recent developments in the production of large currents of low-energy protons. Cyclotrons, proton linear accelerators,and other devices have been proposed,and studies are underway to determine an optimal source configuration.

1. BIODISTRIBUTON OF B-10 COMPOUNDS

Track-etch autoradiography has been extensively used to determine the macrodistribution of B-10 compounds in tissue [1]. Adequate resolution has been achieved to determine B-10 distributions in regions of brain in animal tumor models and in vascular structures. However, the determination of such distributions on a cellular and sub-cellular basis will require the development of new techniques. Studies are underway to determine the application of computer image

processing to determine the origin of tracks seen on solid-state detectors and to predict the location of B-10 reactions on a micro scale. These studies may lead to techniques that will permit subcellular distribution to be determined.

An interesting alternative is the use of a wavelength dispersive scanning electron microprobe to determine B-10 distributions by measurement of characteristic X rays. Preliminary studies indicate that B-10 can be observed using this device, but questions concerning sensitivity and spatial resolution remain to be answered. Studies in this area are under way.

2. PRODUCTION OF EPITHERMAL NEUTRONS

Thermal neutrons provide the catalyst for producing intense radiation dose on a cellular level via the $^{10}B(n,\alpha)^{7}Li$ reaction -- the basis for neutron capture therapy. Several factors have led to the search for an epithermal neutron beam. At higher neutron energies, the 1/v behaviour of the ^{10}B cross section results in a significant reduction in (n,α) reactions. In addition, the high hydrogen content in tissue can be exploited to thermalize the beam as it penetrates the tissue. The combination of these two factors results in skin sparing and a peak of thermal neutron flux at some depth beneath the surface.

We have studied the use of (p,n) reactions near the reaction threshold for the production of epithermal neutrons. We believe that there exist many attractive features of this source of neutrons for neutron capture therapy.

A number of studies have been conducted in the past to examine the dose-depth behavior of epithermal neutrons in tissue[2]. The question of optimal neutron beam energies for therapy, however, remains a question. The therapeutic gain, defined as the ratio of effective dose to tumor relative to the maximum effective dose to normal tissue, has been found to be a maximum at approximately 3 cm depth in tissue. In the range from 0.5 eV to 10 keV, this depth of maximization changes very little (Fairchild and Bond) (1). Finally, in terms of minimizing induced background dose due to $H(n,\alpha)^{2}H$ reaction (dominant at lower neutron energies) and proton recoils due to elastic neutron scattering (dominant at higher energies), it has been found that the "optimal" neutron beam energy that minimizes both of these background components occurs at 500 keV (Marstin, Kawecka, Feinendegen) (1).

Most of the work carried out on the production of epithermal neutron beams has been with filtered, reactor-produced neutrons. In principle, with proper selection of isotopes one can effectively produce a "window" of neutrons that would be emitted within a specified energy

range. Other sources of epithermal neutrons, however, are charged-particle reactions that make use of accelerators. (p,n) reactions appear attractive due to their low energy threshold. If the incident proton beam is kept close to the threshold energy for reaction, low-energy neutron emission can be achieved. Table I lists a number of possible reactions and their characteristics. Group 1 consists of medium atomic number nuclei as targets. These appear to be attractive, in particular ^{45}Sc, because neutron energies obtained at 0^{o} are low. At greater angles of neutron emission the neutron energy decreases even further. Additionally, many of the elements are metals and can withstand intense proton beams with minimal degradation of the target provided proper cooling is maintained. The disadvantage of these isotopes, however, is their relatively low reaction cross sections. Group 2 consists of the two light targets, ^{3}H and ^{7}Li. Although the neutron yield of ^{3}H

Table I - Partial list of (p,n) reactions commonly used for low-energy neutron production

Group 1 - medium-weight target nuclei

Reaction	Threshold energy (keV)	Energy of first excited state (keV)	Energy range of neutrons at 0^{o} (keV)
$^{45}Sc(p,n)^{45}Ti$	2909	37	5.6 - 52
$^{51}V(p,n)^{51}Cr$	1564	749	2.36- 786
$^{57}Fe(p,n)^{57}Co$	1648	1378	2 -1425

Group 2 - low-weight target nuclei

Source reaction	Target	0^{o} Neutron yield ($n = sr^{-1} \cdot \mu A^{-1}$)	Neutron energy range (MeV)
$^{7}Li(p,n_{o})^{7}Be$	Solid (Li-metal)	6×10^{6}-3×10^{7}	0.2-0.7
$^{3}H(p,n)^{3}He$	Gaseous Tit 1.5	3.3×10^{7}-1.6×10^{5} 5×10^{6}-1.7×10^{7}	0.7-3

is higher, its neutron energy values are significantly greater than for ^{7}Li.

Considering the characteristics of the reactions listed in Table I, ^{7}Li appears to be the target of choice owing to the relatively low neutron energies and high neutron yields. The proton threshold energy is 1.881 MeV, and a pronounced resonance exists at 2.25 MeV with a small resonance just above threshold at 1.92 MeV. The integrated cross section at 2.25 MeV is 580 mb.

Although the ^{7}Li(p,n)^{7}Be reaction is widely used in nuclear physics, data pertaining to absolute neutron yield and neutron energy spectrum, particularly near the reaction threshold, are almost nonexistent. Some work has been published [3], although a number of aspects such as target material, angular emission, and prompt and delayed gamma contamination were not specifically addressed.

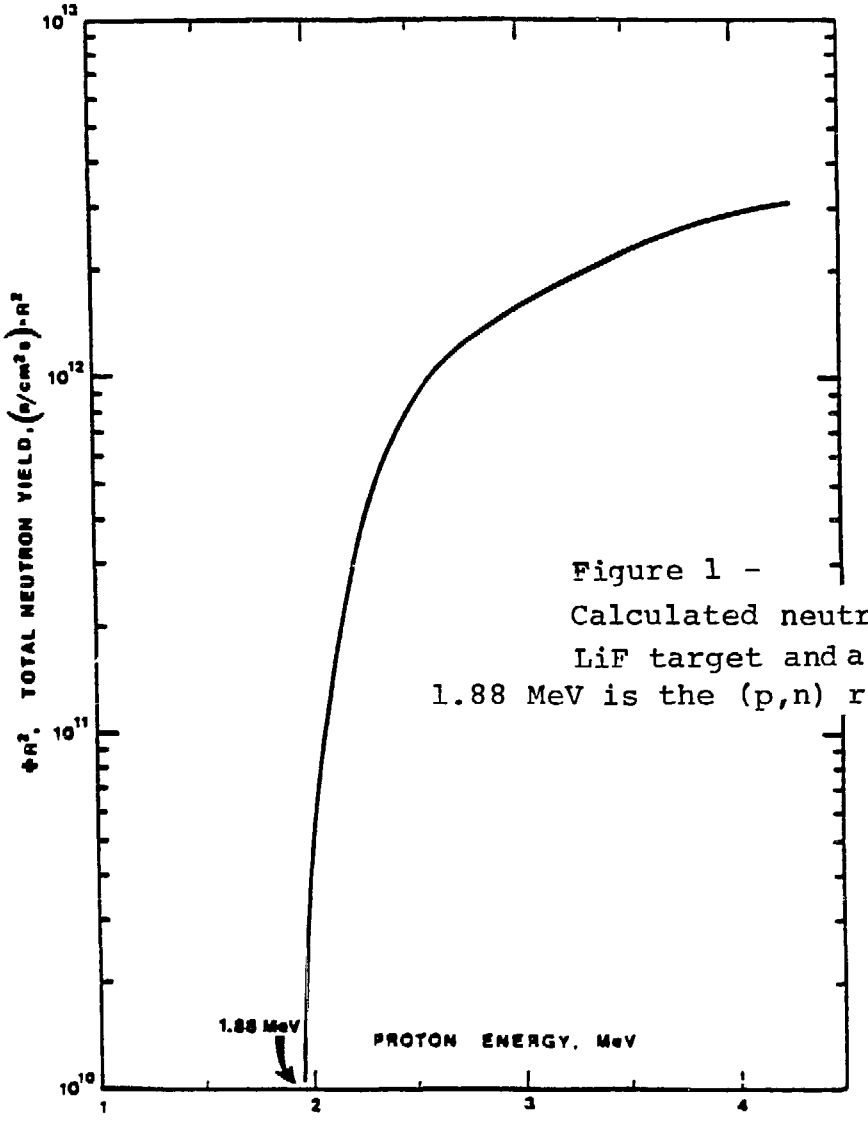

Figure 1 - Calculated neutron yield for a LiF target and a 1-mA beam current. 1.88 MeV is the (p,n) reaction threshold.

A semi-analytical computer code using linear interpolation of proton energies was developed by us and used to evaluate some of the features of this reaction as it would relate to its use for neutron capture therapy [4]. For a LiF target and a current of 1 mA, the absolute yield versus incident proton energy is shown in Figure 1. From a proton energy of 2 to 3 MeV, the total yield increased by nearly two orders of magnitude. Neutron yields for LiF were examined versus angles of emission at different proton energies. This is shown in Figure 2, and the corresponding numbers indicate

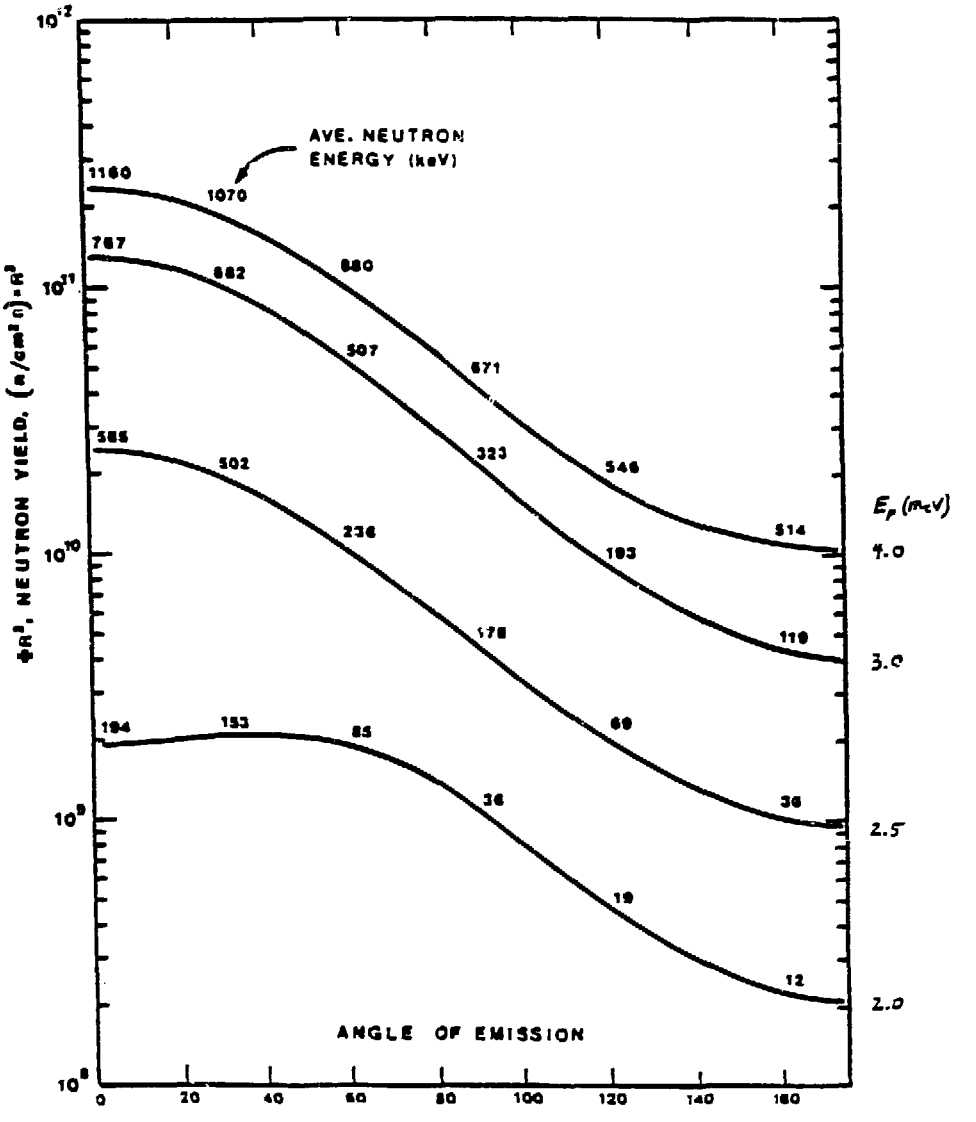

Figure 2 - Neutron yield curves for 4 different proton beam energies on a LiF target integrated and smoothed over 5-degree intervals. Average neutron energies at different angles are indicated for each proton energy.

average neutron energies at a particular angle of emission. Figure 2 also demonstrates the potential of (p,n) reactions as variable-energy neutron sources. Neutron energy spectra can be shifted significantly either by changing the proton beam energy or changing the angle of emission.

A number of accelerators could be considered for the production of intense, low-energy proton beams. These include cyclotrons, linear accelerators, and electrostatic systems (4). Studies are underway using computational methods to determine the optimum source energy and intensity and to determine the resultant neutron spectra and spatial distributions.

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A Clinical Trial of Neutron Capture Therapy for Brain Tumors at New England Medical Center and the Massachusetts Institute of Technology

Robert G. A. Zamenhof, Ph.D., Hywel Madoc-Jones, M.D., Ph.D.
Dept. of Therapeutic Radiology
New England Medical Center
Boston, MA 02111

Otto K. Harling, Ph.D., John A. Bernard, Ph.D.
Nuclear Reactor Laboratory
Massachusetts Institute of Technology
Cambridge, MA 02139

ABSTRACT

Neutron Capture Therapy (NCT) is a potentially effective form of radiation therapy for certain forms of cancer that are not amenable to treatment by existing modalities, such as external beam radiation therapy, surgery, chemotherapy, or even a combined modality approach. First proposed in the 1930's, NCT has not yet achieved clinical success in the United States although in Japan over 86 patients with high-grade brain tumors have been treated by NCT with extremely encouraging results. A very large amount of preclinical research has been accomplished in NCT by a few groups in the United States, primarily at the Massachusetts Institute of Technology (MIT) and at Brookhaven National Laboratory (BNL). What has been noticeably lacking thus far is a strong multidisciplinary approach, including expertise in nuclear reactor design, operation, safety, and dosimetry; and senior clinical expertise in the areas of radiation therapy, neurosurgery, neurology, neuroradiology, medical oncology, and pathology. The group of scientists who are involved with this proposal carry precisely the credentials mentioned above. The MIT Nuclear Engineering Laboratory consists of scientists whose expertise lies in the areas of nuclear reactor design, operation, and safety, nuclear track-etch autoradiography, neutron activation analysis, the use of sophisticated radiation transport computer codes, and radiation measurements. The Department of Therapeutic Radiology and the Brain Tumor Therapy Group at Tufts New England Medical Center (T-NEMC) consist of approximately fifteen scientists whose expertise covers

the medical specialties mentioned above, including one of the coinvestigators who has accomplished extensive research in NCT while at MIT and the Massachusetts General Hospital. The T-NEMC group has an established track record of research on innovative methods of brain tumor therapy. The equipment resources at T-NEMC and MIT are so extensive that we are not aware of any measurement, either laboratory on in vivo diagnostic, that might be needed for the proposed research and clinical program that we would not be able to accomplish.

The proposal we are submitting is based on the conclusions of a NCT expert panel recently convened at BNL by the Department of Energy to evaluate the status of NCT and to recommend what preclinical tasks should be accomplished prior to a clinical study being undertaken. Our proposal is for two years of preclinical research and preparations, followed in the third year by a pilot clinical trial of ten patients with grade-IV astrocytoma brain tumors, for whom the prognosis with existing treatment modalities is less than a 5% three-year survival rate. Our preclinical tasks would include modifying the MIT Nuclear Reactor medical facility to produce an epithermal as well as the existing and highly thermalized neutron treatment beam; characterizing the transport behavior of these beams in both physical and mathematical models of the human head, and developing a treatment planning scheme for NCT; further development of the neutron-induced alpha-autoradiography track-etch method for measuring macro- and micro-distributions of B-10 uptake in tissues and blood; investigations into the B-10 cellular uptake pattern of human tumors; and examination of the nature of endothelial cell vascular damage in B-10-containing animals undergoing irradiation with neutrons. With the successful completion of the above preclinical tasks we feel we will be in a position to embark in the third year on a pilot clinical evaluation.

I. INTRODUCTION

This proposal explains how we at the New England Medical Center (NEMC) and the Massachusetts Institute of Technology (MIT) propose to carry out preclinical scientific and clinical studies in neutron capture therapy (NCT) employing the joint resources of our two institutions. We will make no attempt here to provide highly detailed descriptions of the proposed tasks; instead, we wish to present a general outline of how we propose to proceed towards a clinical trial of NCT building on the extensive base of research which we have already accomplished. A strong impetus was provided for such an effort by the tremendous success of and the widespread interest aroused by the two recent International Symposia on Neutron Capture Therapy held at the Massachusetts Institute of Technology in 1983 and at Teikyo University, Japan, in 1985 (1,2). The success of NCT would save many lives

and eliminate much human suffering, and would visibly demonstrate more of the medical and societal benefits of nuclear technology. In contradistinction to the contemplated use of high-LET particle cancer therapy using alpha particles or pi mesons, we believe that NCT, if successful, would be a very cost-effective form of cancer treatmet and would eventually decrease rather than increase health care costs.

II. GENERAL GOALS

The thrust of our proposal is based to a certain extent on the recommendations of the NCT expert panel recently convened at Brookhaven National Laboratory on which two of us were active participants.

Our principal aim would be to mount a 3-year research and clinical implementation program to explore whether NCT offers a superior alternative strategy to existing combined modality treatment of cancer. Although development of this technique to date has been oriented to the treatment of brain tumors, some recent work has been accomplished with other cancers, in particular melanomas, References (1,2) summarize the current status of research in NCT in all areas. Although initially we propose orienting our work on NCT to brain tumor therapy, we would eventually not limit ourselves to this single goal. We believe, however, that because of the experience that currently exists with brain-tumor-seeking boron compounds and the US and Japanese clinical experiences in treating more than 100 brain tumor patients by NCT, to direct our initial clinical efforts to brain tumor therapy would be a logical first step.

III. PARTICIPATING PERSONNEL, SERVICES, AND INSTITUTIONS

The co-principal investigators in this effort are the authors of this proposal. Dr. Madoc-Jones would take the lead role in the direction and supervision of the proposed animal studies, and the subsequent clinical pilot study. Dr. Zamenhof and Dr. Bernard would be principally responsible for the radiation physics, dosimetry, nuclear engineering, and computer modeling aspects of the proposed project. The project would be jointly undertaken by NEMC and the Nuclear Reactor Laboratory at MIT, through its director, Professor Otto K. Harling. The NEMC research group would include the existing NEMC brain tumor therapy group, which includes services from radiation therapy, neurosurgery, neuroradiology, neurology, adult and pediatric medical oncology, pathology, medical physics, and radiobiology. Additional technical support is available at MIT and NEMC in the areas of nuclear engineering and radiation dosimetry, while consultants would be engaged, as needed, from among the experts in the various specialized areas of NCT. NEMC and MIT graduate student participation would also be actively encouraged and supported.

The NEMC brain tumor therapy group is an established multidisciplinary group of faculty who have worked cooperatively on a number of innovative brain tumor therapy projects, the most recent of which is the treatment of glioblastomas by stereotactic intracranial implantation of extremely "hot" 193-Ir seeds. The commitment of NEMC to the NCT project therefore ensures that the vitally important medical aspects of this work will be carried out by a first-rate life-science team. Similarly the participation of the MIT group ensures that high quality expertise in all relevant areas of physical science and engineering will be applied to this project. The MIT capabilities complement those of the NEMC staff and assure that all relevant expertise and experience which is needed will be focused on this project. The MIT Research Reactor with its unique medical irradiation facility, designed epecially for NCT, will be made available.

IV. BASIC PRINCIPLES AND HISTORICAL BACKGROUND OF NCT

(i) Basic Principles of NCT

The technique of NCT depends on the selective loading of a tumor with a B-10 enriched boron compound and subsequent irradiation of the tumor with neutrons. The neutron capture reaction, $^{10}B(n,\alpha)^{7}Li$, releases an alpha particle and a recoiling 7-Li ion with an average total kinetic energy of 2.33 MeV. These charged particles have a range in tissue of less than 10μm (comparable to a cell diameter), and due to their extremely high ionizing density (LET) are capable of destroying cells with little or no possibility of subsequent repair. Also, the low oxygen enhancement ratio (OER) associated with these particles would prevent selective sparing of hypoxic cancer cells. The radiation dose distribution due to these particles follows the boron compound distribution in the irradiated tissue at the microscopic cellular level. Therefore NCT combines the attractive features of both external photon beam and internal radioisotope therapy to deliver a large differential high-LET low-OER radiation dose to boron-loaded cancer cells even when these are interspersed within healthy tissue.

The annual death rate in the United States due to primary brain tumors is estimated at approximately 12,000. Of these, about 6,000 deaths result from grade III-IV astrocytomas. The radiobiological and histological characteristics of high-grade astrocytomas (often referred to as glioblastomas multiforme) have continually frustrated attempts at their treatment using available therapeutic modalities. Currently the most effective therapy involves a combination of surgery and photon irradiation, for which only a 5.7 percent 5-year survival rate has been reported (3). The infrequency with which high-grade astrocytmas metastasize combined with their aggressive local growth, low radioresponsiveness, and very poor

prognosis make them a good test site for NCT, or indeed for any other innovative cancer therapy modality.

(ii) History of NCT

Neutron capture therapy for the treatment of cancer was first suggested by Locher in 1936 (4). During the early 1940's, several workers investigated this technique in animals using various boron and lithium compounds (5-8). Sweet and Javid (8) first demonstrated that certain boron compounds would concentrate in human brain tumor relative to normal brain tissue, and subsequent studies originally at Brookhaven National Laboratory (9-11) and at MIT and Massachusetts General Hospital resulted in clinical trials of NCT at Brookhaven during 1951 and 1952, at the MIT Research Reactor from 1959 to 1961 (12), and at Teikyo University, Japan, since 1968 (1,22). Unfortunately, from the viewpoint of clinical outcome the American clinical trials were a failure due to various physical and chemical factors which we now feel we understand, while the later and more extensive Japanese clinical trials showed--and continue to show--encouraging results (1,2).

One reason for the historical emphasis on applying NCT to brain tumors is the presence of the blood-brain barrier, which provides an effective mechanism for concentrating the 10-B isotope in tumor while excluding it from normal brain tissue. The pharmacokinetic characteristics of the boron compounds used up to now made the brain the only part of the body where differential tumor vs. normal brain B-10 concentrations could be achieved despite the lack of impressive tumor binding by most of these agents. More recently, however, the development of hybridoma research has enabled B-10 to be attached to tumor-specific monoclonal antibodies (MABs), thereby greatly increasing the spectrum of potential applications of NCT. A preliminary theoretical evaluation of the MAB approach was done at the Massachusetts General Hospital and NEMC (13) and showed that, given the right combination of immunologic properties, B-10-carrying MABs have interesting potential applications in NCT. Table 1 illustrates such a biophysical/immunological analysis. The concept of Advantage Depth (AD), or Maximum Useable Depth, was defined by Zamenhof (16) to enable the relative dosimetric efficacies of various NCT scenarios to be compared. The Advantage Depth is the depth in tissue along the neutron beam axis where the total macroscopic dose to tumor tissue equals the maximum total macroscopic dose to non-tumor tissue. Simply expressed, at lesser depths than the AD, tumor will always receive more dose than non-tumor, while at greater depths non-tumor tissue may receive more dose than tumor tissue. The AD is dependent on a large number of parameters, the most important of which are the level of B-10 loading and its distribution in blood, normal

Table 1. Illustration of how biophysical modeling can be utilized to evaluate the effectiveness of MABs for neutron capture therapy. Biophysical model from Wellum and Zamenhof (13) is used with immunologic parameters for B-10-ATG monoclonal antibody targeted to colorectal carcinoma cells supplied by Dr. Rolf Barth, Department of Pathology, Ohio State University School of Medicine. A pure thermal neutron beam was assumed.

μg ^{10}B/ml Blood	μg Ab/ml Blood	μg ^{10}B/ml Tumor	Tumor/Blood Ratio	Approx. AD (cm)*
0.05	0.5	8.4	168	3-4
0.1	1.0	15.0	150	4
0.2	2.0	18.5	92	4
0.5	5.0	21.4	43	4
5.0	50.0	24.0	4.8	3

*Advantage Depth (AD) computed from nomograms published by Zamehof (13) and Wellum assuming an advantage ratio of 1.

brain, and tumor tissues; the characteristics of the neutron treatment beam in terms of neutron energy spectrum, type and intensity of adventitious radiation components in the beam, and beam size; the geometry of the patient's head and the craniotomy site (if present); and the distribution of RBE factors that is chosen. Very recently it has been shown (22) that very slow administration of the monomer of the sulfhydryl compound $Na_2B_{12}H_{11}SH$ can result in tumor-to-blood ratios of approximately 4-to-1 being obtained in mice carrying transplanted tumors. Further, the dimer of the above compound, $Na_4B_{24}H_{21}S_2$, was shown to possess even more favorable tumor-binding properties, with observed tumor-to-blood ratios of up to 6-to-1 being obtained. Unfortunately, the superior performance of the dimer is associated with somewhat higher toxicity. Encouraging clinical results have only been reported by Hatanaka, who did research on NCT at Massachusetts General Hospital in the late sixties and upon returning to Japan implemented a pilot clinical trial. Since 1972 Hatanaka has treated over 38 previously untreated patients by NCT with grade III - IV astrocytomas (62% grade IV). A summary of Hatanaka's clinical results is shown in Table 2. One grade-IV astrocytoma patient (one of the first treated) is currently alive and disease-free after more than 13 years. The

Table 2. Clinical results of H. Hatanaka in treating high-grade astrocytoma tumors by NCT. Patients were treated in Japan in 1972-1975, using the compound $Na_2B_{12}H_{11}SH$ and a thermalized neutron beam.

	All Cases[a]	Unfavorable Geometry[b]	Favorable Geometry[c]	10-cm-diam. beam[d]
No. Patients	38	12	6	5
Mean Age (yr)	50.2	44	41.5	45.4
Mean Survival (yr)	1.68	3.62	5.98	7.05
5-yr Survival Rate (%)	19	58	83	100
10-yr Survival Rate (%)	9	29	42	50
Presently Alive	8	5	3	3
Karnofsky Rating[e]	73%	87%	95%	100%

[a]Deepest tumor margin was <6 cm; 62% grade IV, 38% grade III.

[b]Due to the design of the irradiation facility, irradiations were limited to along the vertex axis, even if for example a tumor was in the temporal lobe and could therefore be more easily approached from the side.

[c]These were tumors best approached along the vertex (irradiation) axis.

[d]These were tumors treated through a large (>10-cm) craniotomy site with a correspondingly large neutron beam.

[e]80% is considered to represent a minimal neurological deficit.

pathology on this patient and other NCT-treated patients has been extensively reviewed by Richardson at Harvard Medical School and Jellinger in Vienna (1).

Work on NCT at MIT was pursued actively between 1975 and 1981 under NCI grants. Although no clinical component was present, a great amount of development work in the areas of radiation dosimetry, boron compound development, boron analysis by nuclear techniques, neutron beam optimization, and tumor monitoring techniques using CT was successfully completed (13-18, 23). To examine the effects of NCT on boron-loaded normal tissue, six healthy beagle dogs were injected with boron compound and irradiated through the intact skull at various radiation dose levels. After 9 months the dogs were sacrificed and their brain tissues examined by standard neuropathologic techniques. The results of this experiment are summarized in Table 3. The fact that despite the large radiation doses delivered to some of the dogs no adverse effects of NCT were observed, neither neurologically not histologically, may be construed as supporting

Table 3. Effects on CNS tissue of NCT in normal adult beagle dogs (23). The total thermal neutron fluence delivered to these dogs (10^{13} cm^{-2}) was approximately twice that employed most recently by Hatanaka in Japan for treating patients (1,2). Irradiation time was 40 minutes.

Administered B-10 dose (mg/kg)	Av. B-10 blood concentration during irradiation (μg/g)	Total dose at skull surface (Rad)	Dose Breakdown (rad)			CNS Tissue effects (fibroid necrosis of blood vessels)*
			n	γ	B-10	
7.5	8.0	1330	150	600	580	none
12.6	12.0	1620	150	600	870	none
30.0	22.6	2390	150	600	1640	none
30.0	25.8	2610	150	600	1860	none
30.0	27.9	2770	150	600	2020	none
30.0	39.3	3620	150	600	2870	none

*It is believed that due to the demonstrated virtual exclusion of the B-10 compound $Na_2B_{12}H_{11}SH$ from normal brain tissue, any radiation effects observed in brain tissue per se are probably secondary to radiation damage to endothelial cells of the blood vessels (11).

two important claims made for NCT: that there is significant protection of the microvasculature from the alpha and lithium-7 particles released by the B-10 reactions in the blood due to the microdosimetric implications of the endothelial cell geometry; and that the low integral dose to the brain compared to the conventional whole-brain external x-ray or cobalt beam therapy allows much greater doses to be delivered than conventional radiotherapeutic wisdom would dictate. It is of significance to note that the neutron fluence of 10^{13} cm^{-2} is more than double that employed by Hatanaka in Japan for treating patients. If human and dog brain responds equally to NCT it would appear that Hatanaka may be irradiating with an unnecessarily conservative safety margin for normal tissue effects. A number of beagle puppies with implanted intracranial gliosarcoma tumors were also treated by NCT. Their progress was monitored by CT scanning and angiography, and after sacrifice the type and extent of radiation effects on tumor and normal tissue were evaluated by neuropathologic techniques. Approximately 33% of the tumor-bearing puppies were thought to have been cured by NCT (1), although due to the small number of animals this result was not statistically significant.

V. PRESENT STATUS OF NCT AND OUTLINE OF THE PROPOSED PROGRAM

(i) Present Status of NCT

The B-10 labeled sulfhydryl compound $Na_2B_{12}H_{11}SH$, originally synthesized by Dupont and presently supplied by the Shionogi Chemical Company in Japan and the Callery Chemical Company in the US, is currently the only compound specifically designed for NCT whose toxicology has been extensively documented and which has pending FDA approval as an investigational drug. It is this compound that was used in the animal studies at MIT and is being used for the clincial trials in Japan. It is the dimer of the above compound that was recently found to exhibit very much more favorable tumor-to-blood ratios when administered very slowly to mice over a period of about 200 hours (22). The microdosimetry of the B-10 reaction in both blood and tumor cells has been studied extensively by the MIT/MGH group using Monte Carlo simulation (14,15,18) and it is believed that for equal blood and tumor cell B-10 concentrations there will be at least a 30-50% higher high-LET dose delivered to the tumor cells due to geometric considerations. Therefore, with tumor cell:blood B-10 ratios of 2:1, the high-LET dose ratios may be 2.5-3:1, resulting in highly favorable therapeutic gains. It is proposed that because of the availability of the "Boralife" drug (Callery Chemical Company's designation for $Na_2B_{12}H_{11}SH$) and its imminent FDA approval, initial preclinical and clinical studies be performed using either this compound or its closely related dimer. The use of monoclonal antibodies attached via polymers to B-10 dodecahedral cages also promises to provide a vehicle for transporting B-10 to the tumor cells of many different cancers. However, we believe that it will be a number of years before MABs can be used for clinical NCT. It should be noted that the therapeutic advantage in conventional fractionated external-beam radiation therapy is rarely as high as 20%, so the Boralife agent's pharmacokinetic properties together with the protection afforded by microvascular geometry makes this compound an acceptable choice for initial precinical and clinical applications.

The design of a suitable epithermal neutron beam is of primary importance in the proposed project. The advantages of such beams were demonstrated by the MIT/MGH group using transport calculations (16-18). Our conclusion was that an epithermal beam of approximately 10-100 eV in energy was theoretically ideal, although beams of up to a KeV or so in energy would still have an advantage over a pure thermal beam under certain pharmacokinetic distribution of B-10. Not included in the optimization calculations was the possibility that neutrons of lower energy than 1 KeV or so might not even produce collision ionization in tissue - a fact that if true would further underscore the desirability of epithermal beams for

NCT. The availability of an epithermal treatment beam would enhance the advantage ratios in treating human astrocytomas and other deeper-seated tumors, and might obviate the need to re-expose the brain prior to treatment. Epithermal treatment beams were studied by the MIT/MGH group (16-18), the Brookhaven group (19), the Atlanta group (1,2,20), and by Brugger (21), who has written a textbook chapter on the topic and performed extensive experimental validations. Although the MIT/MGH group's studies showed that large amounts of Cf-252 optimally moderated and filtered could produce a good epithermal treatment beam of adequate intensity, the quantity of Cf-252 required would be prohibitively expensive. The alternate approach of using a combination of special moderators such as aluminum mixed with heavy water and composite resonance scattering filters such as aluminum/sulfur in a reactor to create epithermal beams in the 1-eV to 30-keV region has been studied extensively by Brugger (22). Noonan (1,2,20) constructed an aluminum/sulfur-filtered epithermal beam for radiobiological studies and showed that the biological effect vs. depth in phantom manifested the predicted shape, namely, a significantly lower bioeffect at the surface than at 2-cm depth. At Brookhaven, an experimental 2-KeV epithermal beam produced by using a scandium-45 resonance filter has been studied extensively and found to have very desirable properties for clinical NCT. However, the quantity of Sc-45 required for therapeutic applications would be extremely costly. Hatanaka (1,2) has continued to treat his patients with a thermalized beam but has on occasion used very large fields to improve the advantage depth (24). However, the use of a thermal beam requires that the brain be re-exposed prior to treatment, which in turn precludes the desirable option of using fractionated treatment. When the medical irradiation facility at the MIT reactor was redesigned and rebuilt during the upgrading of the MITR-II in 1973-1975, provisions were incorporated to vary the neutron spectrum of the neutrons used for medical irradiations. Several filters were provided for the beam and a blister tank of D_2O was incorporated in the reactor's moderator to permit significant manipulation of the neutron energy spectrum available at the exit port in the medical irradiation room. Thus, although the MITR-11's therapy beam is presently optimized as a thermal neutron beam, and as such is probably the best of this type anywhere in the world, the engineering design of the MITR-II reactor makes it possible to manipulate the neutron energy spectrum so that an epithermal neutron beam suitable for therapeutic applications can be readily produced. Although the DOE Advisory Panel (22) strongly endorsed the development of epithermal neutron beams for NCT, their reasoning was predicated on the assumption that it is much more acceptable to treat through an intact scalp and skull using an epithermal beam than to have to reflect scalp and skull to permit treatment with a thermal beam. The issue boils down to either obtaining (typically) a 5-cm advantage depth through the intact scalp using an

epithermal beam, where maybe 3 or 4 cm of this AD would actually be within the brain, or obtaining a 3-cm AD with a thermal beam through a reopened craniotomy site, where all 3 cm of the AD would be within the brain. Despite the necessary re-exposure of the brain, there are advantages with a thermal beam of not having to fractionate the treatment (since the beam contains very little low-LET contamination); delivering the necessary dose rapidly in 5-10 minutes (at the MITR-II); providing the neurosurgeon with the ability to examine the craniotomy site prior to treatment; and allowing the actual neutron fluence delivered to the brain surface to be physically monitored. The corresponding advantages of an epithermal beam are that treatment through the intact scalp and skull can be fractionated in order to minimize the effects of the low-LET radiation components, most of which are absent in the first place in a good thermal beam; and that the epithermal beam can be delivered in two parallel-opposed fields through the intact scalp and skull, thereby providing a favorable advantage ratio even for midline seated tumors frequently not amenable to surgical debulking. If NCT were to become a routine clinical procedure there is no doubt that overall the concept of an epithermal neutron beam is attractive. We believe, however, that in a non-randomized pilot clinical study, where patients with relatively superficial and surgically excisable grade IV gliomas can be selected, a good thermal treatment beam is still eminently attractive. Neurosurgeons have in the past performed procedures of great surgical complexity and risk to the patient in order to obtain increased survival ratios in high-grade glioma patients. We do not believe that in order to validate the efficacy of NCT we should shy away from relatively routine surgical procedures. The medical therapy facility at the MITR-II is designed as an operating room, and indeed was used as such in 1959-61 without any complications that could have been ascribed to the surgical procedures carried out there.

(ii) Proposed Research Program

A program of 3 years in total duration is envisioned. Our program plan generally agrees with the recommendfations from the DOE NCT Advisory Panel, convened at Brookhaven National Laboratory, January 22-23, 1986 (22). However, our program does not address all areas of necessary research and development which were recommended at the Workshop. The NEMC/MIT program is designed to emphasize those areas which we judge are essential in preparation for our proposed clinical trials and for which the NEMC/MIT team is particularly well suited in terms of expertise and facilities, i.e., the excellent reactor and nuclear engineering capabilities at MIT and the first-rate medical resources of NEMC. We expect to rely on other groups, e.g., those already developing and testing

improved boron compounds, to provide us with the additional necessary scientific support so that our program can support a pilot clinical trial by the third project year. The proposed tasks are described in more detail below.

(1) Further refinement of neutron-induced alpha-track auto-radiography for micro-and macroscopic tissue samples.

This provides a method for quantitating the spatial distribution of boron in tissues and cells: an absolute necessity before any clinical trial is initiated. The MIT group has completed most of the preliminary work in this area, while the capability exists at NEMC to automatically read and quantitate track-etched polycarbonate films using sophisticated artifical intelligence techniques.

(2) An examination of the effects on cerebral microvasculature of B-10 reactions originating in blood.

Both theory (14,15) and experimental evidence (11) suggest that the primary mechanism of normal brain tissue damage in NCT is damage to the endothelial cells of the microvasculature. The damaged microvasculature then produces ischemic and necrotic conditions in the actual neural tissues. In the adult beagle dog study that was performed at MIT (see Table 3), where non-tumor-bearing dogs were infused with B-10 resulting in blood concentrations of 8-39.3 μg B-10/g blood, the B-10 doses resulting from the $10^{13}cm^{-2}$ neutron fluence delivered (580-2870 Rad by B-10) were not sufficiently high to produce any observable microvascular damage 9 months post irradiation. This was unfortunate since such neuropathologic data are totally lacking in the NCT research area. We feel that it would be of enormous help to the neuropathologist on our team if he were able to observe the characteristic patterns of microvascular damage in NCT. To this end we propose to exploit the fact that cerebral microvascular anatomy is extremely similar in human beings and in certain small animals such as rats. Rats would be infused IP with B-10 compound and after 30 min to 1 hour would have blood samples taken and be irradiated with neutrons to a fluence of $10^{13}cm^{-2}$. A range of B-10 doses from 2000 Rad to 6000 Rad would be covered using approximately 20 animals and achieving a variation in B-10 doses by varying the administered amount of B-10 compound. The rats would be allowed to survive up to 2 months, after which they would be sacrificed, their brains fixed, and frozen sections prepared for neuropathologic examination. The results of this experiment will not be useful in providing tolerance B-10 dose levels which could be extrapolated to human

beings since the dissimilar irradiation geometry (very small neutron beam and large thermal neutron leakage out of the small volume of tissue) and comparatively high volume dose to the rat brain would be expected to overestimate the B-10 tolerance dose even if it were assumed that human and rat brain reacts equally to comparable radiation insults. We believe that the results of the adult beagle dog experiments performed at MIT, showing that B-10 doses of up to 2870 Rad to the surface of the brain can be tolerated, are more valuable in this respect than the proposed rat experiment would be.

(3) Computer-aided design and implementation of an epithermal neutron treatment beam at the MIT Nuclear Reactor.

Measurements on the MITR-II medical therapy beam by Ashtari (23) indicate that even simple filtration using "1/v" absorbers (which essentially remove thermal neutrons from the beam) increases the beam's penetration substantially. However, such simple beam filtration results in too large a component of adventitious radiation such as gamma rays and fast neutrons. We propose to design an epithermal beam having an energy range of 1 eV-3 KeV by using s-wave resonance scattering filters; specifically a combination of aluminum and sulfur. These filters would be installed in the upper region of the MITR-II medical beam port where they would subtend a large fraction of the reactor core. The existing heavy water blister tank would be drained and the existing patient collimator raised upward to decrease its distance from the core. Relatively short lengths of aluminum and sulfur would be employed to maximize the intensity of the epithermal beam while taking advantage of the inherently low gamma contamination in the existing design. Initial calculations and measurements suggest that such an epithermal beam would have excellent spectral characteristics for NCT with enough intensity to enable a therapeutic dose to be delivered in less than 10 fractions. Another interesting direction for neutron beam optimization is the use of relatively large beam apertures. Matsumoto and Aizawa (24) have demonstrated that the use of large collimators, up to 22 cm in diameter, can greatly improve the depth-dose distribution for NCT. At the 100-kW reactor used by Matsumoto and Aizawa (50 times lower in power than MITR-II) it has been possible to demonstrate advantage depths of up to 5.5 cm for realistically achievable B-10 concentration ratios. We also plan to look into the potential advantages of large thermal neutron beam diameters for optimizing the advantage depth in the MITR-II medical therapy beam. Overall optimization of the MITR-II medical therapy beam will consider filtration and beam geometry effects, and will be accomplished with the use of state-of-the-art radiation transport codes such as ANISN and ANDY.

(4) An examination of the B-10 uptake patterns in human glioma specimens.

One of the crucial concerns expressed by the DOE expert panel on NCT was that significant amounts of tumor cells might survive NCT treatment due to the fact that for one reason or another they did not take up sufficient quantities of B-10 compound. Calculations indicate that although an average of 10^9 B-10 atoms would be taken up by each glioma tumor cell only about 10-20 B-10 reactions per tumor cell would be required to deliver a therapeutic dose. This implies that statistically a certain fraction of the tumor cell population would receive hypotherapeutic B-10 dose while a very small fraction would receive no dose at all; not necessarily because of a lack of uptake of B-10 but due to the stochastic rules governing the interaction of neutrons with B-10. These are inherent characteristics of the physics of NCT. To minimize the number of tumor cells receiving hypotherapeutic B-10 dose one must ensure that there is a relatively homogeneous concentration of B-10 among tumor cells. To examine this problem we propose to use the technique of neutron-induced alpha autoradiography, as studied extensively over the past five years by the MIT group (1), to look at the geographical distribution of B-10 in human glioblastoma tumor tissue. After the Boralife B-10 compound has received FDA approval as an investigational drug we will infuse it into a small number of glioblastoma patient volunteers a day or two prior to their debulking craniotomy. At the time of craniotomy the neurosurgeon will obtain a number of samples of tumor tissue from different regions of the tumor and immediately freeze them in liquid nitrogen. The samples will then be sectioned by the neuropathologist and prepared for both microscopic and autoradiographic analysis. The autoradiography will be performed by the MIT Nuclear Reactor Laboratory and analyzed by the neuropathologist at NEMC using computerized image analysis software developed by the Medical Physics Division, NEMC. This approach should help to answer the questions of how homogeneous B-10 compound uptake in tumor cells is, where in the tumor cells the B-10 compound binds, and what the tumor-cell-volume to gross-tumor-tissue-volume ratio is. At the time of craniotomy a blood sample will be obtained and analyzed for B-10 content either by autoradiography or by prompt-gamma neutron activation analysis. From these measurements we will be able to obtain not only information regarding the geographical distribution of B-10 but also average tumor-cell to blood B-10 ratios. It is unlikely that the ratios and absolute cell concentrations o B-10 obtained in this way will be representative of the real therapeutic situation where tumor-cell uptake of B-10 will take place without the presence of tumor bulk. The increased blood flow and decreased pressure on

the tumor bed associated with post-craniotomy B-10 infusion (as in the real therapeutic situation) will most likely increase the tumor cell B-10 concentrations and tumor-cell to blood ratios. However, we believe that much valuable data nevertheless can be obtained from the proposed experiments.

(5) Radiation dosimetry on phantoms leading to a computerized treatment planning scheme based on the Monte Carlo method of radiation transport.

The MIT/MGH group did extensive work in the late 1970's in the use of discrete ordinates and Monte Carlo transport codes to study NCT dosimetry and treatment planning. We believe that it is very important in planning a clinical trial of NCT to be able to characterize the spatial radiation dose distributions of the various radiation components within the brain of the specific patient to be treated. The relatively small volume of the head and the shape and size of the craniotomy site (if present) have been shown to greatly influence the spatial distribution of the radiation dose, specifically the rate of fall-off with depth of the B-10 dose component. The MIT group has shown (14) that the Monte Carlo radiation transport method can accurately predict the measured thermal neutron fluxes within a model of a human head with a craniotomy exposed to the MITR-I thermalized medical therapy beam. Other studies have shown that the other radiation components in NCT (fast neutrons, incident gamma rays, and induced gamma rays) can similarly be quantitated using the Monte Carlo method.

We propose developing a Monte Carlo based treatment planning technique based on our earlier work which would allow our radiation therapist to examine the precise spatial distributions of the various dose components for each individual patient to be treated. The Monte Carlo calculations would be implemented on the Digital Equipment Corporation VAX computer located at NEMC with the required geometric parameters obtained from multiplane reconstructions of CT scans through the patient's head. The resulting three-dimensional dose distributions will be overlaid on the CT scans and the required neutron fluence to be delivered would be obtained as a function of B-10 blood concentration immediately prior to irradiation. Such accuracy in estimating the dose levels in each patient's brain will also enable important information to be obtained in the unfortunate instances of treatment failure, such as correlations between B-10 dose and micovasculature damage, and B-10 dose and foci of tumor regrowth. The proposed experiments would further validate the Monte Carlo method as the computational gold standard for radiation transport.

(6) Clinical Pilot Study.

The final year of the program would constitute a clinical applications phase of the program, where a group of ten superficial glioblastoma patients would be treated by NCT. This final phase of the program would extensively utilize the clinical expertise and experience of the NEMC brain tumor therapy group. The patients would be followed using CT, MRI, conventional and digital angiography, and other appropriate diagnostic methods, to observe the response of their tumors to NCT. Contingent on the success of these clinical trials and approval by the appropriate agencies, a routine treatment program would be developed in an expeditious manner.

VI. PRINCIPAL REASONS FOR A COLLABORATIVE EFFORT BY NEMC AND MIT ON NCT

(1) There is world-wide growing interest in neutron capture therapy. This may in large part be due to the comparative lack of success with both conventional and other innovative radiotherapeutic modalities, such as fast neutrons, alpha particles, and pi mesons, all of which lack the physiological selectivity of NCT.

(2) The existing experience and documented track record of researchers at NEMC and MIT in the area of NCT is a valuable resource which would permit a continuity of effort based on extensive previous work.

(3) The reputation of NEMC as a preeminent teaching hospital will ensure that the highest levels of patient care and continual scientific review will be provided in the clinical phase of the proposed program.

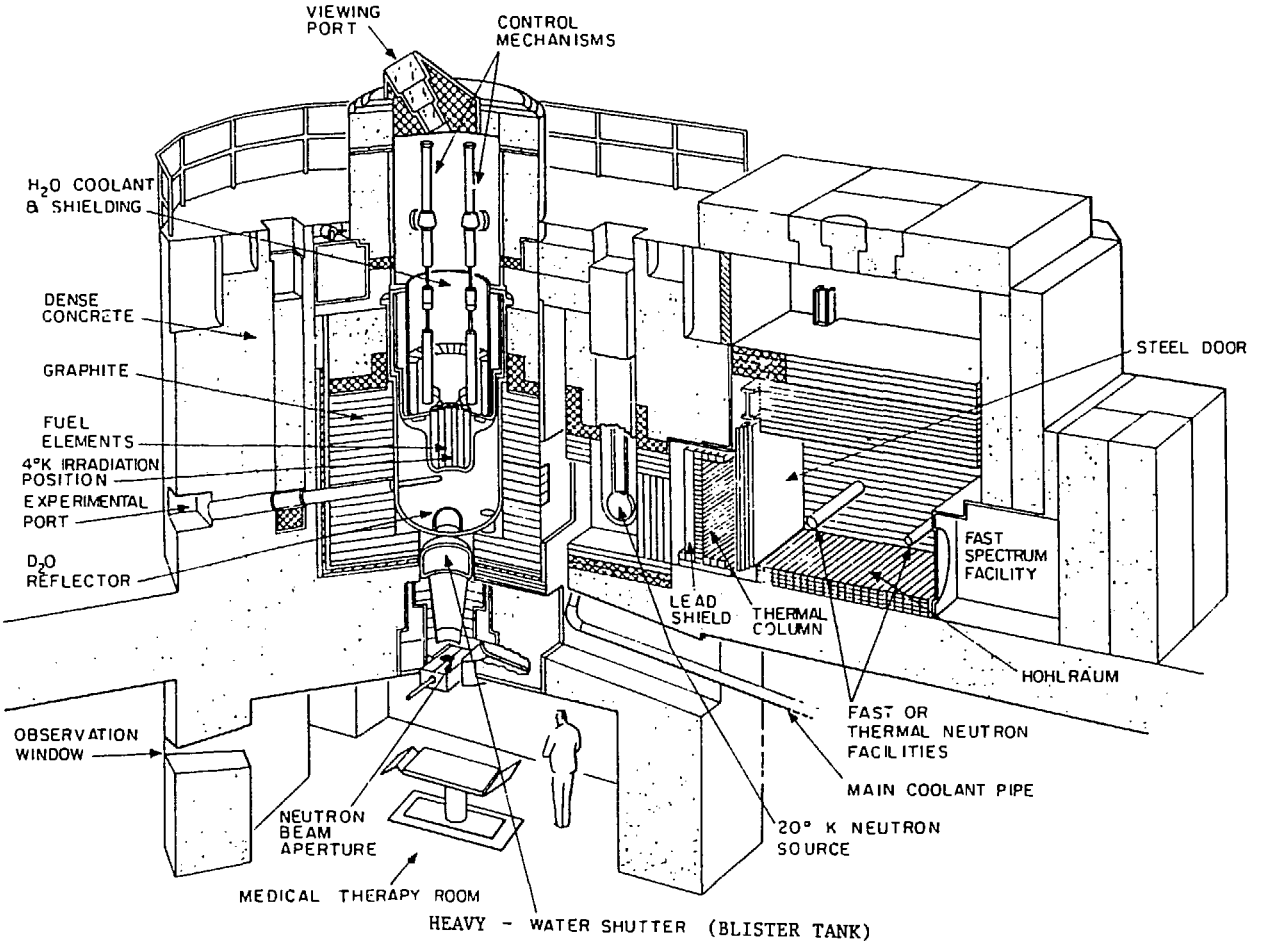
(4) The MIT Nuclear Reactor Laboratory, under the direction of Professor Otto K. Harling, will make available its full resources including the MIT Nuclear Reactor. It is important to realize that this would constitute a powerful springboard for our proposed program due to the immediate availability of all the research and development and modifications which have been carried out to the MIT Nuclear Reactor to optimize it for NCT. Also, the extensive software program library at MIT containing programs needed for epithermal neutron beam optimization and treatment planning development would be available, as would the expertise and experience in transport calculations and nuclear measurements provided by the NEMC and MIT based investigators.

VII. FACILITIES AT NEMC AND MIT

(1) MIT Research Reactor (MITR-II)

The MIT Reactor first achieved critically in 1958 and was designed specifically with NCT in mind as an important future medical application. The MITR-II was extensively upgraded in 1975-1976 with NCT applications being an important consideration in its new improved design. The MITR-II is an enriched U-235, high power density, H_2O-moderated, graphite and D_2O-reflected 5-MW (thermal) research reactor. A diagram of the new MITR-II is shown in Figure 1. The MITR-II has a number of horizontally oriented neutron beam ports which are ideally suited to experimental applications such as prompt gamma neutron activation analysis for measuring B-10 concentrations in macroscopic biological specimens, the

Fig.1. VIEW OF MIT RESEARCH REACTOR, MITR-II, SHOWING MAJOR COMPONENTS AND EXPERIMENTAL FACILITIES



experimental validation of neutron spectrum modifying strategies (such as resonance scattering filters), and the calibration of dosimetry equipment such as tissue-equivalent ionization chambers and activation foils. When high-intensity, highly thermalized neutron fluxes are required for applications such as neutron-induced alpha-track autoradiography the MITR-II has an irradiation hohlraum where a thermal neutron flux of 10^{11} cm^{-2}-sec^{-1} is available. Located under the reactor is a medical room, which was designed as a small operating theater with easy access for patients on stretchers through an external ambulance entrance and a large inside elevator. This room is tiled and supplied with sinks, perimeter bacteriostatic ultraviolet lights, and a central surgical bed mounted on a vertically adjustable pedestal. In the ceiling of the medical room is the mouth of a circular 23-cm-diameter vertically oriented neutron therapy port. There are three shutters mounted above the mouth of this port. There is a water tank which can be filled or emptied in a matter of minutes, a thick lead shutter, and a boron/aluminum shuter. With all three shutters closed there is an absolute minimum of radiation present in the medical room making it absolutely safe for physicians and ancillary staff to attend to or operate on patients. With the shutters open a beam of highly thermalized neutrons emerges through a bismuth filter. Above the three shutters is a heavy-water blister tank which can be filled or emptied either completely or partially providing a selectable spectrum of neutrons through the treatment port. In the modifications made on the MIT Reactor in 1975-1976 the quantity of heavy water present in the blister tank and the thickness of the bismuth filter were optimized using theoretical neutron and gamma transport calculations to provide the most thermalized neutron beam possible at an intensity adequate for NCT with the minimum amount of adventitious radiation components such as core gammas, fast, and epithermal neutrons. The present treatment beam has a thermal neutron flux of $4\text{-}9 \times 10^{9} cm^{-2}$-$sec^{-1}$, and low associated exposure rates of 3.2-10 Rads/min gamma, and 0.35-10 Rad/min fast neutron. The lower dose rates are with the blister tank filled, the higher ones with it empty. There is adequate space in the beam port above the medical room to insert additional filters such as aluminum and sulphur. Such filters would be used to further reduce the incident gamma and fast neutron flux, remove the thermal neutron flux, and pass through a 1-100 eV epithermal neutron spectrum. Such relatively simple measures are expected to provide us with a good therapeutic neutron beam for NCT. The presence of the three shutters in the treatment beam also means the treatment beam can be turned on and off without affecting the normal routine operation of the reactor; a very important advantage if the reactor were eventually to be used for routine treatment of patients.

(2) Neutron-induced alpha autoradiography capability.

As part of the previously NIH-funded NCT progam project at MIT/MGH, an autoradiography capability for measuring biological distributions of B-10 in various tissues (including blood) at both macro and microscopic levels was developed and extensively validated. The Medical Physics Division at NEMC has the existing capability to automatically analyze track-etched films using sophisticated artifical intelligence programs. This would greatly facilitate the quantitative analysis of B-10 microscopic distributions in tissue sections.

(3) Neutron activation analysis facility.

The MIT neutron activation analysis laboratory has the capability of performing neutron activation analysis on a large number of elements contained in biological or non-biological matrices. In particular, the availability of high-resolution intrinsic germanium detectors makes it possible to measure B-10 concentrations in larger samples (>1cc) by prompt gamma-ray neutron activation analysis.

(4) Software capabilities in the MIT Department of Nuclear Engineering.

The first ever discrete ordinates and Monte Carlo studies of NCT were done at MIT in 1975-1977 using the codes ANISN and ANDY supported by the MIT Nuclear Engineering Department. These codes can be used for the design and optimization of filtered epithermal treatment neutron beams and for dosimetry and patient treatment planning for NCT. Extensive preliminary work in this area has already been done by the MIT/MGH group.

(5) Graduate Student Support.

Access to highly motivated graduate students from both institutions is available at NEMC and MIT.

(6) Resources at New England Medical Center and Tufts University School of Medicine.

The New England Medical Center is the primary teaching hospital of the Tufts University School of Medicine. NEMC is a 500-bed tertiary care hospital with a documented track record of research achievements.

More specifically, NEMC's clinical departments possess the most sophisticated and up-to-date equipment in the departments of neurology, surgery, pathology, nuclear medicine, anesthesiology, radiology, and radiation therapy, which are among the principal specialties that would be intimately involved with a clinical trial of NCT. Imaging equipment

available in the Department of Radiology includes two Siemens DR CT scanners (one with dual energy capability), a Magnetom 1 Tesla NMR Imaging System, two Angioskop biplane angiography rooms with digital imaging capability, and a SPECT nuclear medicine tomographic imager. The departments of therapeutic radiology, diagnostic radiology, neurology, neurosurgery, adult and pediatric medical oncology, and pathology constitute the "brain tumor therapy group", which has collaborated on a number of research protocols for the past three years. This group has formally expressed its desire to participate in a NCT project. The immediate availability of such an interdisciplinary group whose members have already successfully collaborated on other projects involving brain tumor therapy is a valuable and probably unique resource of NEMC and is judged to be essential for clinical trials of NCT.

Tufts University School of Medicine is deeply involved in basic biochemistry and molecular biology research using a recently acquired Brucker 9-Tesla NMR spectrometer. The resources of that laboratory would be made available to us for the purposes of monitoring the purity of any boron-carrying agents that we might use.

The Medical Physics Division at NEMC is able to provide secondary calibration facilities from Co-60 energy up to a 25-MeV linac x-ray spectrum for calibrating ionization chambers that would be used for dosimetry for NCT. The division also possesses extensive experience in radiotherapy treatment planning and dosimetry. It also has access to graduate students from the faculty of science and engineering at Tufts University who in the past have completed their doctorates in the division. The Image Analysis Laboratory in the Medical Physics Division already collaborates on a number of projects with the Pathology Department and has the capabilities for automatic analysis of track-etch films using artificial intelligence techniques.

The Radiobiology Division at NEMC is able to provide the facilities needed for animal care in any animal experiments which would be done. Both the Medical Physics and Radiobiology Divisions are in the Department of Therapeutic Radiology under the chairmanship of one of the co-investigators.

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The NCT Program at Nuclear Medicine, Inc.

Denise J. Noonan
Nuclear Medicine, Inc.
900 Atlantic Drive, N.W.
Atlanta, GA 30332

ABSTRACT

The Neutron Capture Therapy program at Nuclear Medicine, Inc. (NMI) is focused on obtaining Food and Drug Administration (FDA) approval of the treatment for malignant brain tumors. To minimize both the time and expense of the approval process, research efforts have been strictly focused and Orphan Drug sponsorship of the boron compound, $Na_2B_{12}H_{11}SH$, has been obtained. The significance of Orphan Drug sponsorship and NMI's initial meeting with the FDA to discuss preclinical and clinical protocols are discussed.

1. PROGRAM OBJECTIVES

The Neutron Capture Therapy (NCT) program objectives at Nuclear Medicine, Inc. (NMI) are straightforward - to obtain Food and Drug Administration (FDA) approval of the treatment for malignant brain tumors.

Nuclear Medicine, Inc. is a commercial research and development company, specializing in radiotherapeutic drugs and devices for cancer treatment. The company is located in Atlanta, GA in an office/laboratory complex adjoining the 5MW Georgia Tech Research Reactor (GTRR). The continuity of a commercial establishment, and the Company's experience with the FDA and in meeting good animal, laboratory, and manufacturing standards are all being brought to play in meeting the far-reaching objectives of the NCT program.

2. FOCUSING THE RESEARCH

The FDA approval process is notoriously expensive and time consuming. To minimize both, two steps have been taken at NMI: first, a very focused and direct research program has been outlined and second, advantage has been taken of the recently enacted Orphan Drug Act, designed to reduce this burden for drugs targeted for small populations.

To assemble a coherent program for testing and presentation to the FDA within a reasonable timeframe, NMI has selected what it believes to be the best characterized and most promising boron compound and neutron beam. All NMI inhouse research is geared strictly toward obtaining FDA approval of these two components.

Enticing as it may be, NMI's role in beam improvements and developing better boron compounds has been restricted to that of financial supporter or interested viewer at this time.

The chemical component of NMI's program centers around the boron sulfhydryl, $Na_2B_{12}H_{11}SH$, and its oxidized derivative, $Na_4B_{24}H_{22}SOS$. Copious data have been generated on the sulfhydryl over the past 20 years, both in clinical[1,2] and in animal[3,4] experiments. While these studies are not generally acceptable to the FDA due to uncontrolled or undocumented variables, they provide time-saving baseline data for further studies.

The second component of NMI's program is an epithermal neutron beam generated by filtration through an Argon-Aluminum-Sulfur filter. A prototype of this epithermal beam was built at the GTRR in 1981 by NMI scientists[5]. The four-year feasibility study on the prototype beam now serves as the basis for studies to obtain Medical Device status for the new facility[6].

In addition to focusing its efforts, NMI is further easing the FDA approval process by sponsoring the boron sulfhydryl as an Orphan Drug[7]. An Orphan Drug is one for which the number of patients benefiting from the drug is so small as to make it economically unfeasible for pharmaceutical companies to pursue FDA approval. The population criterion is generally 200,000 or less. There are approximately 8000 primary gliomas[8] diagnosed annually in the US, and therefore the boron sulfhydryl qualifies as an Orphan Drug.

To encourage the adoption, or sponsorship, of these drugs, the Orphan Drug Act provides various tax and marketing incentives to Sponsors. More important, though, is the close working relationship fostered by the law between the FDA and Orphan Drug Sponsor. Ordinarily, an application for clinical studies is reviewed after a lengthly and expensive series of animal tests. Adjustments are made in the original program at that time. In the case of an Orphan Drug, the FDA is required by law to provide written recommendations prior to the animal studies, and protocol assistance and review thereafter. The time and money saved with the close, day-to-day relationship can be invaluable.

3. PROTOCOL REVIEW BY THE FDA

Over a year ago, NMI met with the FDA as an Orphan Drug Sponsor to review proposed preclinical protocols. Interest in the treatment within the FDA was high. Representatives from both the Drug and Device sides of the agency were present, as were the head of the agency and numerous interested parties.

Figure 1 is an outline of the major preclinical studies agreed upon. Approval for clinical trials of NCT will require three submissions:

(1) Application for an Investigational New Drug (IND) exemption for the boron compound. Such an exemption would allow the use of the compound in human pharmacological studies. Preclinical studies for the application are based on a careful and complete chemical

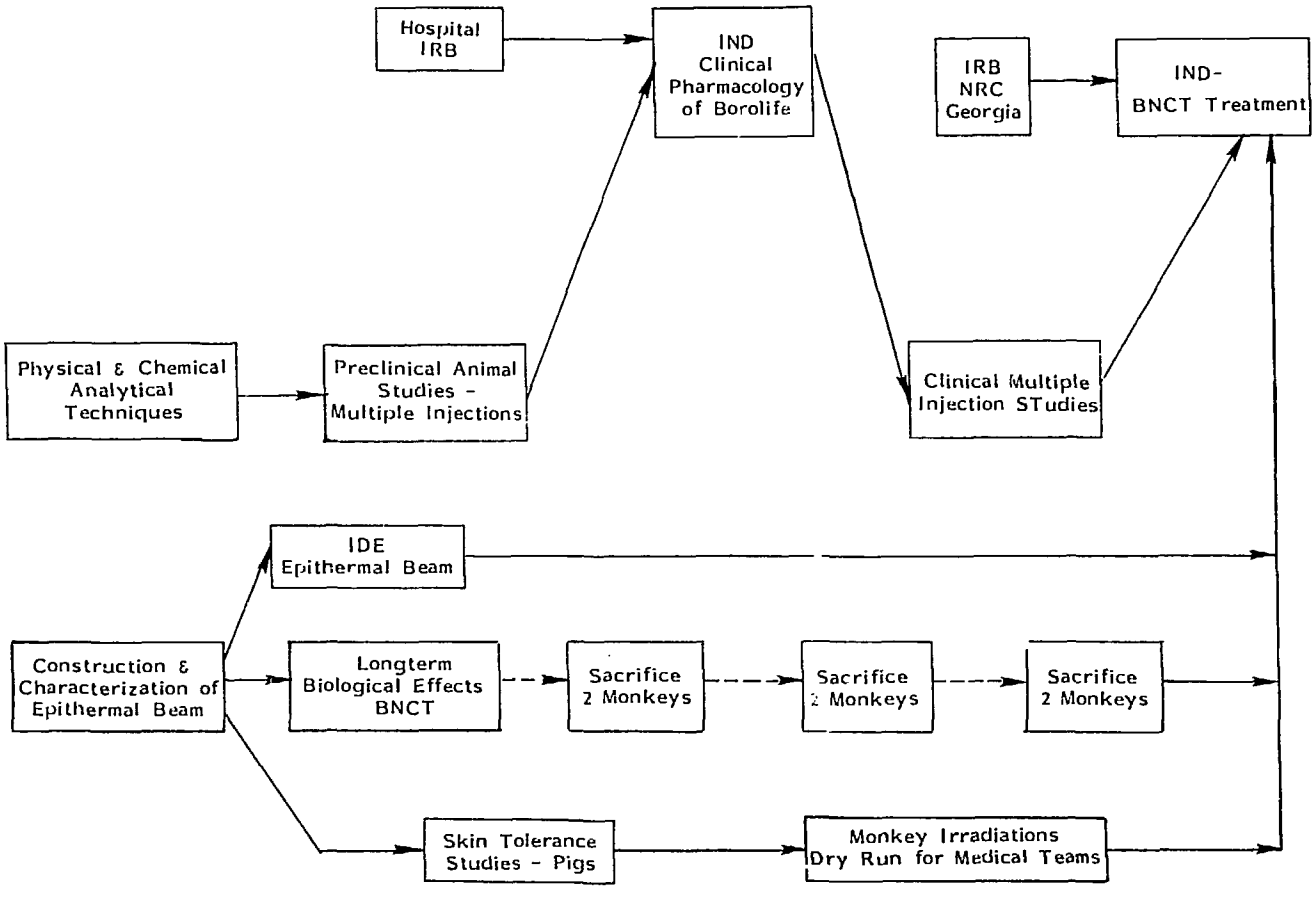


Figure 1

characterization of the drug, followed by pharmacological and toxicological studies in at least two animal species. Callery Chemical Co. is assisting in the chemical characterization work; the toxicology and pharmacology studies will be farmed out to large centers specializing in such work.

(2) Application for an Investigational Device Exemption (IDE) for the beam. Similar to the IND, an IDE allows the epithermal neutron beam to be used as a Medical Device in clinical trials. Traditionally, preclinical studies for a device are much less stringent than for a drug. To be included in the application are spectroscopy results in the neutron beam, flux measurements, and dosimetry in both air and phantoms.

(3) Amendment of the original drug IND to include the neutron beam. Approval of this application would initiate clinical trials of NCT. Preclinical workups include skin tolerance studies in pigs, acute and extended radiation effects in monkeys and dogs, and multiple monkey irradiations as dry runs for the medical and health physics teams.

In addition to establishing an official structure for the application process, a number of interesting points came out of the meeting. First, the FDA reiterated that its primary interest was safety -- not efficacy; proof of efficacy comes later. Consequently, NMI was urged to expand their studies of the combined effects of the compound and beam. Other safety concerns included the effect of fractionation on the blood-brain barrier and identification of major organ toxicity with multiple or prolonged infusions.

The FDA was also concerned that to date both preclinical and clinical studies have been performed with two different sources of the boron chemical, i.e., Shionogi Pharmaceuticals and Callery Chemical Company. Furthermore, due to undocumented or uncontrolled variables, these studies were ruled submissable only as baseline data. It was strongly suggested that before further studies commence, a sensitive analytical technique be developed to quantitate impurities and a standard be devised for the boron compound.

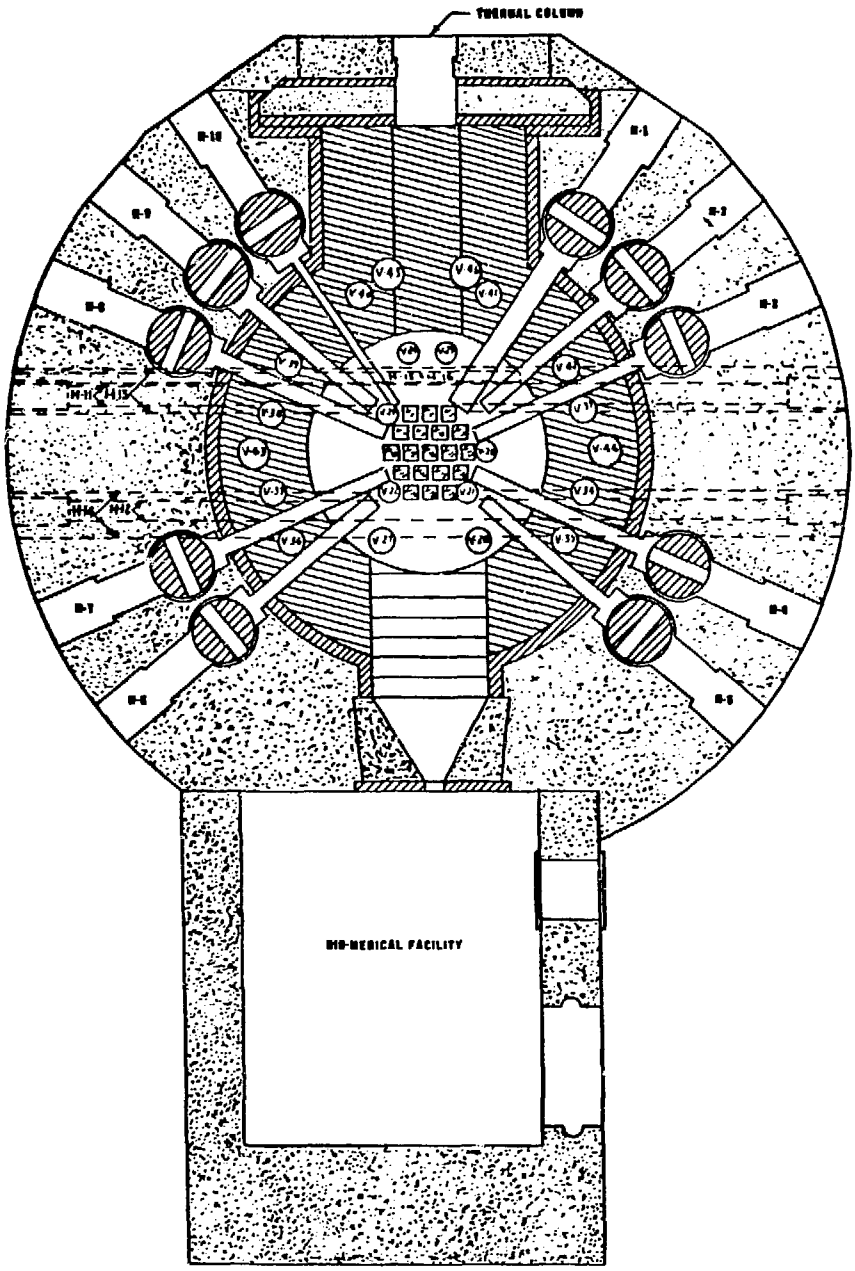
4. CURRENT EFFORTS

The FDA meeting clearly established that before animal studies could proceed, techniques to establish and quantitate the purity of the SH, SS and SOS series of compounds were required. Two are proving quite fruitful: Track Etch/TLC and HPLC[9]. Callery Chemical Company has been of great assistance in providing successively purer samples of each of the chemicals and in initiating a program to meet Good Manufacturing Practices, a requirement if these compounds are to be used in humans.

As the purity of the compounds is resolved, a study is being undertaken in nude mice bearing human gliomas to determine which of the two compounds, SH or SOS, will be pursued hereafter. The compounds are being infused slowly into the mice via osmotic pumps[4] to determine whether the reported toxicity of the SOS compound can be overcome with a prolonged infusion and whether compound retention is enhanced with this technique over the SH entity. The Brain Tumor Study Group at Duke University is working with NMI on the project. Pharmacology and toxicology studies will then be farmed out for whichever compound is selected.

To complement the compound studies, an improved epithermal neutron beam based on filtration has entered the design stage. The facility will be moved from the tangential port of the prototype beam to a port looking directly at the core. The direct port will boost the epithermal flux and, hence, the filtration possibilities.

Two ports are under consideration at the GTRR (figure 2). H1 is a six-inch-diameter port flush with the reactor core, with an eight-inch-diameter opening at the biological shield. Very few reactor modifications would be required for its use. However, only a small collection area is available for the neutrons, and construction of a treatment room would be required.



Horizontal section of reactor at the core mid-plane

Figure 2

An alternative site in the GTRR is the Biomed Facility. This port, complete with treatment room, was originally built for BNCT with a thermal neutron beam, but was never used as such. Insertion of a void or an aluminum block into the reactor vessel would allow collection of neutrons from an entire face of the core and enhance filtration possibilities. The port comes complete with a pneumatic shutter and a four-inch-diameter exit which could be easily enlarged for whole-brain irradiations.

With the completion of port selection and design studies, reactor modifications will commence. At that point, measurements to characterize the beam will be undertaken, culminating in an Investigational Device Exemption Application to the FDA for clinical studies in the beam.

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An Intermediate-Energy Neutron Beam for NCT at MURR*

R. M. Brugger, T. J. Less and G. G. Passmore
Research Reactor, Nuclear Engineering and Physics Departments
University of Missouri
Columbia, Missouri 65211

ABSTRACT

The University of Missouri Research Reactor (MURR) is one of the high-flux reactors in the USA and it can be used to produce an intense beam of intermediate-energy neutrons for neutron capture therapy. Two methods are being evaluated at MURR to produce such a beam. The first uses a moderator of Al_2O_3 replacing part of the graphite and water on one side of the core of the reactor to produce a source of predominantly intermediate-energy neutrons. The second method is a filter of ^{238}U between the core and the patient position to pass only intermediate-energy neutrons. The results of these evaluations are presented in this paper along with an outline of the other resources at the University of Missouri-Columbia that are available to support an NCT program.

I. INTRODUCTION

In neutron capture therapy (NCT)[1], boron that has been selectively implanted in a tumor is fissioned by thermal neutrons. The high-LET fission products deliver a large dose to the tumor while the triggering particles, the neutrons, deliver a lower dose to the healthy tissue. Past research has used beams of thermal neutrons, but recent trends are toward development of an intermediate-energy beam that will allow the neutrons to penetrate several centimeters into a patient before these neutrons are moderated to thermal energy at the location of the tumor.

At MURR two methods of producing an intermediate-energy beam are being studied. The first method is a moderator of Al_2O_3 placed near the core to give a source flux of intermediate-energy neutrons. The second method is a filter of ^{238}U placed between the source and the patient. This filter passes only intermediate-energy neutrons. The results to date of the studies of these two methods are presented in this paper.

II. Al_2O_3 MODERATED BEAM

A. Calculations The diffussion code DISNEL has been used to calculate the neutron flux in the core, moderator and out to a patient position in the MURR. First, DISNEL calculations were made of the MURR as it is usually

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configured to confirm that DISNEL and the parameters being used give the correct fluxes. Comparisons with the original design calculations and with flux measurements that have been made over the 20 years of operation of MURR indicate that DISNEL is working satisfactorily.

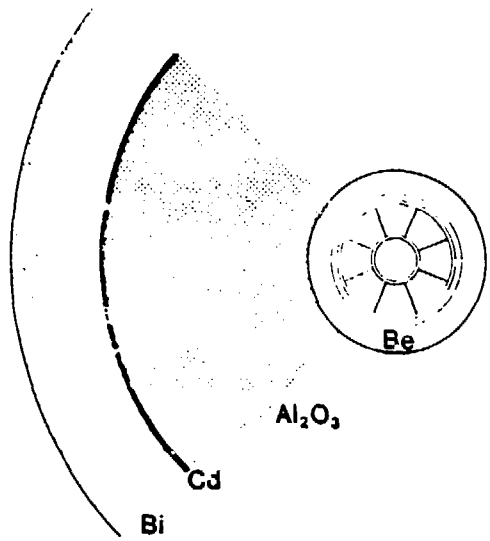

Fig. 1

Figure 1 shows the cylindrical geometry that was used to approximate the MURR for the moderator calculations. The Be reflector was not replaced with Al_2O_3 because replacing the Be in the reactor would be difficult and would reduce the reactivity a little. Leaving the Be reflector does reduce the intermediate flux some as compared to replacing this zone with Al_2O_3. For the calculations, the graphite and water reflector out to an 80-cm radius have been replaced with Al_2O_3. Outside the Al_2O_3 moderator is a 35-cm shield of Bi. Following the Al_2O_3 and before the Bi is 0.25 cm of Cd to reduce the thermal neutron flux. The patient position is at 2 m from the core centerline.

Since the diffusion code DISNEL does not simulate boundaries well, the fluxes have been calculated for Bi out to 2 m. Then the flux at 115 cm has been reduced by a factor of 2 for flux suppression by a beam. A source size of 40 cm x 40 cm has been selected and the flux at the patient has been calculated by the beam equation

$$\Phi = \Phi_S \frac{A_1 A_2}{4 \pi d^2}$$

where Φ_S is the source flux, A_1 is the source area, A_2 is 1 cm^2 and d is the distance from the source to the patient.

Figure 2 shows the intermediate flux (0.15 eV to 9.1 keV), the thermal (< 0.15 eV) flux and the fast flux (9.1 keV to 10 MeV) calculated for the above geometry. The 9.1-keV transition was selected as the division between intermediate and fast fluxes because this was the division between two groups in the DISNEL code and thus was convenient. The Be is around the core and the Al_2O_3 moderator extends out to 80 cm. A 0.25-cm layer of Cd is bewtween the Al_2O_3 and the Bi, and the Bi is 35 cm thick. There is 0.2% of Li metal added to the Bi. In Figure 2, as the radius increases, the fast flux is suppressed much faster than the intermediate flux decreases. At the outer edge of the Bi the fluxes drop because of flux suppression, and at the patient position, 2 m from the

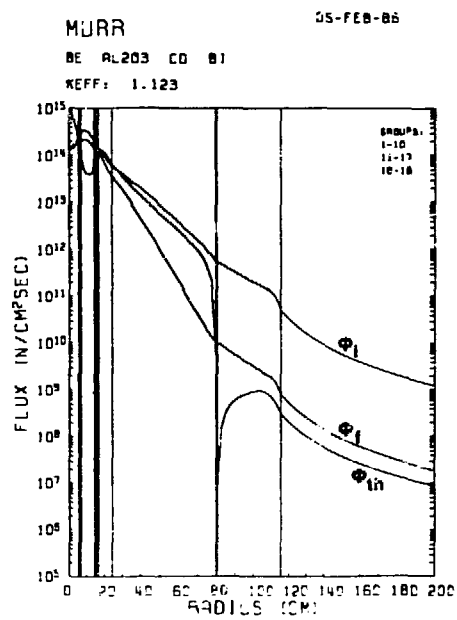

Fig. 2

center of the core, the intermediate current is 1.3 X 10^9 n/cm^{2}sec, while the fast current is smaller by about two orders of magnitude. Figure 3 shows the neutron flux spectrum at the patient position. The flux is truly peaked in the intermediate range and most of the dose to the patient will come from the intermediate-energy neutrons. Table 1 summarizes the neutron currents and Kerma.

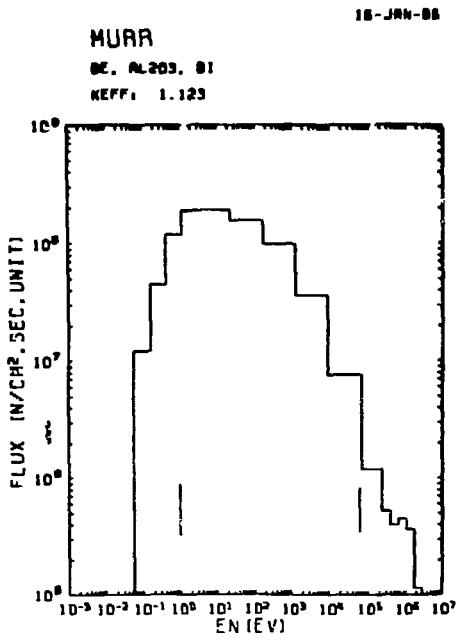

Fig. 3

Most of the dose to the patient by gamma rays comes from thermal neutron capture in the Cd and in the Al of Al_2O_3. As a first approximation of the gamma dose, the MURR core and the Al_2O_3, Cd, and Bi moderator sections were treated as infinite-slab volumetric photon sources 1 to 10 MeV in increments of 1 MeV. To establish the spectrum and the magnitude of the gammas coming from the core, the ^{235}U prompt photon spectra[2] and the known MURR gamma-heating were used as benchmarks. The core volumetric source strength spectra were estimated and treated as constant over the diameter of the core. In the moderator sections it was found that the major contribution to the photon dose was from thermal neutron (n,γ) reactions with Al and Cd. The volumetric photon source strength in these regions varied with the thermal neutron flux.

Table 1. Fluxes and Doses at Patient Position with Al_2O_3 Moderator

Intermediate flux	1.3 x 10^9 n/cm^{2}sec
Kerma from intermediate flux with boron (50 μgm/gm)	21 Gy/hr
Kerma from intermediate flux without boron	0.3 Gy/hr
Thermal Flux (thermal Maxwellian)	9.3 x 10^6 n/cm^{2}sec
Kerma from thermal flux with boron (50 μgm/gm)	0.14 Gy/hr
Kerma from thermal flux without boron	0.005 Gy/hr
Fast flux	2 x 10^7 n/cm^{2}sec
Kerma from fast flux	0.3 Gy/hr
Kerma from gamma rays	0.8 Gy/hr
Kerma from $^{10}B(n,\delta)^7Li$ gamma ray	0.9 Gy/hr

The calculations of the dose for uncollided and in-scattered photons were performed using ray analysis technique and the Burger build-up formula.[3] The results of this first approximation are that 35 cm of Bi keeps the photon dose rate to the patient to 0.8 Gy/hr. The fractional contributions of this dose rate from (n,γ) reactions in Al, Cd, and Bi are about 23%, 73%, and 4% respectively. Most of that portion from the Bi originates near the outer edge of the shield. Bismuth with a small amount of Li^6 would further reduce the thermal neutron dose to the patient. If small amounts of Li^6 were also in the Al_2O_3, the number of Al(n,γ) reactions would be reduced, thus reducing the gamma dose and/or the thickness of the Bi shield required, and the need for Cd.

Alumina should be a good moderator in a reactor. It is a common substance and may be easily obtained with a high purity. Silica (SiO_2) is the main impurity found in Al_2O_3 and this poses no problem in neutron moderation or radioisotope production. Alumina is a hard white ceramic that is commercially available at a cost of about $6000 per cu yd, with densities ranging from 3.4 to 3.95 gm/cm^3, and it can be purchased in preformed shapes. The highest density Al_2O_3 is preferred for neutron moderation and photon shielding, thus a density of 3.95 gm/cm^3 was used in all calculations. Alumina has a melting point of 2323°C with a suggested maximum use-temperature of 1540°C. Alumina is an insulator with a thermal conductivity of 25 W/mK at 130°C, and a low thermal expansion of 3.4 X 10^{-6}/°C in the range of 25-700°C, thus low heat conducting may pose a problem with gamma-heating, and ways to cool the moderator blocks are being investigated. Alumina is relatively inert, insoluble in water and would only be affected superficially in the bond phase if hydrofluoric acid or strong caustics were present. Alumina is relatively inert to radiation damage and should hold up well close to the core.

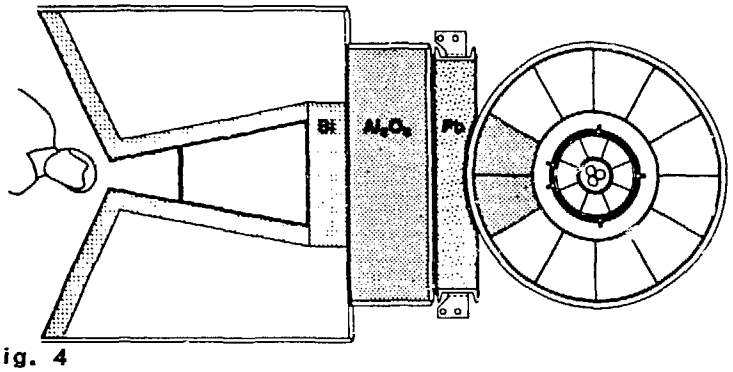

Fig. 4

B. MURR Geometry The actual MURR is not quite as simple as is represented in Figure 1. Figure 4 shows a section at the mid-plane. The graphite wedges on the west side of the core can be replaced with wedges of Al_2O_3. The 6 inches of lead that shield the thermal column will be difficult to move, but leaving it in is not too much of a compromise since Pb reduces the neutron fluxes very slowly as the radius increases. Next comes the pool liner, which is about 3/4 inch of Al, and this is not much of a compromise. Next Al_2O_3 would be stacked in the thermal column followed by Bi.

A tank that can be filled and drained quickly would fill the space between the Bi and the patient, and a high-density liquid filling the tank would act as a radiation shutter. An alternate design for a shutter is sliding doors following the Bi. The fluxes and doses with the actual geometry should be similar to the fluxes and doses calculated for the simpler geometry.

III. ^{238}U FILTERS

A. Measurements Several years ago measurements were made at MURR of the spectra of neutrons passing through several different thicknessess of natural U metal.[4] A Bonner sphere detector was used as the energy spectrometer and the code BONAB was used to process the data. Figure 5 shows these data, which indicate that a thick ^{238}U filter does pass only intermediate-energy neutrons. At the time these spectra were measured, a spectrum with zero thickness of U was not measured so that it is difficult to convert these data to transmissions or put the spectra on an absolute scale.

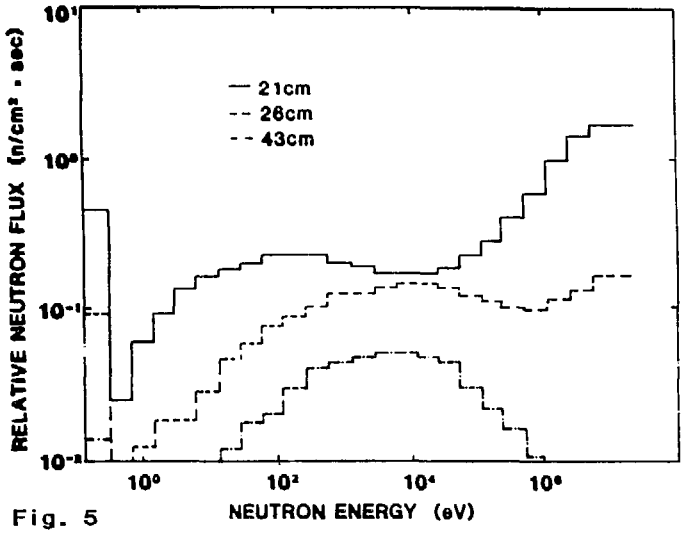

Fig. 5

B. Calculations The transmissions of thick filters of ^{238}U have been calculated using the total cross sections of ^{238}U as given by ENDF/B-V. Neutrons interact with matter by the neutron-nuclei reaction and the probability that neutrons of a specific energy react with nuclei is expressed as a cross section $\sigma(E)$. The attenuation of a beam of neutrons through a filter can be described by the formula $I(E) = I_0(E)e^{-n x \sigma}$, where the number of neutrons I(E) that pass thru a filter of length x and atom density n is equal to the product of the original number of neutrons from some source, $I_0(E)$, times the exponential of the product of the cross section, length, and atom density.

In order to calculate the spectrum of neutrons that would be passed by a thick ^{238}U filter, the initial source flux of MURR was considered. F.Y. Tsang has shown that a flux profile of the outer edge of the Be reflector for MURR can be calculated from the following equations:

1) For the thermal region (0.0001eV-0.64eV) the equation is
   $\phi(E) = 1.35 \times 10^{14} \times e^{-E/0.028} \times E/(0.028)^2 \times 10^6$ in units of n/cm^2-sec-MeV
2) For the resonance region (0.64eV-0.8MeV), the equation is
   $\phi(E) = 5.698 \times 10^{12} \times 1/E$ n/cm^2-sec-MeV
3) For the fast spectrum (0.8MeV->10.0MeV) the equation is
   $\phi(E) = 4.794 \times 10^{13} e^{-E} \sinh(2E)^{1/2}$ n/cm^2-sec-MeV

These three primary energy regions were applied to the 25 energy group structures used in previous filter measurements at MURR. Equation 1 applies to BONABS groups 1 and 2 (thermal to 6.826×10^{-7} MeV); equation 2 applies to BONABS groups 3 thru 21 (6.826×10^{-7} MeV to $\sim 9.072 \times 10^{-1}$ MeV); and equation 3 applies to BONABS groups 22 thru 25 (9.072×10^{-1} to 2.5×10^{1} MeV). One further group was added to the calculations to include energies over the BONABS limits but suggested by the ENDF/B data.

The data used to calculate the intensity, I(E), or the flux, $\phi(E)$, were derived from ENDF/B data supplied as a series of (E,σ) pairs. These data pairs represent a series of ascending but unequally spaced points describing a function f(x). To integrate this function and thus derive I(E), the rectangular method of integration was modified where $\Delta E = (E_{i+1} - E_{i-1})/2$. The equation describing the total flux for an energy group becomes $\Sigma I(E) = \Sigma(I_0(E)e^{-\sigma n x}\Delta E)$, where ΣI(E) has limits equal to the specific limits for the BONABS group being calculated.

The attenuation relationship, or the transmission factor, is the ratio of the number of neutrons passed through the filter to the number of neutrons incident to the filter, and is defined by the equation $T = \Sigma I(E)/\Sigma I_0(E)$. This transmission factor was also calculated for each BONABS group.

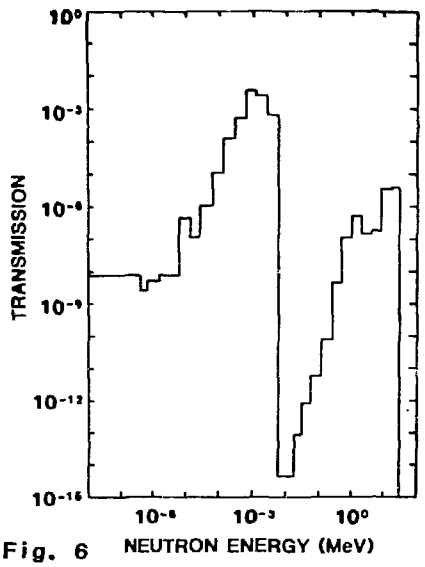

Fig. 6

Figure 6 shows the transmission that was calculated for a filter of ^{238}U that is 43 cm long. One notes that the transmission is small in the thermal region and increases as the neutron energy approaches the keV region, but drops suddenly near 4 keV. This drop corresponds to the energy at which ENDF/B stops treating individual nuclear resonances and shifts to a smoothed average value. Thus, above 4 keV the transmission calculations for thick filters probably exclude transmission through some windows and underestimate the transmission. This transmission curve indicates that the number of intermediate-energy neutrons through a thick ^{238}U filter may be 50-100 times more than the number of neutrons transmitted at the single window at 186 keV. The peak of the band passed by this filter is centered at 1 keV.

Possibilities of gamma-ray contributions to patient dose exist with any filter. Other U filters have a reported gamma contribution of < 1 mR/hr at neutron fluxes of ~10^5 n/cm^2-sec. Very low gamma flux is to be expected of a metal with a density greater than lead and a large mass energy attenuation coefficient. With a 43-cm-long filter there is 850 gm/cm^2 of material in the beam.

Possible problems that need to be assessed include the probability of thermal flux activation of the 0.2% ^{235}U found in depleted ^{238}U and the subsequent production of fission neutrons and gamma rays at the less self-attenuated patient exposed end of the filter. Also, physical properties of ^{238}U as a metal need to be investigated, including malleability, any pyrophoric attributes, melting point, and thermal conductance.

Depleted ^{238}U is a readily available metal/radionuclide that has a commercially reported cost of $15.00/kg in bulk form. Shipping regulations are delineated by NRC Regulation 75.31. MURR has three sections of ^{238}U currently on hand to use as a filter, enabling the expected implementation of further Bonner sphere tests.[4]

The above indicates that ^{238}U possesses the qualities of a good filter, adequate neutron flux over a desired energy range with minimal gamma-ray contribution to dose, and a reasonable cost factor. Rough calculation starting with a source flux of the MURR, a 100-cm x 100-cm source area, a

source-to-patient distance of 2 m and the transmissions of Figure 6 show that an intermediate flux of near 10^9 n/cm^{2}sec could be obtained at the patient position.

IV. OTHER RESOURCES IN COLUMBIA

Besides the research reactor as a source of neutrons, there are other resources at the reactor facility, at the University of Missouri-Columbia, and in the city of Columbia that can add to the effectiveness of an NCT program.

A. At MURR There is room on the reactor floor and a shielded room can be added at the irradiation position; Figure 7 shows a sketch of such a room. The door, which will have several windows for viewing the patient, will roll back and forth on the tracks that are already in place. A shutter will need to be added in the irradiator, and one possible shutter, as shown in Figure 4, is a tank that can be rapidly drained and filled with a high-density liquid.

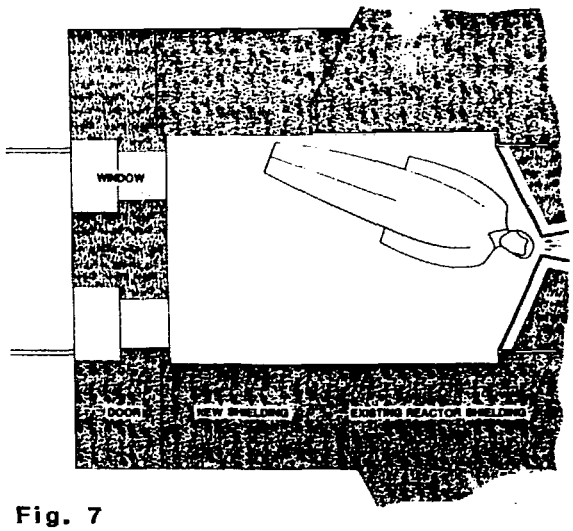

Fig. 7

The NCT irradiation facility at MURR would be accessible to patients by the path through the front door of the reactor building, through the air lock, down the elevator, and across the beam-port floor to the irradiation room. Five hospitals are within one to five miles of the front door, and patients would be shuttled by car or ambulance.

The reactor now operates at 10 MW more than 150 hours a week--more than 91% of the time. The reactor is shut down for 4 to 16 hours on Thursdays for maintenance. Neutrons will be available most of the time. The cost of operating the reactor is shared by a number of users, so the cost of operating an NCT program would be relatively modest. At MURR, a program is underway to increase the power of the reactor to 30 MW, which will increase the flux by a factor of three.

B. At the University The University of Missouri at Columbia has a medical school on campus about one mile from the MURR. This school has a radiology department including diagnostics and therapy. The medical school has a professional staff of 300 faculty and a hospital of 495 beds. The School of Veterinary Medicine is also at the Columbia campus with an excellent staff and animal care facilities.

C. In Columbia Besides the University's medical center, there are five other hospitals and/or cancer research facilities in Columbia. These are Boone Hospital Center, a 334-bed hospital with radiation treatment facilities; Columbia Regional Hospital, a 301-bed hospital with radiation treatment facilities; Ellis Fischel State Cancer Center, a state-supported cancer treatment center with 64 beds and radiation treatment facilities; and the Cancer Research Center, a private cancer research institution. These are all

within five miles of the MURR. In addition to these facilities, there is, across the street from the University Medical Center, the Harry S. Truman Veterans Administration Hospital, with a nuclear medicine department.

V. OTHER RADIOTHERAPY AND DIAGNOSTICS

The MURR has participated for many years in the development of radioisotopes for diagnostics and therapy. For many years the MURR supplied the most widely used diagnostic radioisotope precursor, Mo-99, and in fifteen years delivered over a million Curies. Recently the MURR has been actively developing and supplying new radioisotope generator designs. The new gel generator designs for the Mo-99/Tc-99m and Sn-113/In-113m systems developed at MURR are uniquely suitable for efficient, inexpensive production of medical generators and for their widespread distribution in large, developing countries such as China. We have recently heard from our Chinese contact, and both of these generators are now in use in China. In addition, MURR produces isotopes for the quantitation of osteoporosis (calcium loss in bone) and for basic studies of the cause and treatment of hypertension and cystic fibrosis. Researchers at MURR have also participated in the development of a new ^{99m}Tc diagnostic nuclear medicine agent for measuring blood flow in the brain that is now being marketed by Amersham.

For a number of years MURR has provided iridium seeds for the radiotherapeutic treatment of cancer, and has also supplied isotopes such as Re-186 for research into radiotherapy using tumor-specific bone and antibody agents. The Re-186 phosphonate bone agent, for example, will help to relieve the often intractable pain associated with bone metastases from breast, lung and prostate cancer, and may serve to reduce the size of such bone tumors. This and similar agents may also effectively eliminate micrometastases to bone in cancer patients before they become detectable by other means, thus serving as a prophylactic treatment.

Currently at least seven different reactor-produced isotopes are under investigation at MURR for such varied uses as the treatment of metastatic liver cancer using Y-90 glass microspheres, therapy to palliate the pain of bone cancer, radiotherapy of tumors using labeled antibodies, and radiation treatment of rheumatoid arthritis. Two of these radiotherapeutic drugs have been submitted to the FDA for Investigational New Drug exemptions to permit human trials, and a third is nearing that stage, with the rest at earlier stages of active development. The use of reactor-produced beta-emitters for radiotherapy is on the verge of a great expansion in which MURR will play an important role. The MURR has a proven track record of development of methods for cancer diagnosis and therapy.

VI. CONCLUSIONS

The effectiveness of an Al_2O_3 moderator and a ^{238}U filter have been evaluated to see whether either could produce a beam of intermediate-energy neutrons starting with the flux of the MURR. The Al_2O_3 moderator looks very promising, yielding a current of $> 10^9$ intermediate-energy neutrons at the patient position but very few fast neutrons or gamma rays. The ^{238}U filter is

also promising, with fluxes of intermediate energy neutrons near 10^9. Either or both such beams could be implemented at MURR once MURR is given the go ahead.

ACKNOWLEDGMENTS

The authors thank Dr. Gene Moum for his help in writing the code to calculate the transmissions from the ENDF/B data. Both Dr. Moum and Prof. Jay Kunze are thanked for their help with implementing DISNEL.

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The Power Burst Reactor Facility as an Epithermal Neutron Source for Brain Cancer Therapy

F. J. Wheeler
Idaho National Engineering Laboratory EG&G Idaho, Inc.
P. O. Box 1625 Idaho Falls, ID 83415

ABSTRACT

The Power Burst Facility (PBF) reactor is considered for modification to provide an intense, clean source of intermediate-energy (epithermal) neutrons desirable for clinical studies of neutron capture therapy (NCT) for malignant tumors. The modifications include partial replacement of the reflector, installation of a neutron-moderating, shifting region, additional shielding, and penetration of the present concrete shield with a collimating and (optionally) filtering region. The studies have indicated that the reactor, after these modifications, will be safely operable at full power (28 MW) within the acceptable limits of the plant protection systems. The neutron beam exiting from the collimator port is predicted to be of sufficient intensity ($\sim 10^{10}$ neutrons/cm^2-s) to provide therapeutic doses in very short irradiation times. The beam would be relatively free of undesirable fast neutrons, thermal neutrons and gamma rays. The calculated neutron energy spectrum and associated gamma rays in the beam were provided as input in simulation studies that used a computer model of a patient with a brain tumor to determine predicted dose rates to the tumor and healthy tissue. The results of this conceptual study indicate an intense, clean beam of epithermal neutrons for NCT clinical trials is attainable in the PBF facility with properly engineered design modifications.

1. INTRODUCTION

Neutron capture therapy (NCT) using epithermal neutrons may offer significant advantages over other forms of therapy for deep-seated malignancies. It may be possible to deliver destructive doses to the internal tumor without surgery and without great destruction to the healthy tissue. For treatment of brain tumors, epithermal neutrons will penetrate the scalp and skull without great damage to tissue or bone. The epithermal neutrons then slow down (thermalize) and form a capture peak a few centimeters into the brain at the tumor site. The greatest local tissue destruction occurs when the neutron is captured in an isotope such as boron-10, which can be introduced preferentially into the tumor with new, developing synthetic compounds. Damage to the healthy tissue from secondary gamma rays, capture in nitrogen, and capture in the residual boron-10 in blood is unavoidable. However, the damage from incident fast and thermal neutrons and gamma rays contaminating the beam can be minimized with proper design. The advantage factor (destruction of cancer

cells compared to destruction of healthy cells) may be high enough to enable destruction of the tumor while sparing sufficient healthy tissue to prevent degradation of life quality. The first principles of this mode of therapy were presented by Locher in 1936 (1).

Clinical trials for this promising therapy require a neutron source of sufficient intensity to deliver a therapeutic dose in a time period corresponding to reasonable immobilization times of critically ailing patients. This neutron beam must be relatively free of fast neutrons, thermal neutrons, and gamma rays since these constituents are the major cause of the non-selective damage to healthy tissue. For support of clinical trials, existing reactors and other neutron sources available for this application must be evaluated to determine merit.

The preliminary study described in this paper is an initial assessment of the PBF reactor employing a weakly moderating, weakly shifting region to tailor the neutron energy spectrum and deliver a collimated neutron beam to the irradiation area.

2. REACTOR DESCRIPTION

The PBF reactor is located at the Idaho National Engineering Laboratory (INEL). This facility has fulfilled its mission in the light-water reactor safety program and is currently on standby status. This national resource is available for application to a program such as NCT.

The PBF reactor core is in an open water-filled tank with a closed-loop coolant system. This system, using light water as a coolant, is capable of removing up to 28 MW of thermal energy during steady-state operation. The cylindrical reactor core is 1.3 m in diameter, 0.91 m in height, and has a central 0.21-m-diameter test space. The cutaway view in Figure 1 illustrates the major reactor components. Figure 2 is a cross-section view of the PBF driver core. Two independent sets of boron carbide rods control core power. Eight control rods maintain steady-state power levels, and four transient rods are used manually or automatically to initiate and control a reactor transient (power burst).

Table 1 partially summarizes some of the characteristics and capabilities of the PBF.

The cross section of a PBF fuel rod is shown in Figure 3. The fuel pellets are ceramic (30% urania, 62% zirconia, and 8% calcia), contained in a ceramic (zirconia, calcia) thermal insulator and a stainless steel cladding tube. The insulator retains the high fuel temperature, and therefore maintains inherent reactor shutdown following an anticipated (or unanticipated) transient. The fuel rods are closely packed, providing an intentionally under-moderated core which results in an intermediate-energy spectrum and effective transport of fast neutrons from the core. The reflector surrounding the core is a row of stainless-steel pins in water followed by rows of aluminum pins in water and an outer water reflector.

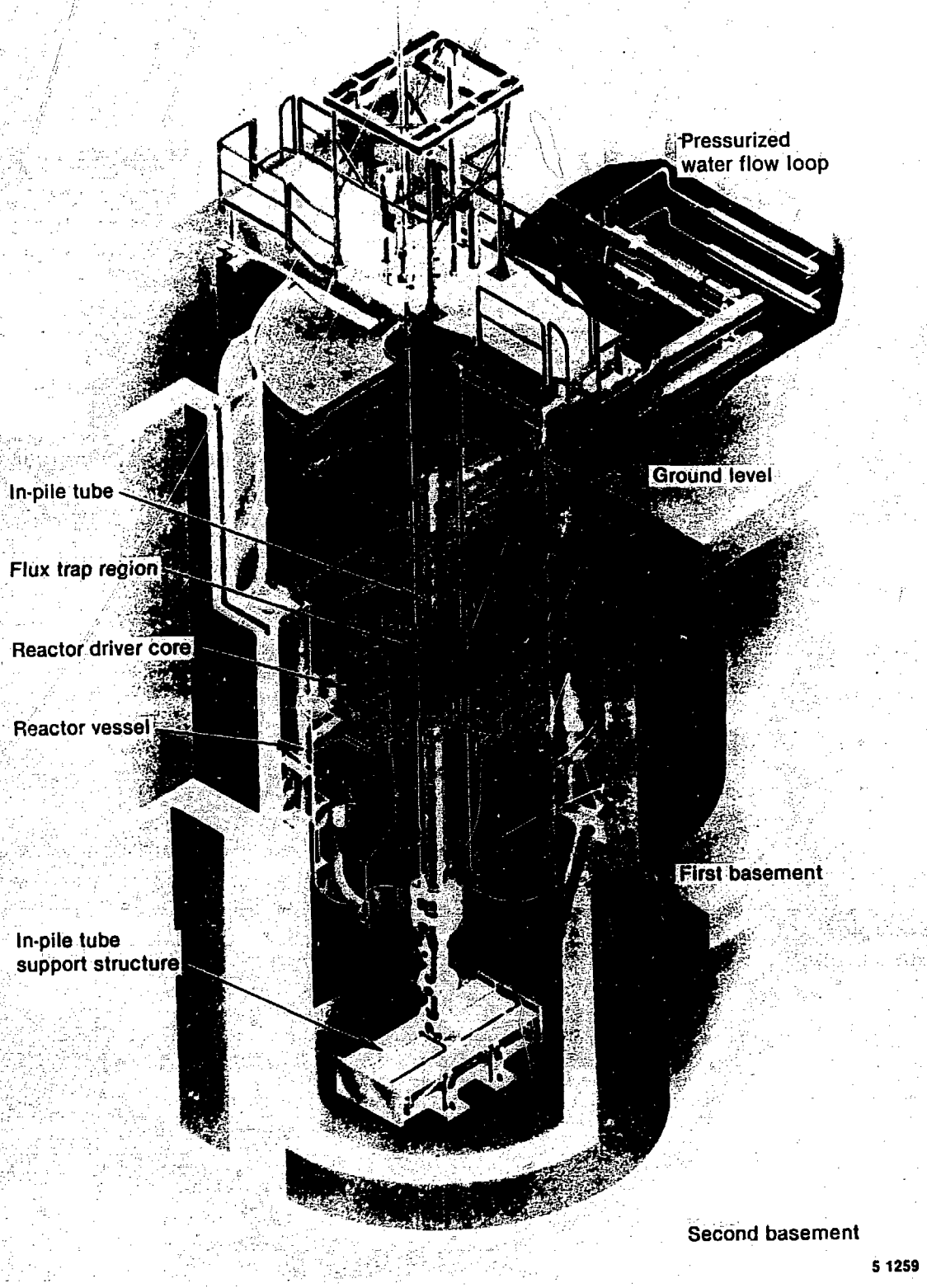


Fig. 1. Cutaway view of the PBF reactor.

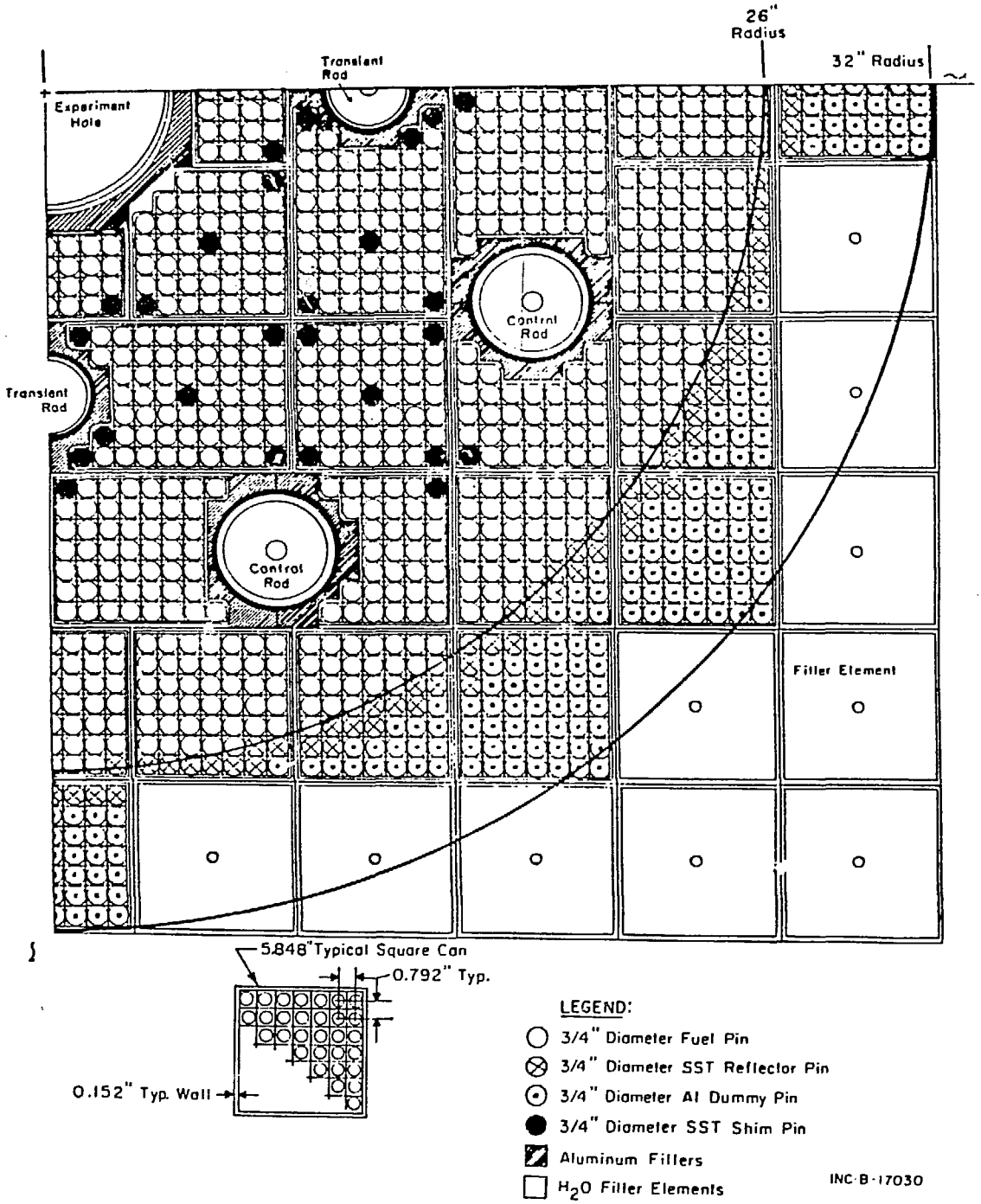


Fig. 2. Quarter-core cross section of the PBF core.

Table 1. Characteristics/Capabilities of the PBF Reactor

Parameter	Nominal PBF Value
Maximum steady state power	28 MW
Maximum shaped-burst period	20 ms
Maximum natural-burst power	270 GW
Maximum energy release in burst	1350 MJ
Number of fuel rod locations	2496
Non-moderator to moderator ratio	2.3
Average 28-MW core flux	
0.821 MeV < E < 10.0 MeV	3.2×10^{13} n/cm^2-s
5.532 KeV < E < 0.821 MeV	5.0×10^{13} n/cm^2-s
0.532 eV < E < 5.532 KeV	4.2×10^{13} n/cm^2-s
0.0 eV < E < 0.532 eV	1.1×10^{13} n/cm^2-s

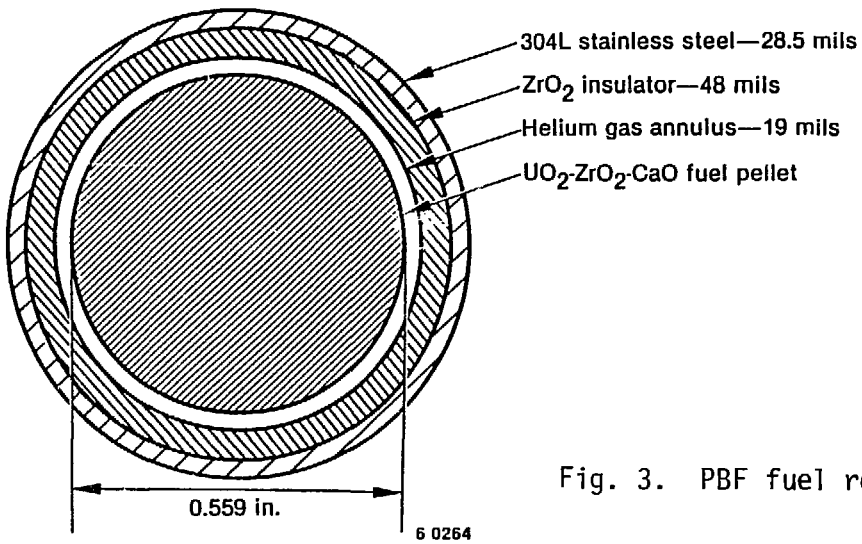


Fig. 3. PBF fuel rod cross section.

3. DISCUSSION

This study attempts to examine most aspects of the neutron-source problem for NCT to determine feasibility of engineering design modifications that will enable the PBF facility to provide the acceptable neutron beam. The study investigated partial replacement of the existing reflector and the installation of a weakly moderating, weakly shifting region (spectrum shifter) between the core and collimator. The spectrum shifter is selected for properties that downscatter fast neutrons to epithermal energies, harden (shift) the low energy part of the neutron spectrum, and effectively transport epithermal neutrons to the collimator. This concept results in a high epithermal flux output with minimal fast and thermal neutron flux and minimal production of capture-gamma energy. Filtering techniques used in the collimator region could then be used to further tailor the neutron energy spectrum, if desired.

The application of aluminum and heavy water (D_2O) for a weakly moderating material has been studied by Oka, et al. (2) at the University of Tokoyo. They have determined that, for their application, a volume percentage of 10-20% D_2O in aluminum was optimum for the generation and transport of epithermal neutrons. Aluminum, with 10% D_2O, was selected for PBF studies since aluminum metal has well-known properties for a nuclear system and because the D_2O can also be circulated to remove heat generated within the aluminum during extended operation. The physical size of PBF is larger than a typical research reactor and this results in a requirement for a relatively low D_2O fraction in the spectrum shifter.

CONCEPT

The concept analyzed for this study is sketched in Figures 4 and 5. The central test space in the core is voided or replaced with an aluminum filler. This increases core reactivity and extends the number of years the reactor could operate in the NCT mode without refueling. This configuration also precludes the possibility of a positive reactivity insertion associated with accidental voiding of the in-core test space.

The neutron reflector selected for this study is bismuth, which is an effective reflector for the PBF core. The bismuth generates polonium in a neutron field and therefore should be clad. The use of a high-mass, non-moderating (except for the coolant) material such as bismuth takes advantage of several inherent PBF characteristics. Replacement of the present inefficient stainless steel and water neutron reflector with bismuth increases reactivity and forces power toward the bismuth, thus increasing neutron leakage into the shifter. The fast neutrons are transported to the shifter more effectively than epithermal or thermal neutrons. This is desirable at this location because epithermal and thermal neutrons will not contribute significantly to the final beam but will cause production of undesirable capture gammas in the shifter. It is

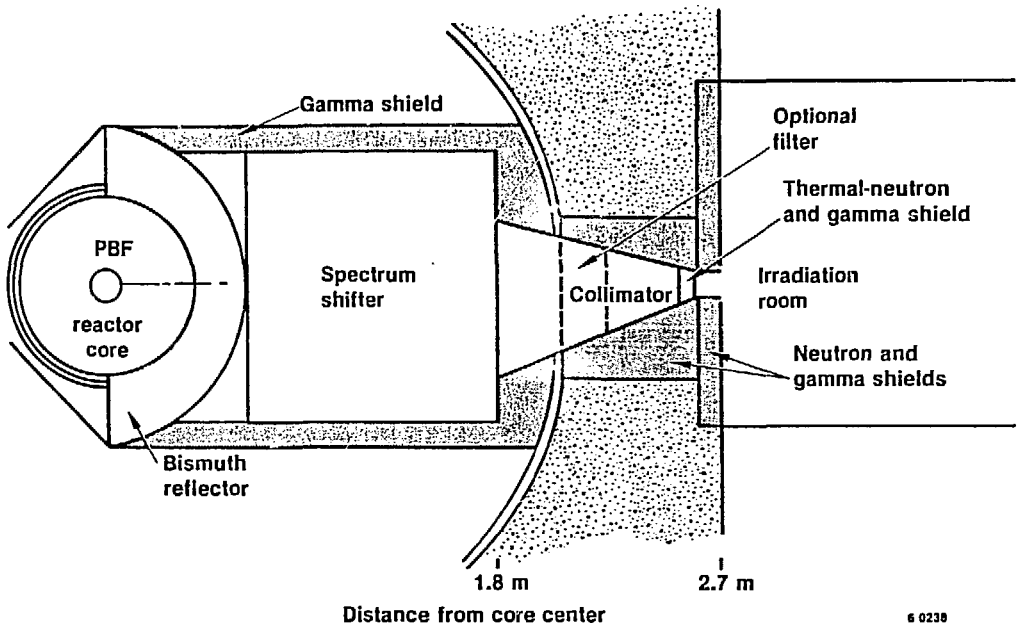


Fig. 4. Cross section of the epithermal neutron beam concept for PBF. Fast neutrons from the core are preferentially transmitted to the Al-D2O spectrum shifter where they are moderated to epithermal energies and transmitted to the collimator. A neutron absorber in the shifter attenuates the undesired thermal flux and reduces the capture-gamma source. The final gamma shield in the collimator may not be required.

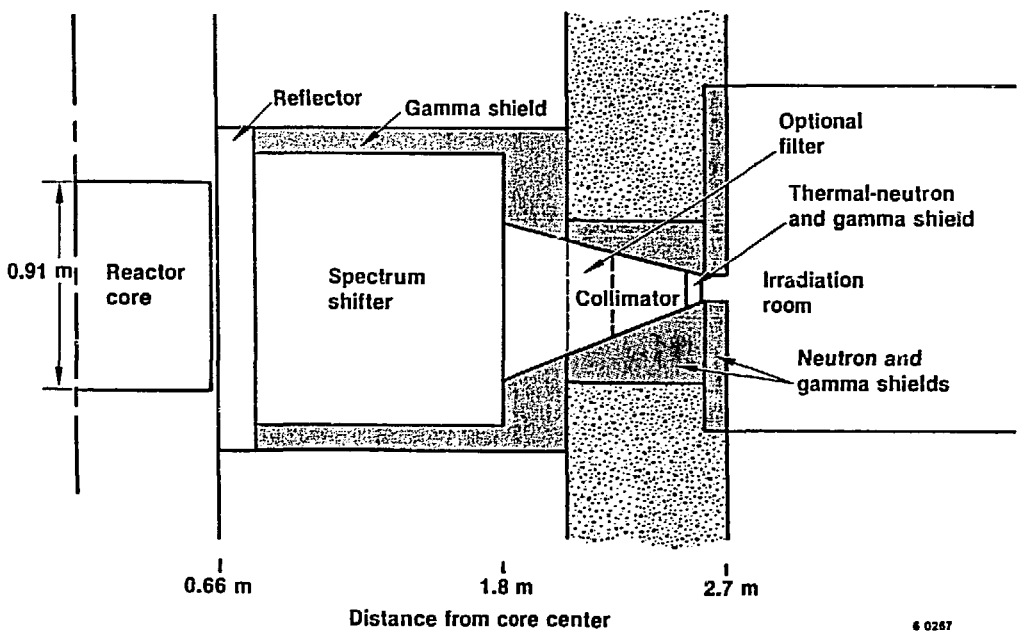


Fig. 5. Side view of the PBF epithermal beam concept.

the fast neutrons that moderate in the shifter and contribute to the desired epithermal flux at the irradiation site. The bismuth reflector effectively decouples the core from the shifter, allowing flexibility in the shifter design (e.g. a thermal-neutron absorbing material can be placed in this region without significant reactivity loss).

The Al-D_2O spectrum shifter region is larger than the face of the core to maximize transmission of epithermal neutrons toward the collimator. A small amount of thermal-neutron absorber is added to the shifter material to preferentially capture the neutrons that are thermalized in the spectrum shifter. This reduces the high-energy Al capture gammas and also reduces the undesirable thermal neutrons in the beam. The leakage current from the spectrum shifter is then collimated and, optionally, filtered before exiting into the irradiation port. Gamma shielding surrounds the spectrum shifter to attenuate core gammas and capture gammas from external reflector regions.

The collimator (refer to Figure 4) may or may not require a thermal-neutron/gamma shield. This shield,if needed, would have an inner cadmium layer to reduce thermal neutrons and a high-mass, thicker layer to attenuate gammas. The high-mass material attenuates epithermal neutrons effectively so it should not be too thick. Some attenuation may be desired, however, to reduce the non-forward component of the epithermal neutron flux and provide the desired beam. The collimator includes a beam shutter (not shown in the illustrations) to conveniently shut off the beam except during the irradiation period. This shutter would be a material with high neutron moderation and gamma attenuation. A combination of polyethylene and lead may be sufficient. Neutron and gamma shielding is also required near the collimator port. The concept accommodates an optional filtering region should one wish to further tailor the flux emitted from the spectrum shifter. The flux could be softened slightly or fully thermalized by a moderator in this region or the flux could be hardened by a neutron absorber or by filters with desirable transmission windows. The flux could also be hardened and intensified by draining the D_2O out of the spectrum shifter. These considerations are left for future analyses as the goal of this work was to see if a desirable epithermal beam could be achieved.

4. METHODS AND RESULTS

Reactor effects were analyzed with the two-dimensional PDQ (3) diffusion-theory code. The transport of neutrons through the spectrum shifter was analyzed with the SCAMP (4) one-dimensional Sn transport code in cylindrical geometry. The calculations used a 32-group cross-section set based on ENDF/B-5 (5) data and generated specifically for the PBF reactor. The three-dimensional RAFFLE (6) Monte Carlo code was used to analyze the neutron transport through the collimator and final gamma shield. The one-dimensional model was validated by running a three-dimensional RAFFLE model of the spectrum shifter. A head phantom (a

15x15x20-cm parallelepiped with scalp and skull) was modeled for the RAFFLE code to determine dose rates from the collimated beam. The QAD code (7) was used to determine the gamma rays in the beam and the dose rates in the head model that result from these incident gammas. These computer codes, data, and methods have been used and extensively validated for PBF.

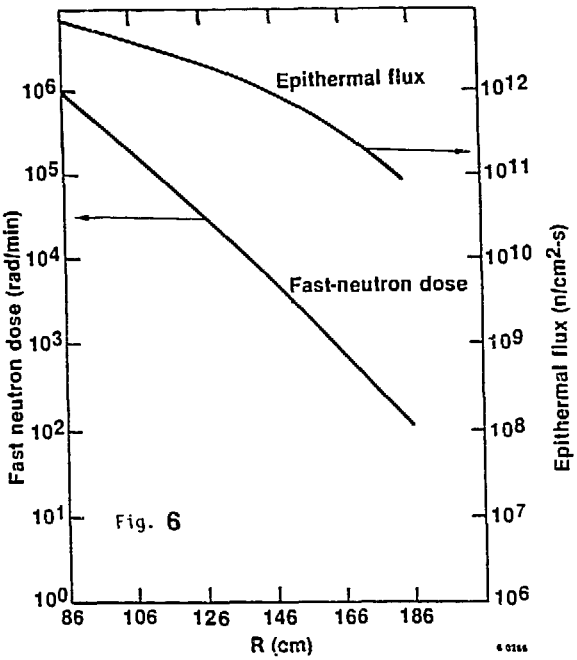
REACTOR ANALYSES

The two-dimensional (xy) PDQ model of the PBF reactor core was modified to represent reflector changes. The calculated eigenvalue for the unperturbed and unrodded core was 1.048. The partial replacement of the existing reflector with bismuth and the Al-D_2O spectrum shifter resulted in an eigenvalue of 1.0569, an increase in reactivity of 0.8%. The power is also shifted toward the bismuth reflector. The relative power density at the periphery of the core is about 0.5 for the existing configuration and increases to about 0.8 near the bismuth for the new configuration. The maximum relative power density in the hot fuel channel is increased by about 7%. This power shift provides more neutrons to the beam side of the reactor and is not severe enough to limit the operation of the core. No difficulties are anticipated with reactor operation at full power.

SPECTRUM SHIFTER ANALYSES

The function of the spectrum shifter is to minimize the transmission of fast neutrons, thermal neutrons, and gammas and maximize the transmission of epithermal neutrons.

Results from the SCAMP one-dimensional model are plotted in Figure 6 for epithermal-neutron (1.86 eV to 24.8 keV) flux and fast-neutron (above 10 keV) dose through the shifter. It is important to establish the validity of the one-dimensional model for calculating the neutron flux into the collimator. To establish this confidence a comparison was made with a three-dimensional RAFFLE Monte Carlo model. In this model, a 100-cm cube was used for the spectrum shifter and the reflector leakage currents were used for the neutron source. The flux-at-a-point method, first suggested by Kalos (8) and developed for RAFFLE by Grimesey (9), was found to be essential to obtain low variance in the pointwise flux from the Monte Carlo run. The results for the uncollimated flux at the irradiation point 274 cm from core centerline are presented in Table 2. The value for the SCAMP flux in Table 2 is the forward component of the flux (the neutron current directed toward the collimator) extrapolated to the irradiation point. This comparison establishes the validity of the SCAMP one-dimensional model. The SCAMP neutron fluxes at the irradiation point are shown in Figure 7 for this case.



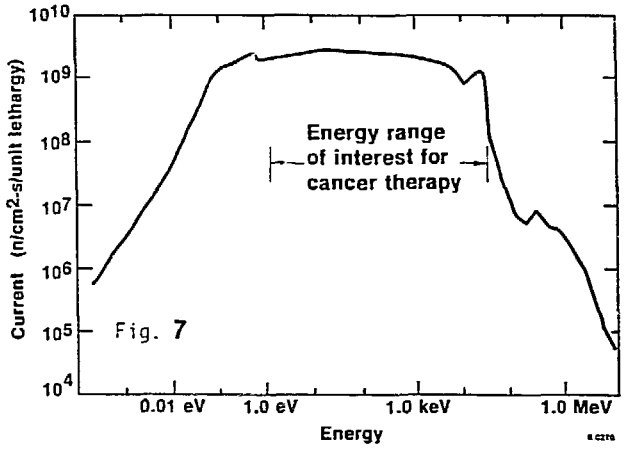
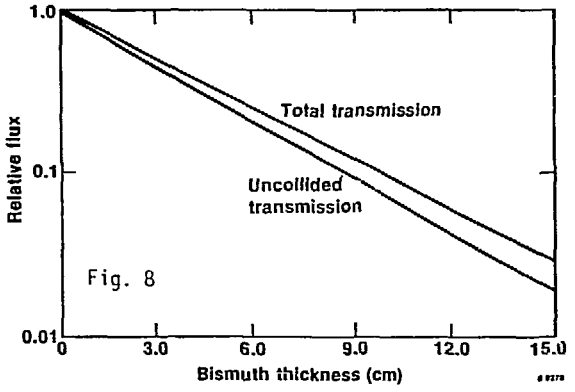


Fig. 6. Attenuation of the fast-neutron dose and the epithermal flux in the shifter region. Fast-neutron flux is reduced more than the epithermal flux. R is the distance from core center.

Fig. 7. Neutron current at the irradiation site for the case with no collimator shield and no added absorber in the spectrum shifter.

Table 2. Comparison of the Uncollimated Epithermal Fluxes at the Irradiation Point for the Case with No Added Absorber Material in the Spectrum Shifter.

SCAMP one-dimensional results	2.45×10^{10} n/cm²-s
RAFFLE three-dimensional results	2.65×10^{10} n/cm²-s $\pm$ 0.15×10^{10} n/cm²-s



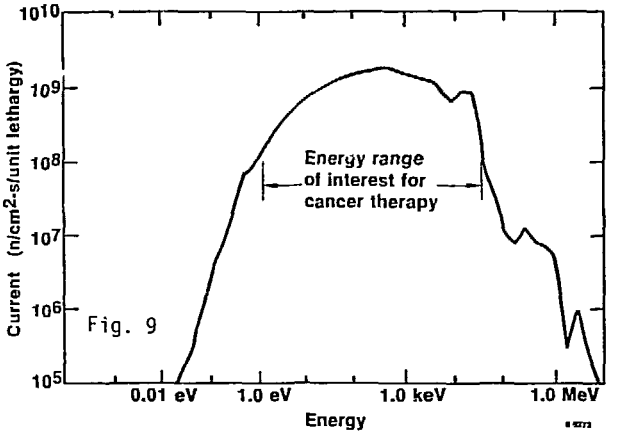


Fig. 8. Transmission of neutrons through the collimator and shield as predicted by the RAFFLE Monte Carlo model.

Fig. 9. The neutron current at the irradiation site for the case with a 5-cm bismuth gamma shield and 4 mg/cm^3 natural boron in the spectrum shifter. This spectrum could be modified by design or with optional filtering materials.

COLLIMATOR AND GAMMA SHIELD

It remains to be determined if a gamma shield is required in the collimator. Studies were performed to investigate the effect of this shield. With a shield in the collimator, the neutron flux is significantly over-estimated by the one-dimensional model. The RAFFLE code, therefore, was used to calculate the neutron flux through the collimator and shield. The leakage currents from the shifter, as predicted by the SCAMP model, were used as an input source. Bismuth was selected as the shield material, and calculations were made to determine neutron transmission as a function of the shield thickness. The results for the attenuation of the uncollided and total flux through this shield are shown in Figure 8. The collided contribution is significant and increases with shield thickness. The angular distribution of the emerging neutron flux was not obtained for this conceptual study. However, this distribution will be strongly forward peaked. The significance of the angular distribution should be investigated in future studies because beam divergence will affect irradiation time. The neutron fluxes at the irradiation point for a 5-cm shield are shown in Figure 9. For this case, the spectrum shifter contained a thermal-neutron absorber equivalent to 4.4 mg/cm^3 boron.

The gamma dose was calculated with the QAD point-kernel shielding code. The gammas from the reactor core are well attenuated by the 500 g/cm^2 of shielding provided by the bismuth reflector and spectrum shifter and were not considered in this calculation. Also the gamma dose

from capture in the bismuth gamma shield and inner cadmium liner is small. The neutron capture distribution, calculated for the spectrum shifter with the SCAMP model, was input to the QAD model to calculate the gamma dose as a function of collimator shield thickness. The 1.78 MeV delayed gamma following the 1.5-minute half-life beta decay of Al-28 was conservatively modeled as a prompt event. Dose rates from the incident gammas were also calculated as a function of distance into tissue by the QAD model.

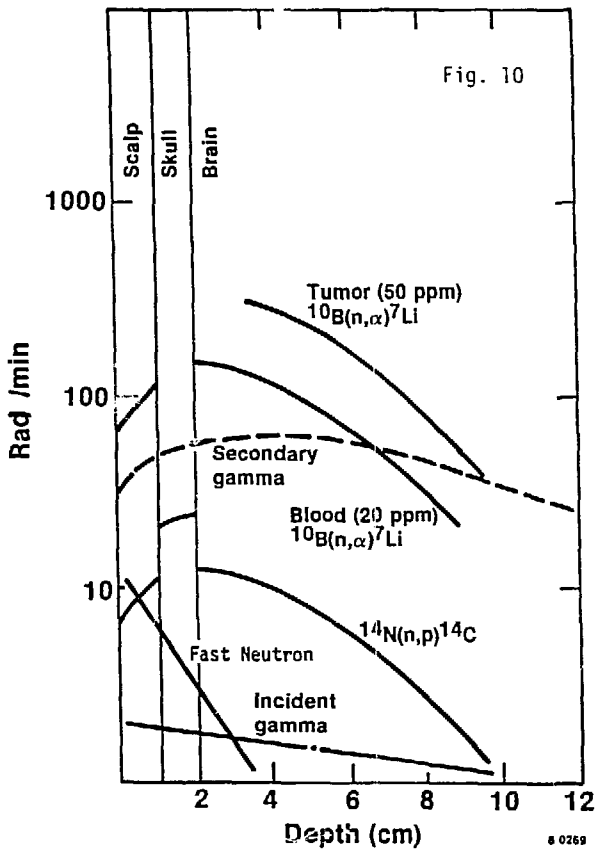
PHANTOM HEAD MODEL STUDIES

The calculated values for the epithermal fluxes and the scalp doses from the incident beam are summarized in Table 3 as a function of collimator-shield thickness.

Table 3. Epithermal Fluxes and Incident Scalp Dose as a Function of the Bismuth Gamma Shield Thickness. Natural boron (4.4 mg/cm^3) is added to the spectrum shifter.

Shield Thickness (cm)	Epithermal Flux (n/cm^2-s)	Fast Neutron Dose (rad/min)	Incident Gamma Dose (rad/min)
0.0	2.21×10^{10}	18.1	18.2
5.0	6.78×10^{9}	11.2	1.8
10.0	2.17×10^{9}	6.9	0.3

SCAMP neutron currents (Figure 9), normalized to the appropriate flux, were input to a RAFFLE phantom head model to estimate induced doses to the scalp, skull, brain, and tumor. The neutron beam was 9x9 cm and monodirectional. The induced gamma dose was calculated with a simple model. The results, combined with the QAD results for gamma dose, are illustrated in Figure 10 for the case with a 5-cm gamma shield and in Figure 11 for the case with no gamma shield. For these illustrations, the concentration of boron-10 was assumed to be 50 ppm in the tumor and 20 ppm in the blood. In reality, the concentrations may be higher or lower depending upon the boron compound and the medical procedure for boron injection and blood cleansing. The graphs can be scaled proportional to boron-10 concentration with little error for concentrations less than 100 ppm. These results indicate very high tumor dose rates with relatively low non-selective doses from undesirable incident fast neutrons and gammas in the beam.



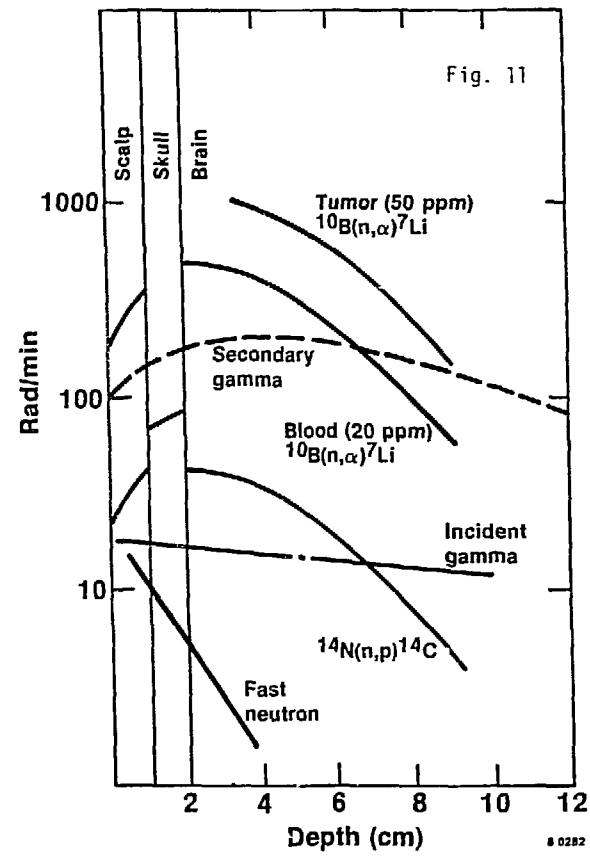


Fig. 10. Predicted head dose rates for the case with a 5-cm bismuth collimator shield (28 MW reactor power).

Fig. 11. Predicted head dose rates for the case with no collimator shield (28 MW reactor power).

5. CONCLUSIONS

These conceptual studies indicate that the modified PBF reactor can provide the necessary epithermal neutron flux intensity for a therapeutic dose in a very short time period (e.g. for the uncollimated beam, 1100 rad can be delivered in one minute). The beam is predicted to have a low contribution from undesirable fast neutrons, thermal neutrons, and gamma rays. The modifications will permit operation of the core at the full 28-MW power level with adequate control. At a use level of 500 patients per year the core can be operated for more than ten years before refueling. The modifications indicated in this concept are achievable with available engineering skills and at far less cost than construction of a new reactor facility. Although this study is conceptual, the system modeled is quite practical. The computational methods are of sufficient accuracy to provide confidence in the results. Optimization studies could improve the predicted performance of the concept.

The PBF dose rates appear to be high enough to speculate about operation in the transient mode. The PBF has the capability to rapidly eject the transient rods from the core, initiating a 1.3-20 ms transient with a maximum core energy deposition of 1350 MJ. The resulting dose would be equivalent to that delivered at full power for 48 seconds. For the case with no collimator shield, a peak boron-10 (50 ppm) tumor dose would be about 900 rad. The natural shut-down mechanism (Doppler effect) of the core would terminate the transient. The fuel pellet insulator would retain the heat (and therefore maintain reactor shutdown) for about an hour before another transient could be initiated. For the transient mode, the dose due to the 1.78-MeV delayed gammas could be eliminated.

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Neutron Capture Therapy at Brookhaven National Laboratory

R.G. Fairchild, D.N. Slatkin, D. Gabel, J. Coderre, J. Glass,
B.H. Laster, D.C. Borg, J.J. Elmore, S. Foster, P. Micca, and J. Kalef-Ezra
Medical Department
Brookhaven National Laboratory
Upton, New York 11973

ABSTRACT

Application of the $^{10}B(n,\alpha)^{7}Li$ reaction to cancer radiotherapy (Neutron Capture therapy, or NCT) has intrigued investigators since shortly after the discovery of the neutron. This paper summarizes data describing recently developed boronated compounds designed to serve as vehicles for boron transport to tumor. Whole-body (mouse) Neutron Capture Radiograms (NCR) of some of the most promising compounds are presented; these graphically demonstrate selective uptake in tumor, at times varying from hours to days post administration. Comparison is made to the ubiquitous distribution of inorganic boron compounds used in the first clinical trials of NCT. Since some compounds are now available that allow physiological targeting of boron to tumor at concentrations adequate for therapy, the NCR technique can be used to evaluate important questions concering the "microdistribution" of boron within the tumor. The implication of these compounds to NCT is evaluated in terms of Therapeutic Gain (TG). The optimization of NCT by using band-pass filtered neutron 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 statistics, mortality is ~50% when averaged over all cancers. Thus despite 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 ensure 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 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

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repopulation rates. The failure of radiotherapy attests to the fact that these conditions do not always obtain. Additional problems are 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 then restrict dose to these cells alone. 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 ^{131}I is a good example of this. A tumorcidal dose is given, while restricting normal tissue dose to <2% of that given to tumor. Another possible example is the treatment of melanotic melanoma with ^{35}S-labeled thiouracil (TU). Following the experimental finding that TU was taken up selectively in growing melanoma (1), studies have shown that a dose rate of $\sim$60 rads/hour could 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 rapidly proliferating and 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 to 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 that 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 when 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 $\sim$1 cell diameter, conditions ideal for radiotherapy are possible, 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 repair, greater effectiveness against hypoxic cells, and a relatively 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 trials in the period from 1951 to 1961 were unsuccessful because of radiation necrosis in normal brain tissues, resulting from boron concentrations in blood which were higher than that in tumor. Also, viable tumor was found at depth because of rapid attenuation of the incident thermal neutron beam (3). More recent clinical

studies in Japan, started in 1968 by Dr. Hatanaka, have shown better results, with an evident increase in average survival of patients with brain tumors relative to that after conventional treatment. These encouraging findings are due in part to a "second-generation" compound, $Na_2B_{12}H_{11}SH$, which shows an improved tumor/blood concentration ratio of ~1.5. Irradiations have been carried out using a thermal neutron beam and irradiation times of a few hours, mainly at the 100-kW Musashi Institute of Technology Reactor (4,5).

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

3 NEW COMPOUNDS FOR BORON TRANSPORT TO TUMOR

3.1 $Na_4B_{24}H_{22}S_2$

Recent studies have indicated that the dimer $Na_4B_{24}H_{22}S_2$ has greater biological activity than the monomer $Na_2B_{12}H_{11}SH$, currently used for NCT clinical trials of NCT in Japan. 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. Tumor concentrations of boron provided by the dimer were ~2x that found with the monomer (6,7). 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.

In general, gross boron concentrations in tissues have been measured with prompt-γ techniques (8). However, following the identification of a compound producing usable quantities of boron in tumor for therapy, it then becomes of great importance to evaluate the "microdistribution" within the tumor itself. This problem has been emphazized during the course of this Workshop, and it can be approached through NCR, with techniques developed by Gabel (9). The NCR in Fig. 1 shows the distribution of $Na_4B_{24}H_{22}S_2$ 24 hr after a single injection of ~35 μg ^{10}B/g mouse. This Harding-Passey tumor is the same as that described by Slatkin et al. (6,7) and shows significantly greater boron accumulation than the rest of the tissues. In particular, boron concentration in brain is only slightly above background, so that the tumor/brain ratio is actually >20. Such ratios are difficult to estimate with prompt-γ measurements because of the large error in determining low amounts of B. Areas of inhomogeniety in boron distribution can also be seen within the tumor in Fig. 1, possibly as a consequence of large necrotic areas observed in these tumors; correlation of necrotic areas with regions of inhomogeniety can be made by histological evaluation of adjacent tissue sections.

It is of interest to compare the distribution of $Na_4B_{24}H_{22}S_2$ with that of inorganic boron compounds which were used in initial clinical trials and which showed no physiological affinity for tumors. Such a distribution is shown in Fig. 2, for boric acid (H_3BO_3), at 30 min post injection of ~50 μg ^{10}B/g. Boric acid is analogous to the various compounds used clinically (sodium borate, sodium pentaborate, paracarboxyphenyl-boronic acid, and sodium perhydrodecaborate). The distribution in Fig. 2 is seen to be

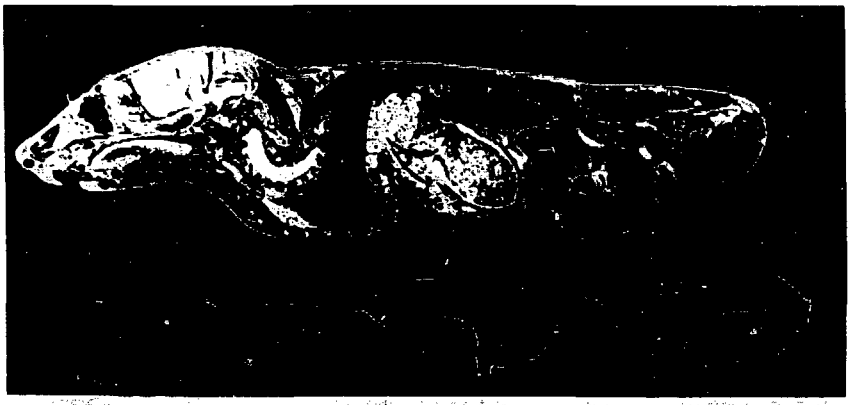

Figure 1

$Na_4B_{24}H_{22}S_2$;
24 h post injection of ~35 µg ^{10}B/g.

Tissue section.

Neutron capture radiograph.

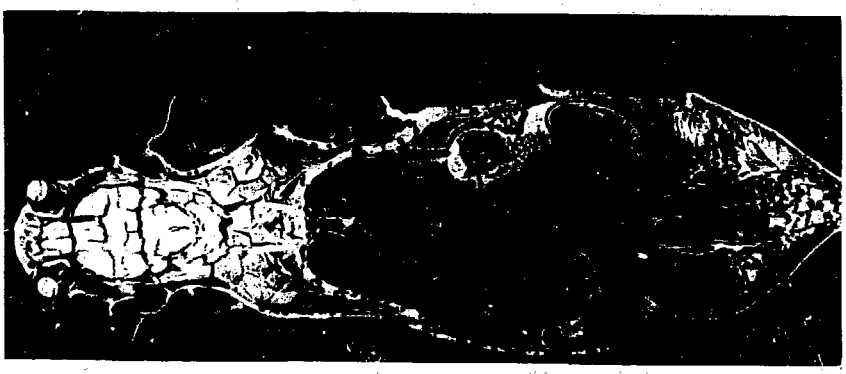

Figure 2

H_3BO_3;
30 min post injection of ~50 µg ^{10}B/g.

Tissue section.

Neutron capture radiograph.

ubiquitous, in agreement with detailed studies published previously showing no preferential accumulation of sodium borate in murine tumor (10).

Comparison of Figs. 1 and 2 clearly demonstrates the potential advantage of $Na_4B_{24}H_{22}S_2$ relative to compounds used in original clinical trials in the U.S. Without selective binding to tumor, TGs greater than 1 could not have been obtained. TGs available with $Na_4B_{24}H_{22}S_2$ are described in Section 4 below.

A number of classes of compounds in addition to the dimer described above are known to exhibit selective binding to tumor. This information stems in part from experience with nuclear medicine procedures, in which numerous biomolecules have been used to diagnose the presence of tumors. However, only a few of these show a selectivity and concentration robust enough to be useful for therapy. The various classes of compounds that have shown some evidence of being useful for NCT are summarized briefly below.

3.2 Amino Acids

Various boronated amino acids are being synthesized and tested by investigators in Europe, Japan, and the U.S. (11). In particular we have found p-borono-phenylalanine (BPA), as initially reported by Mishima (12,13), to have selective accumulation in murine melanoma with concomitant clearance from normal tissues. Following i.p. injections, absolute concentrations of ~15 to 30 μg ^{10}B per gram tumor can be obtained, with a tumor/blood concentration ratio of ~5 to 10. Use of the L-form of this compound has allowed background boron concentrations to be reduced (14). The distribution of BPA is shown in a neutron capture radiograph in Fig. 3. Boron is found distributed throughout the body, including brain. However, the tumor/normal tissue concentration ratios are ≥ 5, thus making therapy feasible. Biological efficacy has been demonstrated at the Medical Research Reactor (MRR), where BALB/c mice carrying Harding-Passey melanoma on the thigh have been irradiated, with and without BPA (Figs. 5 and 6) (15). At 8 MW/min, tumor growth was controlled indefinitely (>100 days) in 4 of 6 mice (tumor dose = 2720 rads x RBE; therapeutic gain in the treatment volume = 2.6). A temporary delay in tumor growth was obtained with controls irradiated with neutrons only, with no mice surviving (each data point represents the average for 6 mice). In addition to demonstrating therapeutic efficacy, the above experiment can be used to evaluate the micro-distribution of boron indirectly; clearly the distribution was sufficently homogeneous to prevent tumor regeneration.

3.3 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 (such as BPA may be). Thus boronated porphyrins 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 (16-18).

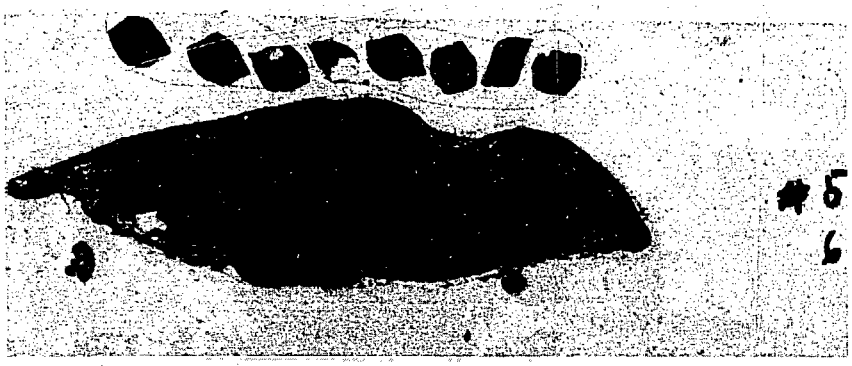

Figure 3

$C_9H_{12}NO_4B$;
p-borono-L-phenylalanine,
6 hr post injection
of ~28 µg B/g.

Tissue section.

Neutron capture
radiograph.

Figure 4

Boronated porphyrin
6 days after initiation
of 5-day i.v. infusion
of 20 µg B/g.

Tissue section.

Neutron capture
radiograph.

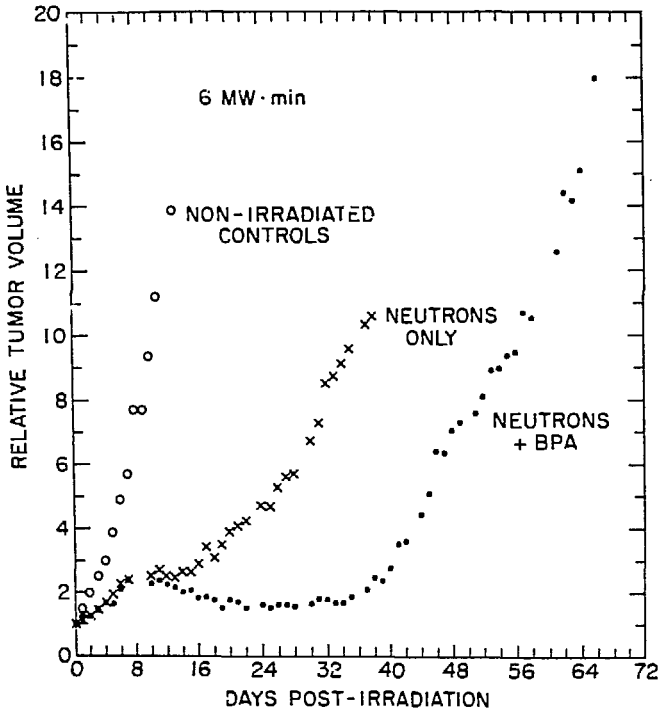

Figure 5

BALB/C mice carrying Harding-Passey melanoma: $\Phi = 5.0 \times 10^{12}$ n/cm^2; tumor dose = 2040 (rads x RBE) (assuming 15 µg B/g tumor); whole-body dose = 288 (rads x RBE) (no boron).

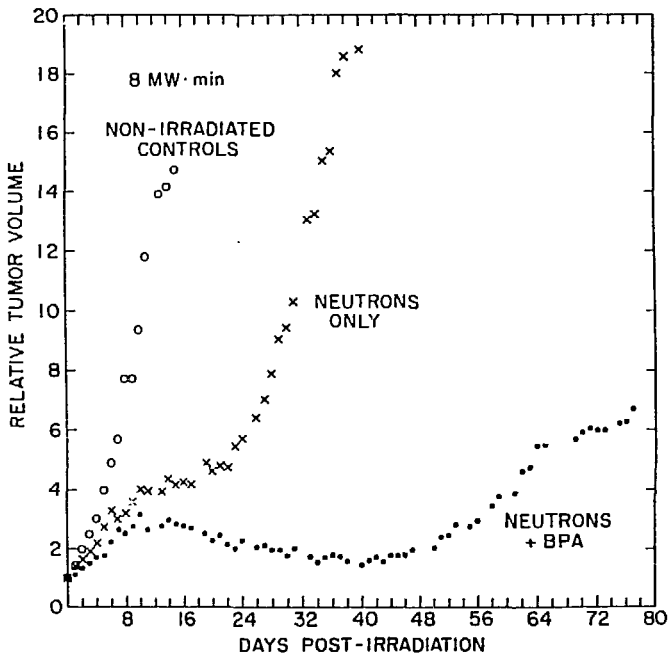

Figure 6

Same as Fig. 5, except $\Phi = 6.7 \times 10^{12}$ n/cm^2; tumor dose = 2720 (rads x RBE); whole-body dose = 384 (rads x RBE) (no boron).

The distribution of a boronated porphyrin (synthesized by D. Gabel) is shown in an NCR in Fig. 4. The boron concentration is higher in the Harding-Passey tumor than in any other organ, and in particular little or none is found in normal brain, indicating a potential application in the treatment of glioblastoma. The concentration in tumor (2 to 12 μg B/g) approaches that which can be used therapeutically. Thus prophyrins should eventually find application in NCT, either alone or perhaps administered together in a "cocktail" along with some form of sulfhydryl boron hydride.

3.4 Nucleosides

Schinazi et al. have synthesized a boronated analog of thymidine (DBDU) (19), which may be incorporated into the cell nucleus, and possibly into the DNA (20). It has been estimated that a 5% substitution (DBDU for Thd) would be adequate for NCT (21). Studies are now underway to evaluate the uptake of DBDU, as illustrated by the survival curves in Fig. 7. Preliminary data indicate that incorporations equivalent to 5% replacement of Thd are achieved, and that DBDU may contribute significantly to the NCT of brain tumors (20).

3.5 Antibodies

The use of boronated antibodies is potentially a most 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) (11,13). More recently, preliminary data have indicated that such conjugates can retain their biological activity and selectivity *in vitro*. This has been demonstrated by Elmore et al. with a boronated antibody in which a dextran "bridge" has been used to enhance boron-carrying capacity (22). Using an Enzyme-Linked Immuno-Sorbent Assay (ELISA), biological reactivity for a boronated monoclonal antibody (MoAb 149.53) directed against melanoma cells (Colo-38) was demonstrated, while no reactivity was observed for a control cell line (Fig. 8). The ^{10}B levels of about 20 μg/g are also within the range calculated for successful NCT, but more ^{10}B-conjugated MoAb must be synthesized for cellular radiobiology or animal distribution studies to be carried out. Regardless of the outcome of *in vivo* studies of ^{10}B-MoAb administered parenterally, however, utilization of boronated antibodies in "closed" compartments appears promising, as suggested by Epenetos (26). Infusion of boronated antibodies into brain tumors might be advantageous. Utilization of the blood-brain barrier to exclude antibodies from normal tissues might prevent any loss of specificity caused by conjugation with large amounts of boron from being debilitating. Uptake of boron-labeled antibodies in other cell pools would not be limiting (as with ^{131}I-MoAbs) as stable ^{10}B is not inherently toxic.

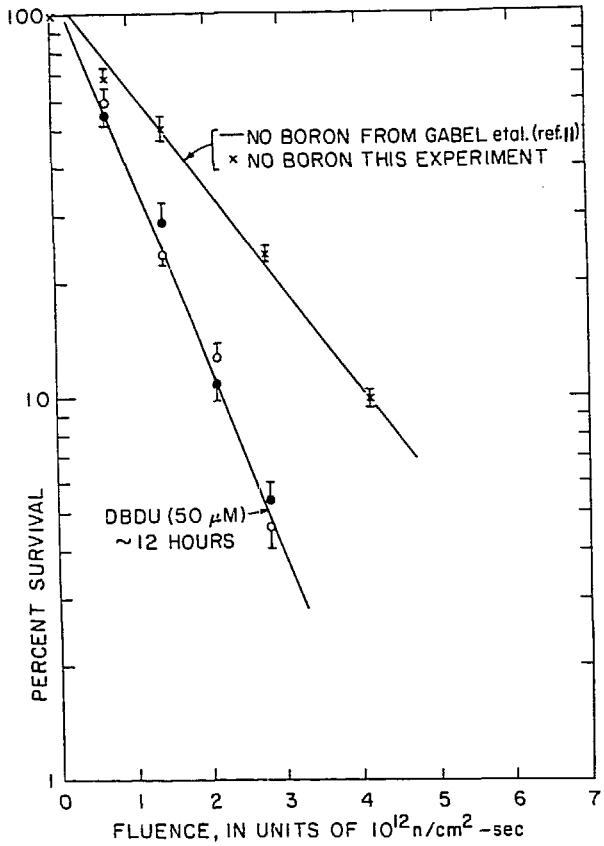

Figure 7

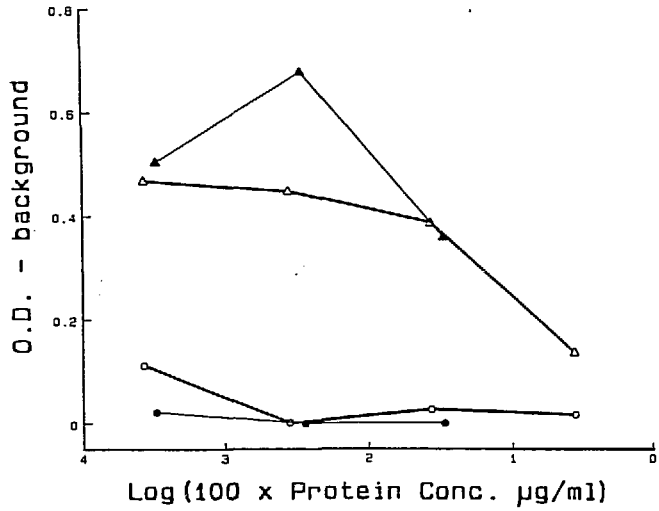

Fig. 8. Reactivity in the ELISA assay of MoAb 149.53 (filled symbols) and ^{10}B-dextran-MoAb 149.53 (open symbols) with melanoma cells, Colo-38 (triangles), and with ovarian carcinoma cells, SKOV-3 (circles). Ordinate is optical density from peroxidase-coupled antimouse antibody reaction with substrate minus background of cells incubated with mouse Ig.

3.6 Melanin-Affinic Agents (Chlorpromazine; Thiouracil)

The pigment melanin in melanotic melanoma provides a physiological handle that should be useful for NCT. 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 (1). Numerous efforts are underway to synthesize a boronated analog of these two molecules (11-13, 23); it is anticipated that this facet of NCT will eventually find clinical application.

3.7 Liposomes

The possibility of directing potentially cytotoxic agents via liposomes conjugated with MABs has been investigate with some indication of success (24). Preliminary studies have shown that boron can be incorporated in liposomes. Depending upon the liposome diameter, it should be possible to direct therapeutic amounts of boron to tumor while addressing only a few of the $\sim 10^6$ available antigen sites per cell (25). The use of heat-labile liposomes and hyperthermia might facilitate boron uptake.

3.8 Steroids

A number of groups have synthesized boronated steriods (11), but no data have yet 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 Section 4 below.)

A number of compounds discussed aboved appear to have promise as vehicles for boron transport. In particular, the dimer $Na_4B_{24}H_{22}S_2$ and the L-form of p-borono-phenylalanine have demonstrated useful tumor and normal tissue distributions in mice. These compounds should provide therapeutic gains significantly higher than those available with conventional radiotherapeutic 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: a stable isotope (^{10}B) is physiologically targeted to tumor, and then activated with an external neutron beam. The second component (the neutron beam) 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 epithermal neutrons. The latter will be employed in order to circumvent problems associated with the rapid attenuation of incident thermal neutrons. Dosimetric aspects of thermal and epithermal beams 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 effects of the various mixed field components. Results are summarized in terms of the minimum ^{10}B concentration required in Table 1 (21).

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 therapy (4,6,7,14)

Compound	Test system	Tumor (μg B/g)	Administration	Hours post start	Concentration Ratio T/Blood	T/Brain	T/Muscle
$Na_2B_{12}H_{11}SH$	Human	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	5-20	
p-borono-phenyl-alanine	Mouse*	15-30	i.p. (single dose)	6	5-10	∿5	∿5

*Harding-Passey tumor in BALB/c mice. †Average of a number of experiments.

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 in Japan) and the two most promising compounds described in Section 3 ($Na_4B_{24}H_{22}S_2$ and p-borono-L-phenylalanine). From these data it is clear that for the latter two compounds:

a) absolute concentrations of B are adequate for therapy, and
b) boron has been cleared from normal tissues, so that tumor/normal tissue ratios are ≥ 5.

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 (21). Thermal 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 irradiations. The therapeutic gain (TG) has been calculated for a Cd-filtered epithermal beam assuming a ^{10}B concentration in tumor of 35 μg/g and a tumor/normal tissue (^{10}B) ratio of 10. Results are given in Fig. 9; a TG of 2 is obtained at all depths ≥ 2 cm. Depth-dose distributions and RBEs, etc., used in obtaining the TG are described in Ref. 21.

Significant further gains should be accessible via development of essentially monoenergetic band-pass filtered beams, which transmit neutrons in the epithermal neutron energy region (∿0.5 to 10,000 eV) but restrict 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. 10; the depth-dose curves used in obtaining these data are shown in Fig. 11. As in

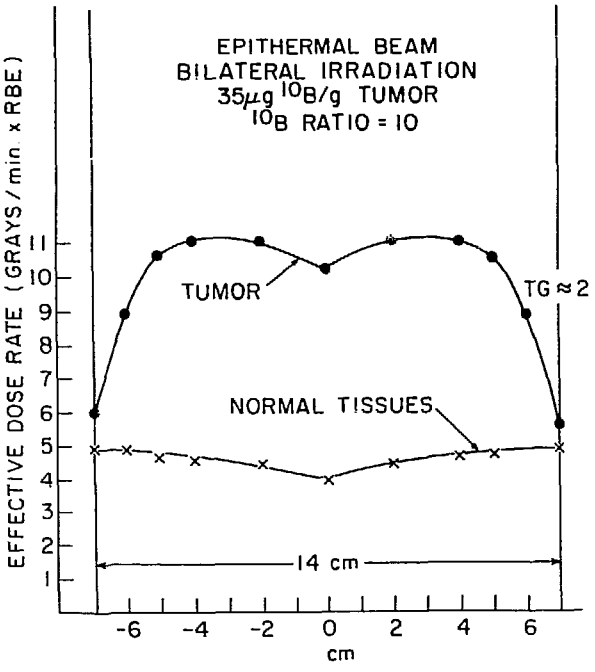

Figure 9

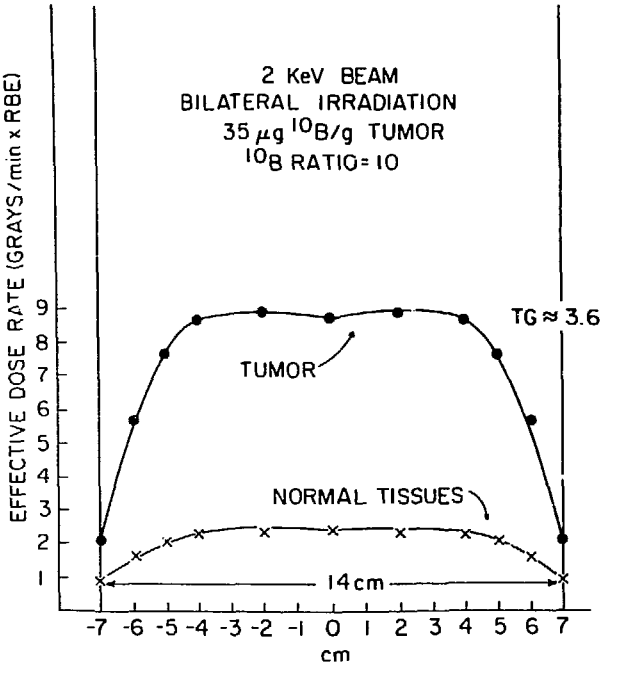

Figure 10

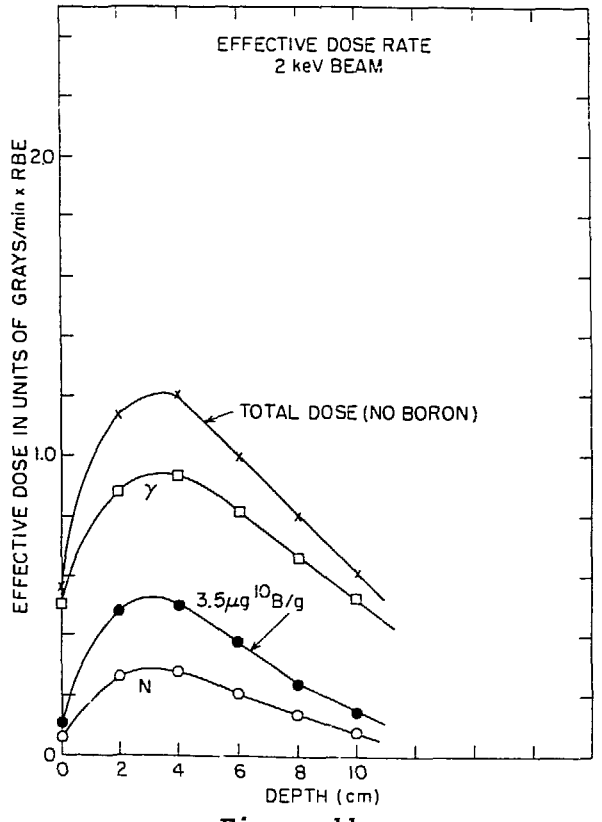

Figure 11

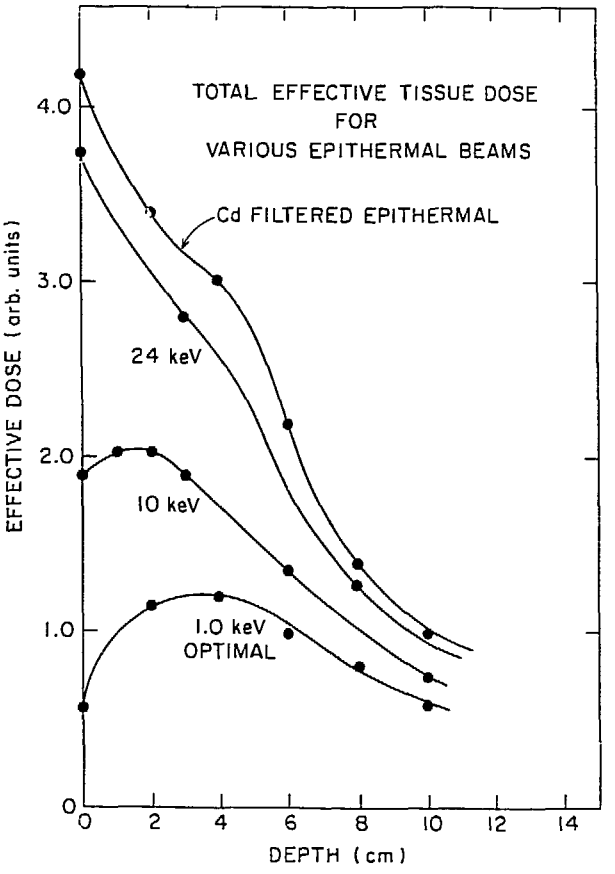

Figure 12

Fig. 9, dose distributions and RBEs are from Ref. 21. Because of the negligible dose from fast-neutron-produced H recoils, the TG approaches 4. The absence of high-LET contaminating radiations in 2-keV band-pass filtered beams also allows the possibility of reducing normal tissue damage from low-LET radiations through fractionation. The possibility then exists that the TG of ~4 would be doubled (see Ref. 21). At incident neutron energies of 1 to 2 keV there is no significant absorbed dose from fast neutrons relative to γ's and protons generated by the $H(n,\gamma)D$ and $^{14}N(n,p)^{14}C$ reactions. However, at 10 and 24 keV, H recoils become predominant. This is illustrated in Fig. 12, where effective dose (grays x RBE per min) is calculated, normalized to an incident flux density of 1.1×10^{10} n/cm^2-sec. It is seen that a 24-keV beam has a contaminating fast neutron dose similar to that of the Cd-filtered beam (assuming a one-to-one correspondance between incident epithermal neutron flux density and thermal neutron flux densities generated in tissue; see Section 5). While center-of-mass calculations suggest that epithermal neutrons might begin to lose their biological efficacy at ~6 keV, this is evidently not the case, as indicated by data from proton recoil spectroscopy as well as biological data from the 24-keV neutron beam at Harwell (31,32). Thus for an "optimal" epithermal neutron beam it would appear necessary to obtain a beam with an average effective energy <10 keV.

While pure band-pass filtered beams have been produced at low intensities (~10^6 n/cm^2-sec) (27), similarly pure beams of intensities sufficient for NCT (~5×10^8 n/cm^2-sec) have yet to be constructed (11). A number of efforts are now underway to provide such a beam at currently existing reactor facilities (11,13,28,29,31).

5 DOSE RATES FROM PASS-BAND FILTERED BEAMS

Dose distributions from band-pass filtered beams offer real advantages, but these 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 (Table 3) (28,30). From these data it seems reasonable to assume 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. 11; Ref. 21), it is then possible to obtain an estimate of possible irradiation time. The peak thermal neutron flux density producing the curves in Fig. 11 was 1.1×10^{10} n/cm^2-sec. Calculations show that the epithermal flux density expected from the MRR patient port using an iron filter (9 in. Fe, 6 in. Al, 3.75 in. S) and the full core as a source is 4.4×10^8 n/cm^2-sec at 3 MW (the highest power at which continuous operation is currently possible) (33,34). The dose rates in Fig. 11 would then have to be lowered by a factor of 25. This would produce effective dose rates in tumor of ~25 rads x RBE/min (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 ~25 (rads x RBE), would produce 2000 (rads x RBE) to tumor in 78 min, which

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.

would be adequate for therapy. Irradiation times for various other band-pass filters (Table 4) vary from 3 to 40 minutes. Suggestions for improved filters are given by Greenwood (34). It may well be that radiobiological and physiological considerations would argue for 2 to 5 separate fractions (35).

Table 4. Delivery time for an effective dose of 2000 rads x RBE to tumor at 4 cm depth, for various filtered beams; 3-MW Medical Research Reactor

Filter	Length (g/cm^2)	Φepi (n/cm^2-sec @ 3 MW)	Φth (n/cm^2-sec @ 3 MW)	Time for 2000 rads x RBE to tumor (min)
Fe	241	4.4×10^{8}	4.4×10^{8}	78
Al/S	105	1.3×10^{10}	1.3×10^{10}	2.7
"	157	3.4×10^{9}	3.4×10^{9}	10.5
"	210	8.8×10^{8}	8.8×10^{8}	40

6 SUMMARY

The development of new boronated compounds showing physiological binding to tumor allows clearance of boron from normal tissue, and thus it is hoped that the requirements for successful NCT have been met. Neutron capture radiographic techniques have been developed which allow measurement of the local distribution of boron within tumors. This distribution can be further evaluated by determining the biological efficacy of the possible NCT reaction in small animal models. Therapeutic gains should now be possible which significantly exceed those attainable with conventional radiotherapy. The availability of improved compounds should stimulate the development of band-pass filtered beams of sufficient purity and intensity to be employed for NCT.

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The Design of Filtered Epithermal Neutron Beams for BNCT*

R. C. Greenwood

Idaho National Engineering Laboratory
EG&G Idaho, Inc.
P.O. Box 1625
Idaho Falls, ID 83415

ABSTRACT

The design principles of filters (installed in nuclear reactors) to provide epithermal neutron beams suitable for use in ^{10}B Neutron Capture Therapy (BNCT) are reviewed. The goal of such filters is to provide epithermal neutron beams within an energy range of 1 keV to 30 keV with fluxes in excess of $5x10^8$ neutrons/cm^2.s, and having acceptably low contaminant fast neutron (>30 keV) and gamma components. Filters considered for this application include ^{238}U, Sc, Fe/Al and Al/S. It is shown that in order to achieve a goal epithermal neutron flux of $>5x10^8$ neutrons/cm^2.s, such filters must be located in radial beam channels which view essentially the complete reactor core. Based on considerations of estimated epithermal fluxes, cost and availability of materials, and transmitted neutron energy spectrum, it is suggested that a filter consisting of elements of Al, S, Ti and V might prove to be an optimum design for BNCT applications.

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1. INTRODUCTION

The greater penetrating power of epithermal neutrons through hydrogenous materials, as compared to thermal neutrons, makes their use in ^{10}B- Neutron Capture Therapy (BNCT) desirable. This increased penetrating power is evident from Fig. 1, where the thermal neutron flux distribution in a semi-infinite slab of H_2O is plotted for different incident neutron energies. For the three epithermal groups considered (1/E, 2 keV and 24 keV), the thermal neutron flux peaks at depths of 2.50, 2.75 and 3.25 cm, respectively, with thermal neutron flux enhancement factors (over the incident flux) of 3.5 to 3.2.

In BNCT it is desirable to maximize the thermal neutron dose to the ^{10}B-loaded tumor while keeping the dose of neutrons and gammas to healthy tissue and blood to a minimum. Based upon these dose considerations, and the penetration of neutrons into tissue, the neutron beam requirements for BNCT can be summarized as follows:

- 1 eV - 30 keV neutron energies
- a low neutron flux component with energies >30 keV (designated as high-energy neutrons in this paper)
- a moderately low gamma flux contamination
- a neutron flux Φ(1 eV-30 keV) $>5\times10^8$ neutrons/cm^2.s.

This last requirement is based upon an assumed therapeutic dose of thermal neutrons of 5×10^{12} neutrons/cm^2 and a desired irradiation time of less than 1 hour.

Without any spectrum tailoring, a beam of neutrons obtained from a fission reactor will contain neutron energies ranging from the thermal (0.025 eV) region, through the 1/E region, and up to the fission region (MeVs). The simplest method of achieving an epithermal neutron beam from a reactor is to impose a thin Cd absorber (σ_{th} = 2450 b) in the beam (e.g. see Ref. 1). While such a "filtered" neutron beam easily removes

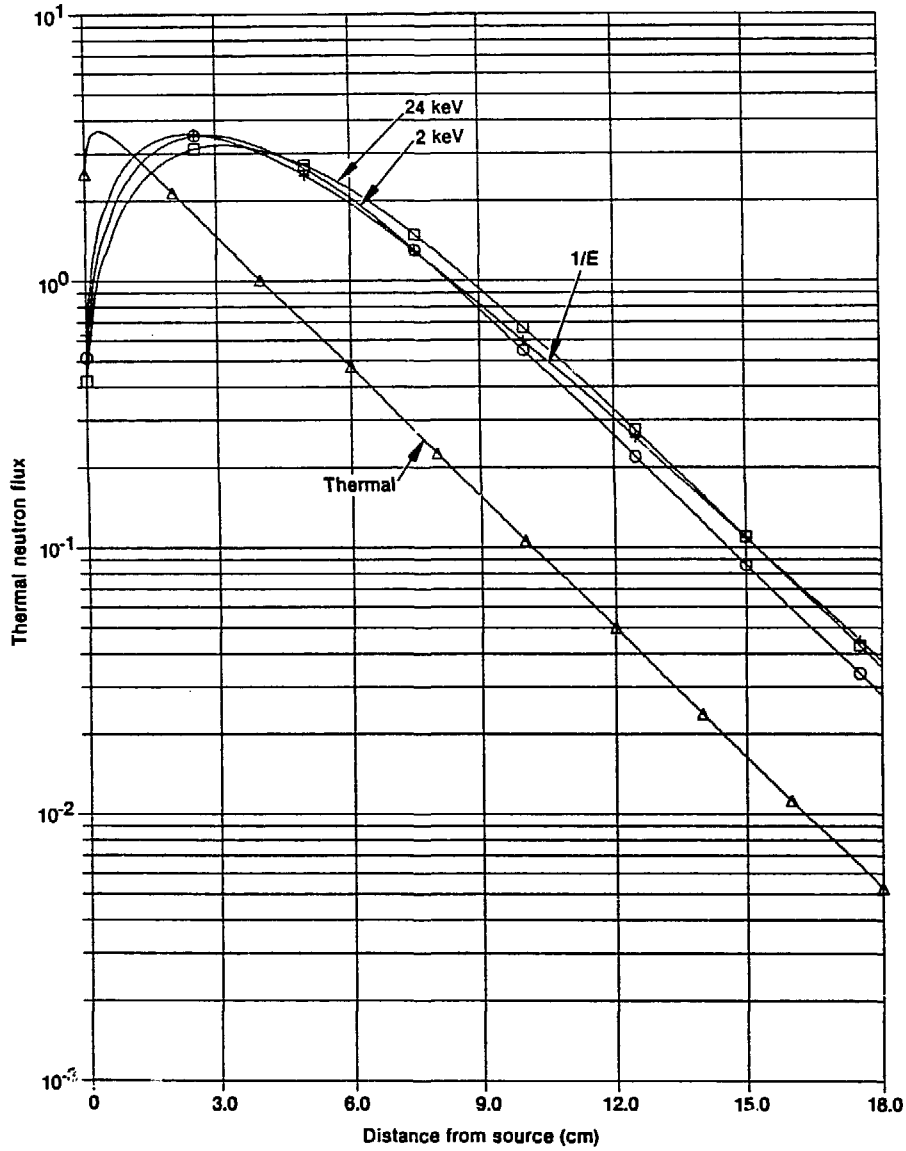

Figure 1. Thermal neutron flux distributions in a semi-infinite slab of water resulting from incident neutron beams having thermal, 1/E, 2-keV and 24-keV energies.

the thermal neutron component, and hence alleviates the problem of high skin dose, it does nothing to reduce the high-energy neutron and gamma fluxes in the beam.

With nuclear reactor sources one can obtain intense quasi-monoenergetic neutron beams, external to the biological shielding, using three separate methods:

1. Using a thick 1/v absorber (such as ^{10}B or ^{6}Li) to absorb the thermal and lower-energy neutron part of the 1/E reactor spectrum.[2]
2. Using a thin resonance scatterer close to the reactor core and located in a tangential (through) beam channel.[3]
3. Using thick filters of material having deep interference minima in the total neutron interaction cross sections.[4]

The use of a thick 1/v absorber can be a satisfactory method of achieving a quasi-monoenergetic beam with a median energy of a few keV, but unfortunately it shares with the Cd absorber an inability to reduce the high-energy neutron and gamma components of the beam. The use of thin resonance scatterers is a relatively untried technique, but its principal problem applied to BNCT would appear to be an inability to produce sufficiently high epithermal neutron beam fluxes (principally resulting from the requirement of a tangential beam channel).

The use of thick filters as a method of producing epithermal neutron beams suitable for BNCT applications would appear to hold more promise, and the balance of this paper will be devoted to this topic.

2. DEVELOPMENT OF NEUTRON FILTERS

The third method, noted above, is in principle very simple. It utilizes the fact that in many low-Z nuclei with widely spaced resonances,

interference effects can produce a dip in the cross-section curve which can approach 0.0 b below large scattering resonances. Hence, as illustrated in Fig. 2a, if we take a reactor spectrum of neutrons, put a thick filter of this material in a beam channel, such that all neutrons coming out through the beam channel must pass through the filter, we will get an external beam of neutrons which is principally composed of neutrons having energies E_d.

In practice, things get a little more complicated since an element of interest for use as such a filter may have other interference dips and it becomes necessary to filter out these unwanted components of the neutron beam by means of additional filtering materials which have neutron resonances at energies of the unwanted interferences dips. The added filtering materials should be selected so that they effectively remove the unwanted neutron energy components, as illustrated in Fig. 2b.

Using this principle, quasi-monoenergetic neutron beams with energies of 2 and 24 keV were obtained through thick Sc and Fe/Al filters, respectively; initially at the INEL[4] and subsequently at the High Flux Beam Reactor (HFBR) at BNL[5]. Specific details of the total neutron cross sections of these materials, showing the interference minima, are illustrated in Ref. 6. A typical example of the transmitted spectrum of neutrons through an Fe/Al filter is shown in Fig. 3. As can be seen from this figure, 24-keV neutrons are the predominant energy group transmitted, with the higher-energy neutron groups being much weaker.

In reviewing the development of filtered neutron beams and assessing their potential use in BNCT, it is important to remind ourselves that essentially all of the reactor filters in operation to date have been designed for nuclear physics applications. The requirements on such reactor filters (for nuclear physics applications) can be generalized as follows:

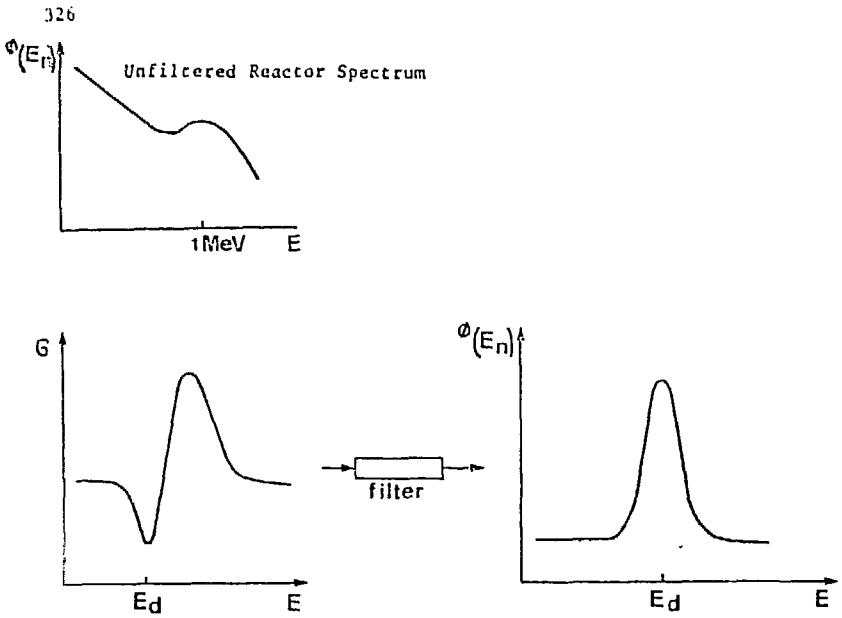

Figure 2a. Transmission of neutrons through a thick filter of a material having a deep inteference minimum in its neutron interaction cross section.

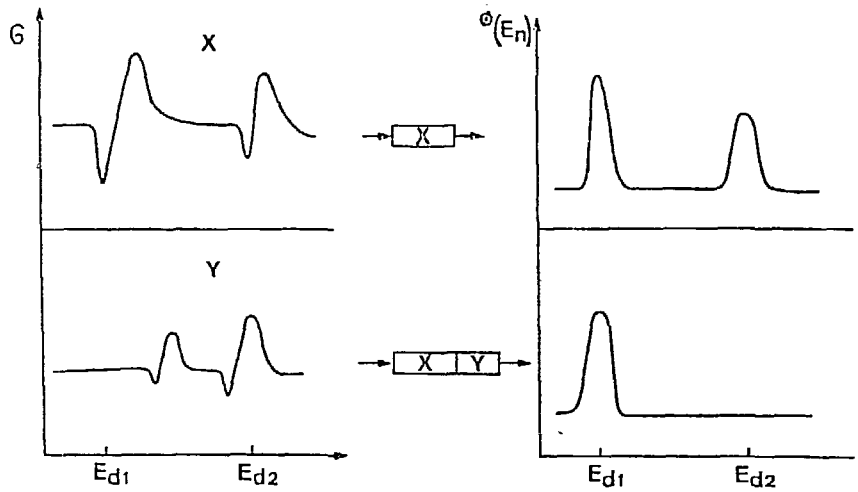

Figure 2b. Transmission of neutrons through a multicomponent filter, with the additional filtering elements being chosen to filter out contaminant neutrons transmitted through secondary minima in the neutron interaction cross section of the primary filtering material.

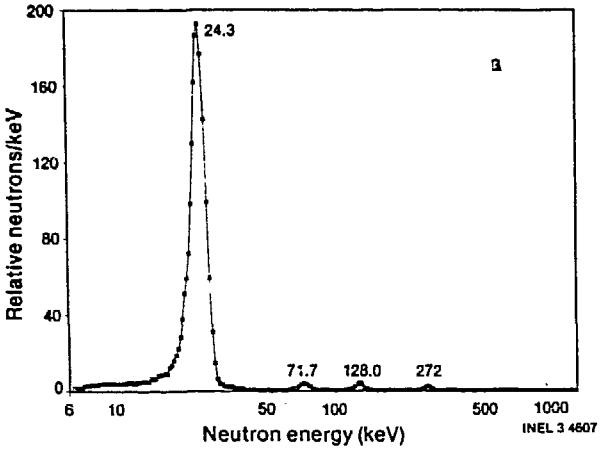

Figure 3. Neutron energy spectrum transmitted through an Fe/Al filter at HFBR.

- o A quasi-monoenergetic neutron beam with the contamination from other transmitted neutron groups minimized.
- o Moderately broad energy spread in the principal neutron group (10-50%).
- o Moderately high neutron flux (>10^6 neutrons/cm^2.s) in a well collimated beam.
- o Very low gamma and thermal neutron background.

Also, it has been found desirable, as discussed in Refs. 5 and 7, to have several different filters, providing neutrons over a wide range of energies. Filters which have been developed to date include[7]:

186 eV	-	^{238}U
2 keV	-	Sc
24 keV	-	Fe/Al
55 keV	-	Si/S
144 keV	-	Si/Ti
235 MeV	-	O

Only the first three of these filters have energies low enough to be considered for use in BNCT, and in fact it is the Sc and Fe/Al filters which have been predominantly used in nuclear physics applications. A detailed discussion of the design of Sc and Fe/Al filters, and their use in nuclear applications, is given in Refs. 5 and 7. It is of particular

interest to note in Fig. 2 of Ref. 5 the rather small neutron source (tip of the beam channel closest to the reactor core) viewed by the filter, together with the extensive post-collimation generally employed in nuclear physics applications. With this arrangement, as shown in Table 1, only moderate neutron intensities are obtained, even with a high flux research reactor such as HFBR. However, it is worth noting that the transmitted gamma fluxes in such an arrangement are also very low.

The neutron flux values given in Table 1, in fact, represent upper limits on neutron fluxes obtained from existing filtered neutron beam facilities worldwide (i.e., see Table VIII.I of Ref. 7). These flux values are then ~100-300 times less than are required for BNCT. (Also, these fluxes are generally obtained in neutron beams having cross-sectional areas of up to only a few cm^2.)

Table 1. Neutron and Gamma-Ray Fluxes Transmitted by the Fe/Al and Sc Filters Installed in the H-1B Channel of HFBR (40-MW Operation)

Filter arrangement	Average flux value for the principal neutron group transmitted ($n/cm^2.s$)		Background fluxes in the beam	
	Measured	Calculated	Thermal ($n/cm^2.sec$)	Gamma flux (mR/hr)
22.86-cm Fe +36.20-cm Al + 6.35-cm S[a]	1.28×10^6	1.6×10^6	~50	~40[c]
188.5 gm/cm^2 Sc[b]	6.54×10^6	9.0×10^6	~230	~340[c]

a. 98% of the filtered neutron beam intensity is at 24 keV

b. 70% of the filtered neutron beam intensity is at 2 keV

c. Extrapolating the neutron fluxes to 5×10^8 $n/cm^2.s$, the gamma fluxes are only ~16 R/hr and ~19 R/hr for the Fe/Al and Sc filters, respectively.

Recognizing that conventional neutron filters such as Fe/Al, Sc or ^{238}U, which rely on interference minima for transmission of selected neutron groups, may unduly restrict the transmitted neutron "window" by using too narrow a slice of the 1/E reactor spectrum, a somewhat different filter concept has been proposed for BNCT. This latter filter concept[8] relies on the fact that the total neutron cross sections of elements with mass number around 30 have lower values in the energy region below the lowest s-wave resonance (typically 10's of keV) than at higher energies. This is illustrated in the cross-section curves shown for Al, S and Ar in Ref. 6 and in Table 2. Thus a filter consisting of Al and S, for example,

Table 2. Average Neutron Cross Sections for Al and S

Element	σ(<10 keV)	σ(10-30 keV)	σ(>30keV)	$\frac{\sigma(<10keV)}{\sigma(>30keV)}$
Al	1.35	1.0	3.5	2.6
S	1.1	0.85	2.2	2.0

will transmit a broad neutron energy band ranging in energy from ~few eV to 30 keV. The estimated transmission spectrum of such a filter is illustrated in Refs. 9 and 10. An epithermal neutron beam using a Al/S filter has been constructed and tested in a tangential through beam channel at the Georgia Tech Research Reactor (GTRR)[9,10]. Using a thick graphite scatterer at the center of the beam channel and a filter consisting of 21.6 cm Al + 25.4 cm S (total thickness ~105 g/cm^2), the transmitted epithermal flux was measured to be ~6.9 x 10^7 neutrons/cm^2.s. While the ratio Φ(>30keV)/Φ(<30keV) was only~4%, the gamma contamination in the beam was ~4 R/min. This high level of transmitted gamma can be attributed to the thinness of the filter which was used. In order to achieve adequate gamma-ray attenuation in the filter, it is generally acknowledged that a minimum filter thickness of ~200 g/cm^2 is needed.

3. FILTER DESIGN FOR BNCT

As we have seen in the previous section, currently operating filters fall short of the goal flux level of ~5 x 10^8 neutrons/cm^2.s by at least an order of magnitude. In order to develop an optimum filter arrangement for BNCT it is useful to review the principles of filter design. The transmitted flux of neutrons through a filter is expressed quite simply as:

$$\phi = \frac{A_s}{4\pi R^2} \sum_i T_i \frac{\Delta E_i}{E_i} \phi_i(u) \qquad (1)$$

where

T_i is the neutron transmission of the filter in the energy region of interest (window),

A_s is the neutron source area viewed directly through the beam channel from the treatment location (external to the biological shielding of the reactor),

R is the distance from the neutron source to the treatment location,

E_i is the energy of a neutron "window" in the filter (e.g., energy of an interference minimum),

ΔE_i is the width of the neutron window (approximately the FWHM), and

$\phi_i(u)$ is the source neutron flux in the 1/E region (in lethargy units).

In maximizing Φ, the filter design is bound by the following constraints:

- the filter must be thick enough to attenuate the other unwanted neutron groups (especially those with energies >30 keV) to a sufficiently low level
- the filter must be thick enough to attenuate the reactor-produced gamma flux to a sufficiently low level.

That we must depend primarily on the filter for such gamma attenation is illustrated in Table 3. From this table we can surmise that, because

Table 3. Comparison of Gamma and Neutron Attenuation of Materials

Gamma energy (keV)	$\mu(cm^2/g)$			
	Al	Fe	Pb	Bi
500	0.084	0.084	0.159	0.163
1000	0.061	0.060	0.070	0.071
3000	0.035	0.035	0.042	0.042
6000	0.027	0.031	0.044	0.044
1/E neutrons			0.032 (<110 keV)	0.026
			0.020 (<110 keV)	

of the similarities of their attenuation coefficients for hard gamma rays (MeVs) and neutrons, Pb and Bi are not generally effective as post-filter attenuators for gamma rays (i.e., hard gammas and neutrons will be scattered by Pb or Bi attenuators at comparable rates).

In order to achieve a maximum flux of the desired energy neutrons transmitted through a filter, it is useful to examine each of the terms in Eq. 1 and compare their values, and constraints on their values, for different candidate filter materials.

$\phi_j(u)$. For a particular reactor design, it is clear that $\phi_j(u)$ is simply proportional to the reactor power level. Also, in comparing different reactor configurations it would appear that with well designed beam channels, which obtain their source neutron flux, $\phi_j(u)$, close to the reactor core, the normalized values of $\phi_j(u)$ (in flux per

MW power level) for compact research reactors are all quite similar, within factors of 2 or 3. Thus for example, typical values of $\phi_i(u)$ per MW (at 24 keV) are 7.5 x 10^{11}, 7.7 x 10^{11}, ~7.6 x 10^{11} and 3.6 x 10^{11} for HFBR[5], GTRR[10], BMRR (derived from 1/E fluxes given in Ref. 1) and PBF[11], respectively. Thus, it is clear that the only significant gain to be obtained in the $\phi_i(u)$ term is by going to higher reactor operating power.

$(\Delta E_i/E_i)$. Values of this term, which represents the width of the neutron "window" in a particular filter in lethargy units, are given in Table 4 for several filter designs of interest to BNCT. Inspection of Table 4 clearly indicates that in respect to this term, the Al/S filter design is superior (by factors of >20) to those filters which depend on interference minima to transmit selected neutron energy groups.

Table 4. Comparison of Neutron "Window" Widths for Selected Filters

Filter type	E_i(keV)	$\Delta E_i/E_i$
^{238}U	0.186	0.008
Sc	2	0.4
Fe/Al	24	0.09
Al/S	0.01-10	6.9 } 8.0
	10-30	1.1 }

T_i. To a reasonable approximation, the transmission through neutron "windows" in a filter with "small" cross-sectional dimensions (such that every scattered neutron escapes from the filter and can be considered as "absorbed") can be calculated using

$$T_i = \exp(-0.6 t_i \Sigma_i) \qquad (2)$$

where t_i is the thickness of a filter element in g/cm^2 and Σ_i is the average value of the total neutron macroscopic cross section [i.e., σ_i(barns)/mass number]. Values of these macroscopic cross sections for different filter materials are given in Table 5. As we have noted previously, it is necessary for the filter to provide sufficient

Table 5. Comparison of Macroscopic Cross Sections (Σ_i) for Selected Filters

Filter Type	Elements	E_i(keV)	Σ_i
^{238}U	^{238}U	0.186	0.01
Sc	Sc	2	0.016
Fe/Al	Fe	24	0.0075
	Al		0.022
Al/S	Al	0.01-10	0.050
	S		0.034
	Al	10-30	0.037
	S		0.026

attenuation of the reactor-produced gamma flux, and this is generally achieved using filters which are ~200 g/cm^2 thick. Transmission factors computed, using Eq. 2, for different filters, with nominal thicknesses of ~205 g/cm^2, are shown in Table 6. As can be seen from this table, with a filter which is approximately twice as thick as that used at GTRR[10] the transmission of epithermal neutrons is significantly lower than that of those filters which use interference minima.

Solid-Angle Term. It is obvious from Eq. 1 that in order to maximize ϕ, R should be as small and A_s as large as possible. The term R, the distance between the source neutron flux (at the core-end of the beam channel) and the patient treatment location, is fixed by the dimensions

Table 8.: Comparison of Transmission Factors (T_i) for Selected Filters

Filter (component thicknesses g/cm^2)	E_i(keV)	t(g/cm^2)	T_i
^{235}U(205)[a]	0.186	205	0.29[a]
Sc(188.5)/Al(17.2)[b]	2	205.7	0.10
Fe(159.8)/Al(48.0)/S(19.7)	24	207.5	0.22
Al(70)/S(136)[c]	0.10-10 10-30	205	0.0076 0.0247

a. Recommended[7] supplementary filter components of Se, Mn and Ge to attenuate a cleaner 186-keV neutron beam, have not been included.

b. Addition of the Al to this filter improves the beam purity for BNCT, with 90% of the beam flux having energies <30 keV.[5]

c. A S-to-Al thickness ratio of approximately 2-to-1 was selected in this thicker filter (which is approximately twice as thick as the GTRR filter) in order to maximize transmission. Even so, the Al component of the filter is still 30% thicker than used at GTRR.

of the reactor biological shielding, and can generally only be changed with some difficulty. As can be seen from Table 7, following, there is approximately a factor of 3 difference in R between the four reactors considered (i.e., a factor of up to 9 in solid angle, which, for example, somewhat offsets the power differential between HFBR and BMRR). The term A_s, the area of source neutron flux (at the core-end of the beam channel) is fixed by the cross-sectional dimensions of the beam channel, and changing this parameter becomes a major reactor modification.

Nevertheless, it is this parameter A_s which provides the greatest opportunity for achieving or exceeding the goal epithermal neutron flux of 5×10^8 neutrons/cm^2.s. The maximum epithermal neutron flux delivered to a patient can clearly be obtained by using a beam channel which views the complete cross-sectional area of the core. Existing beam channels which are tangential to the reactor core generally have source neutron flux areas which are simply too small to achieve a goal neutron flux at a patient. Futhermore, increasing the cross-sectional dimensions of a tangential beam channel will generally have the effect of decreasing the source flux $\phi(u)$ correspondingly.

4. FILTER COMPARISONS

In Table 7, epithermal neutron fluxes at a patient location are computed for the four filter designs discussed in the last section (^{238}U, Sc, Fe/Al and Al/S). In order to provide a quantitative comparison, relative to a goal epithermal neutron flux of $>5 \times 10^8$ neutrons/cm^2.s, computations have been made in Table 7 for four different reactors. For the first two reactors listed, HFBR and GTRR, existing tangetial beam channels were considered for filter location[5,10]. (In the case of HFBR however, these data are in fact representative of <u>all</u> of the existing beam channels.) For the final two reactors listed, BMRR and PBF, radial beam channels which each view the entire cross-sectional area of the core were considered. The existing patient treatment port at BMRR is such a beam channel, while for PBF a proposed modification to that reactor to incorporate a beam channel specifically for BNCT is considered.[11]

A number of spcific observations that can be made, based upon the data presented in Table 7, are as follows:

Table 7. Comparison of Selected Filter Designs for BNCT

Parameters	HFBR[a]	GTRR[a]	BMRR[a,c]	PBF[b,c]
Reactor Power	60 MW	5 MW	3 MW	28 MW
$\Phi(u)$	4.5×10^{13}	3.8×10^{12}	2.3×10^{12}	1.0×10^{13}
A_s	(62 cm^2)[e]	177 cm^2	3700 cm^2	11000 cm^2
R[d]	387 cm	356 cm	169 cm	263 cm
$\phi(u)A_s/4\pi R^2$	1.48×10^9	4.2×10^8	2.4×10^{10}	1.27×10^{11}
^{238}U(205 g/cm^2) Filter				
ϕ	3.4×10^6	9.8×10^5	5.5×10^7	2.9×10^8
Sc(188.5)/Al(17.2) Filter				
ϕ	5.9×10^7	1.7×10^7	9.5×10^8	5.1×10^9
Fe(139.8)/Al(48.0)/S(19.7) Filter				
ϕ	2.9×10^7	8.4×10^6	4.7×10^8	2.5×10^9
Al(70/S(135) Filter				
ϕ[f]	1.2×10^8	3.4×10^7	1.9×10^9	1.0×10^{10}

a. Parameters for existing beam channels at the High Flux Beam Reactor (HFBR)[5] and the Medical Research Reactor (BMRR)[1] at Brookhaven National Laboratory, and the Georgia Tech Research Reactor (GTRR).[10]
b. Parameters for a proposed beam channel at the Power Burst Facility (PBF) at the Idaho National Engineering Laboratory.
c. The cross-sectional area of these filters can no longer be considered as "small", and hence multiple scattering will occur in the filter. The quoted fluxes are computed for unscattered neutrons. The actual transmitted neutron fluxes may however contain contributions from such multiple scattering in the filter and may thus be higher, depending upon the geometry of the post-filter collimation.
d. These source-to-patient distances assume a patient location of 50 cm in front of the reactor biological shielding.
e. This is the cross-sectional area of the HFBR beam channels at the core end. In order to utilize the full source area, an existing plug collimator would have to be removed from the beam channel.
f. It is estimated that 64% of this flux is in the region 10 eV-10 keV, with the remaining 36% being in the region 10 keV-30 keV.

- A goal epithermal flux of >5 x 10^8 n/cm^2.s cannot be reached with any of the filters considered using a conventional tangential beam channel, as illustrated by the HFBR and GTRR examples.

- Although HFBR is one of the four highest-flux research and test reactors in the world, the small cross-sectional diameter of its beam channels at the core-end severely reduce the filtered epithermal neutron beam fluxes (to values of <1 x 10^8 neutrons/cm^2.s).

- Reactors of rather modest power level with radial beam channels viewing the entire core area (e.g., BMRR at 3MW) can be utilized to achieve filtered epithermal neutron beam fluxes of 5 x 10^8 neutrons/cm^2.s.

- The narrowness of the 186-eV interference minima in ^{238}U severely attenuates the transmitted neutron intensities, to the point that none of the four reactor configurations achieve a flux of 5 x 10^8 neutrons/cm^2.s. It is worth noting, however, that Brugger[12] has suggested that since higher-energy "windows" in ^{238}U appear to extend in energy to only a few keV,[6] a ^{238}U filter without secondary filtering materials (used to limit transmission to the 186-eV window) might pass as much as ten times more epithermal flux with energies below 30 keV. This suggestion clearly must be checked out experimentally since the neutron transmission data in Ref. 6 on ^{238}U appear not to have sufficient resolution to locate interference minima above 4 keV. Nevertheless, if a factor of 10 improvement was realized with such a ^{238}U filter arrangement, we note that fluxes of >5 x 10^8 neutron/cm^2.s would be possible at both BMRR and PBF.

- The Fe/Al and Al/S filters, which are constructed from inexpensive and readily available materials, would appear to be capable of achieving epithermal neutron fluxes of >5 x 10^8 neutrons/cm^2.s in BMRR and PBF. While one would like to suggest that they therefore be considered the filters of choice for BNCT, a question has been raised as to whether neutrons above a few keV produce too much damage to be useful for BNCT[13].

- While the Sc filter has a desirable transmitted energy (2 keV) and would appear to quite easily achieve epithermal neutron fluxes of >5 x10^8 neutrons/cm^2.s in a radial beam channel viewing the complete core (BMRR and PBF), the quantity of Sc necessary for such a filter arrangement would make its cost prohibitively expensive. Thus, we must regretfully rule out the use of a Sc filter for BNCT.

If neutrons with energies above a few keV indeed produce too much damage to be useful for BNCT, this would tend to rule out the use of both Fe/Al and Al/S filters for this application. While the suggestion of Brugger[12] to use ^{238}U without secondary filtering materials might provide a suitable epithermal neutron flux distribution, its use must still be considered speculative without experimental confirmation. An alternate approach is to further tailor the neutron flux distribution transmitted by an Al/S filter to remove the neutron component between a few keV and 30 keV. This can be accomplished rather straightforwardly using additional filtering components of Ti and V. In parallel with Table 7, transmitted fluxes are estimated in Table 8 for such an Al/S/Ti/V filter at BMRR and PBF. From the data shown in Table 8 it is clear that an Al/S/Ti/V filter can achieve the goal epithermal neutron flux, while providing a transmitted epithermal neutron distribution which is suitable for BNCT.

Table 8. An Al/S/Ti/V Filter for BNCT

Filter (component thickness g/cm^2)	$t(g/cm^2)$	E_i(keV)	ϕ	
			BMRR	PBF
Al(70)/S(120)/Ti(10)/V(5)	205	0.01-3	6.0×10^8	3.2×10^9

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13. Comments at this Workshop.

A Plan for Neutron Capture Therapy Studies with a 2.5-MeV Proton Beam on ^{7}Li

J.W. Blue, W.K. Roberts, J.W. Bay, and S. Chou
Cleveland Clinic, Cleveland, OH 44106
and
T.E. Blue and R. Gahbauer
Ohio State University, Columbus, OH 43210

This paper is intended to bring you up to date on the progress towards an evaluation of the $^{7}Li(p,n)^{7}Be$ reaction as a source of low energy neutrons for NCT. We presented this idea at the recent meeting in Japan, and it was also presented at the same meeting, independently, by Dr. Brownwell.

Calculations indicate that a proton beam of 2.5 MeV and a current of 20 mA will produce an adequate neutron fluence for BNCT in a treatment time of 10 to 20 minutes. The radio-frequency quadrupole accelerator (RFQ) appears to be the best choice for meeting the beam current specifications in steady-state operation. As far as I know an RFQ with these beam specifications has not been built. Present emphasis on RFQ development is for acceleration of heavy ions or for hydrogen ions in a pulsed mode at much higher beam current. I have been advised by people working in this field that a steady current of 20 mA is feasible and that the cost of the accelerator would be about $2.5 million. Assuming these estimates to be correct, NCT would be possible in the setting of a major medical center. The alternative source of neutrons for NCT, a nuclear reactor, would have many problems if siting were in or near a hospital.

Several years ago Lone et al. (1) proposed an RFQ they called CANUTRON to generate low energy neutrons. The tasks proposed for CANUTRON were typical reactor applications, i.e., neutron activation analysis, neutron diffraction, etc. This idea was not adopted because these tasks could all be done at existing reactors. For NCT the situation is quite different if the ground rule is adopted that the treatments be at a hospital complex. The RFQ would be much less expensive to put in a hospital than a reactor that would be adequate for NCT. If NCT provides the impetus to put an RFQ accelerator in a hospital, the availability of thermal fluxes of 10^{11} or more will generate some of the applications that Lone suggested. In other words, the availability of thermal neutrons in a hospital setting is likely to generate medical applications that are not now contemplated.

A preliminary step to acquisition of an RFQ for NCT is the demonstration of the soundness of the proposal. We plan to do this using an available proton accelerator which the NASA Lewis Research Center in Cleveland is considering decommissioning. This accelerator (Dynamitron*) has a steady-state current about a factor of ten below that of the RFQ. However, the neutron output scales with the proton beam current and the Dynamitron should provide an excellent basis for prediction of the RFQ performance in this application of NCT. Specific tasks will be the following:

1) Study some of the engineering problems of designing a lithium-7 target which must dissipate 50 kW of continuous beam power in the NCT application.

*Radiation Dynamics Inc. Melville, NY 11746.

2) Study the neutronics of a specific target design, one in which the amount of moderator can be selected, thereby allowing selection of the average energy of the neutron reaching the patient.

3) Conduct physics experiments to determine the effect of close coupling of hydrogenous moderator (the patient) and the neutron target assembly with regard to the neutron depth-dose and the boron capture depth-dose.

4) Study in vitro cell survival without boron, with boron-11, and with boron-10.

5) Conduct animal experiments; this work involves collaboration with the Ohio State University School of Medicine.

6) Drs. Bay and Chou at the Cleveland Clinic plan to carry out tumor and blood distribution studies of the boron cage sulfhydryl compound in patients with glioblastoma multiforme.

We plan a preliminary step to the operation of the Dynamitron which is to construct a prototype of the Dynamitron target and to run this on the OSU Van de Graaff with 2.5-MeV protons and beam currents at the microampere level. These physical measurements will be compared with concomitant Monte Carlo calculations. Dr. Thomas Blue at OSU will have the responsibility for these measurements.

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APPENDIX

A Study of Low Energy Proton Accelerators for Neutron Capture Therapy*

J.W. Blue and W.K. Roberts (Cleveland Clinic Foundation)
T.E. Blue and R.A. Gahbauer (Ohio State University)
J.S. Vincent (University of British Columbia)

After the First International Conference on Neutron Capture Therapy, serious consideration was given to acquiring an appropriate source of neutrons for BNCT studies. The Cleveland Clinic Foundation was at that time, and still is, engaged in a clinical trial of fast neutron therapy using the NASA (National Aeronautics and Space Administration) Lewis Research Center cyclotron to generate neutrons. For BNCT, of course, a more copious source of lower energy neutrons is required. A test reactor which had operated at 60 MW had been placed in standby condition by the Lewis Research Center in 1972. The suitability of this facility was investigated.

The core design is shown in Figure 1. It is seen to be well suited to BNCT because of the large (229-mm) pipe passing through a large amount of beryllium reflector. Scattering material placed in the tube, in the central region, would scatter neutrons that had been moderated by the beryllium so that they would exit both ends of the pipe. The intensity would be adequate to allow filtering of thermal and fast neutrons and of gamma radiation, with sufficient intensity remaining for BNCT. However, the idea of using the reactor was abandoned after consulting the regulatory agency that has jurisdiction over it. The present policy of this agency will not permit the use of fully enriched uranium, for which the reactor was designed, and when 20% enriched fuel is substituted the reactor becomes a "new" design with large and uncertain costs in recommissioning.

In the search for another neutron source, we have investigated the possibility of a proton accelerator, wherein the protons cause nuclear reactions in which neutrons are emitted. At the First BNCT Symposium, this approach was discussed (1) for source reactions in which the neutrons arising from the nuclear reactions are far above the energy required for BNCT. With such high energies the patient must be far removed from the target area; these fast neutrons are very penetrating and require a considerable amount of moderator; also, there is penetrating gamma radiation.

Another approach is to generate much lower energy neutrons, so that only small amounts of moderator are required, and to use reactions in which very little gamma radiation is generated so the patient could be placed in close proximity to the neutron source. The investigation described in this paper has as its goal the design of a low energy proton facility as a source of neutrons for BNCT. In order to generate low energy neutrons and no fast neutrons, it is necessary that low energy protons be used and, since low energy protons have short range, that a reaction with a large cross section be used. One reaction seems to be outstanding for this application, and that is the $^{7}Li(p,n)^{7}Be$ reaction at a proton bombarding energy of 2.5 MeV. This reaction has been used by nuclear physicists for

*Proc. Second Int. Conf. on Neutron Capture Therapy. Tokyo, Oct. 1985.

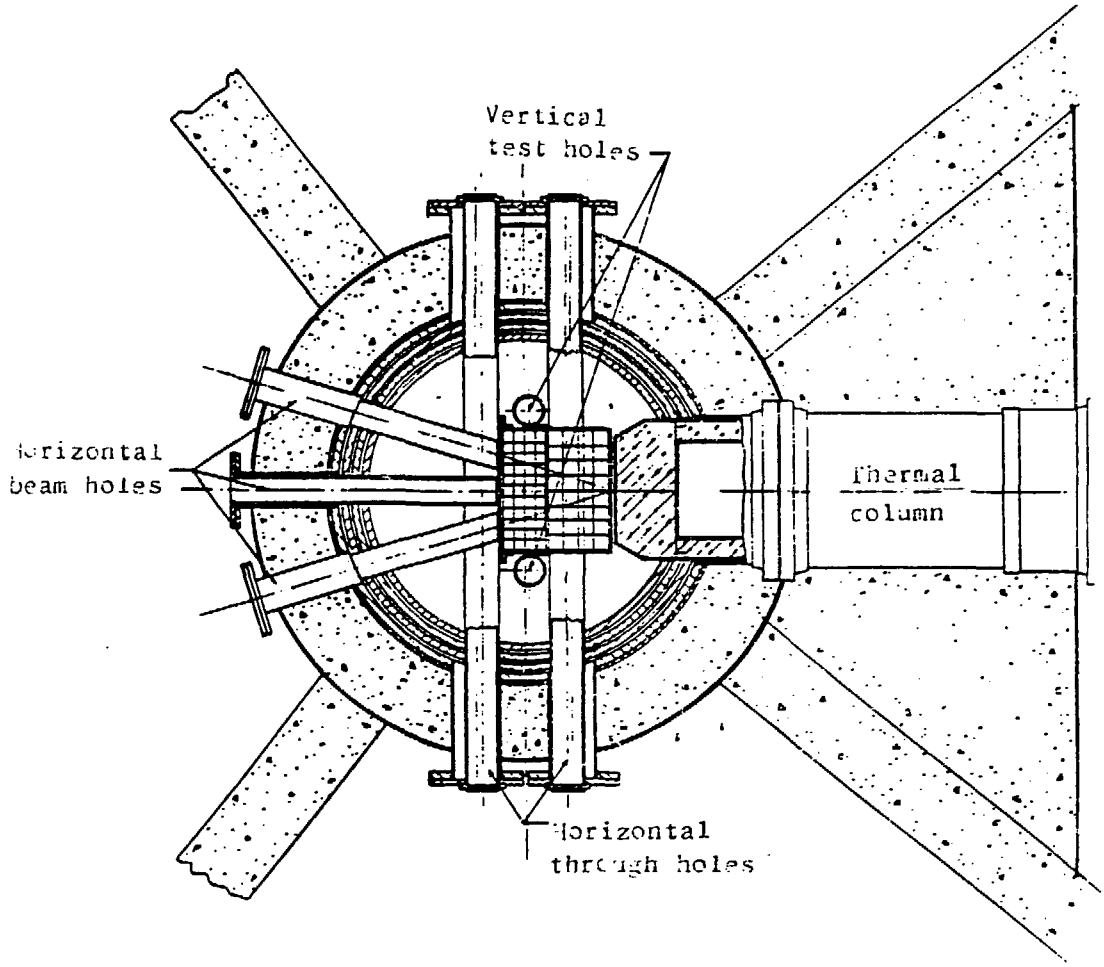

Fig. 1. Horizontal section of NASA Lewis Research Center 60-MW test reactor.

nearly 50 years, most often as a source of monoenergetic neutrons. The production cross section is well known (2) and has the features of a sharp threshold at 1.88 MeV, a large resonance peaked at 2.2 MeV, and neutrons preferentially emitted in the forward direction.

By limiting the bombarding protons to 2.5 MeV, the neutrons are emitted with energies less than 800 keV, yet full advantage is taken of encompassing the large resonance peak in the cross section. Gamma radiation arising from proton reactions comes from $^{7}Li(p,p')^{7}Li^{*}$ and from $^{7}Li(p,n)^{7}Be^{*}$, when $^{7}Li^{*}$ decays with emission of a 478-keV photon and a lifetime of 1.15×10^{-13} sec and $^{7}Be^{*}$ decays with emission of a 430-keV photon and a similar lifetime. ^{7}Be is also radioactive and emits a 478-keV gamma with a half-life of 53 d. There is also a low probability of proton capture, i.e., $^{7}Li(p,\gamma)^{8}Be$ with emission of 16- and 19-MeV radiations.

The forward directedness of the neutrons can be appreciated in Figure 2, which shows the relative yield of neutrons emitted into a forward cone with an angle of 100°, a second grouping of the remaining neutrons in the forward hemisphere from 50° to 90°, and a third grouping of all the neutrons emitted into the backward hemisphere, which amounts to only 18% of the

total. The differential energy spectra of the two forward-directed groups are shown in Figure 3 for the case of 2.5-MeV protons incident upon a thick ^{7}Li target. These spectra show the most forward-directed neutrons to range between 100 and 800 keV, with an average energy of 430 keV, and the 50° to 90° group to range from 25 to 625 keV, with an average energy of 240 keV. Consequently, to reduce the energies of the neutrons to values that are most effective for BNCT, only a relatively small amount of heavy water is required.

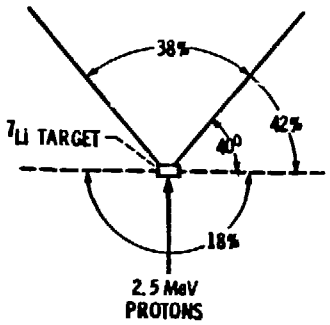

Fig. 2. Angular distribution of neutron yield from $^{7}Li(p,n)$.

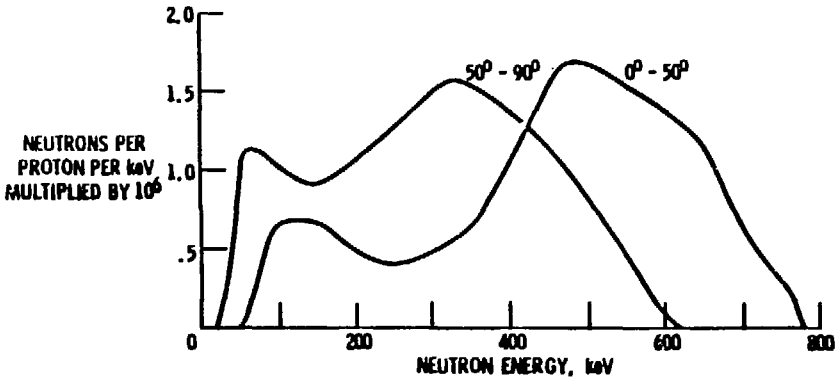

Fig. 3. Differential energy spectra from 2.5-Mev protons on thick ^{7}Li.

The energy range of the forward-directed neutrons is rather narrow in terms of the average logarithmic decrement, and, in addition, the average energy of the neutrons need only be reduced by a factor of 10 to be about an optimum. This is quite a different situation from that when a reactor is used, in which case fission neutron energies cover a wide range and a considerable amount of moderator is required to eliminate the most energetic neutrons. Then, the resultant energy spectrum is so wide that many of the neutrons are below the energy best suited for BNCT.

Brenner and Zaider (3) recently described a proposed facility for radiobiology studies at Columbia University, using a Van de Graaff accelerator to generate 2.4-MeV protons with which to bombard a thick, natural lithium target. Their plan is to use this machine, which can operate at beam currents as high as 100 to 150 μA, to study fundamental problems of biological interactions of neutrons in the few-keV energy range. Figure 4 shows the arrangement of the lithium target, located in the center of a right circular tank of 0.5-m diameter with reentrant tubes into which the biological samples are inserted. For this arrangement, using a 100-μA beam, they reported Monte Carlo calculations that predict dose rates of 1.7 and 1.0 Gy/h, respectively, at two angles, 90° and 135°, at a distance 90 mm from the lithium target.

For BNCT, neutron yields at least a factor of ten larger than generally achievable with the Van de Graaff are required. The Lewis Research Center has an accelerator called a Dynamitron (4) which is fed with radio-frequency power that is rectified and used to maintain an acceleration potential across a 3.2-m beam tube. The accelerator is shown in Figure 5 with a lithium-7 target assembly closely coupled to the patient.

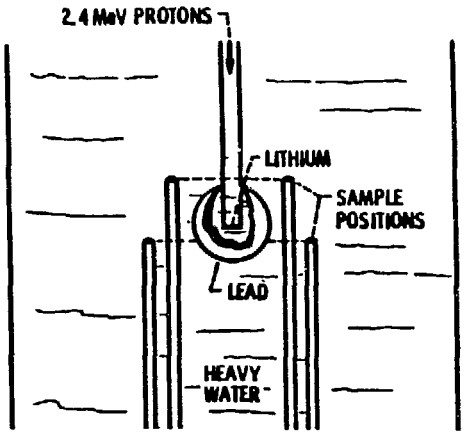

Fig. 4. Schematic of Columbia University radiobiology facility.

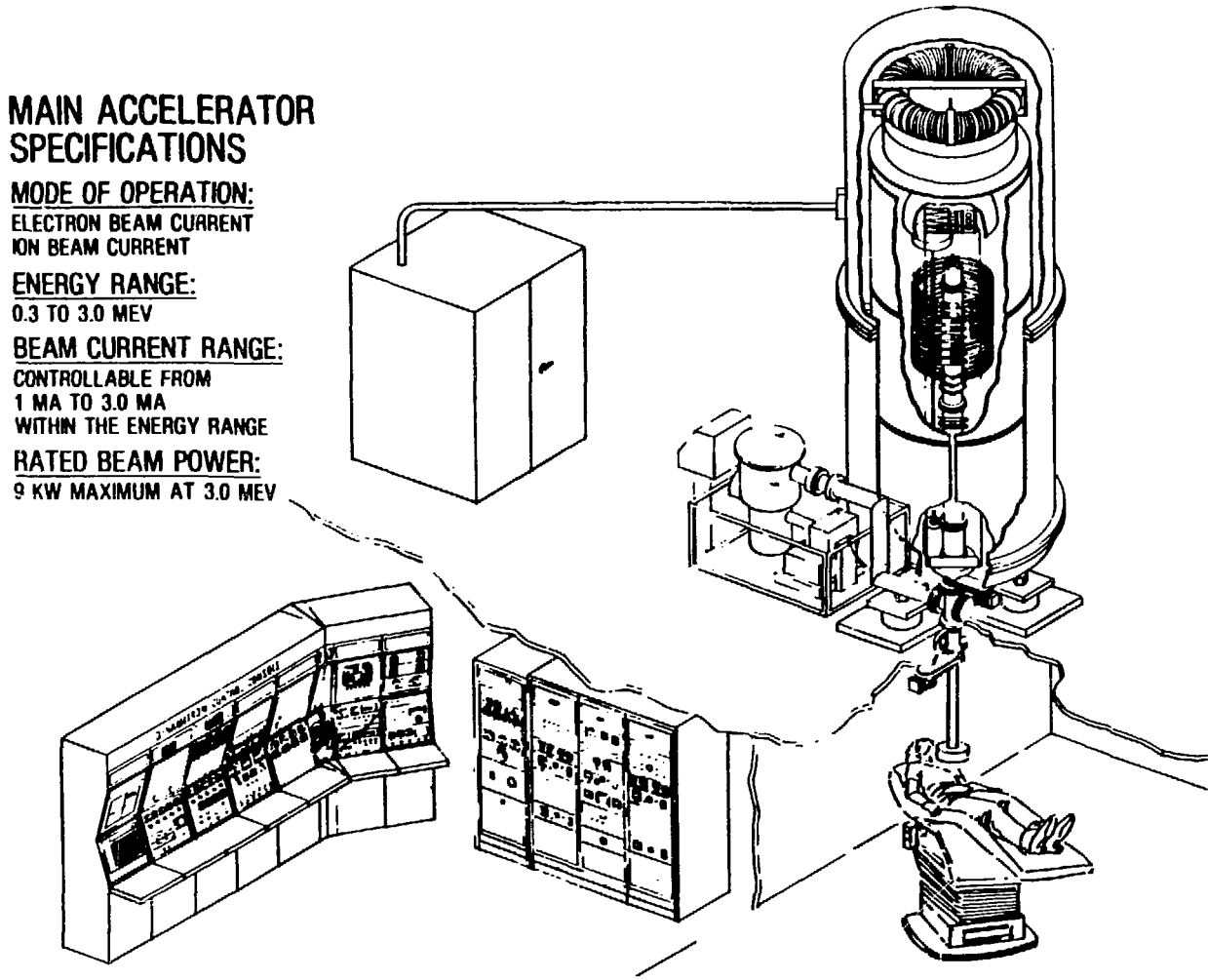

Fig. 5. Diagram of 3.0-MeV Dynamitron linear accelerator.

The details of this target design are shown in Figure 6. The materials selection has been made to make the gamma-ray dose as low as possible. The forward-directed neutrons are moderated by D_2O, and control of the average energy of the neutrons emerging from the Teflon window is achieved by adjusting the level of the D_2O. It is anticipated that when treating deep-seated tumors, more energetic neutrons will be required than for superficial tumors. The forward-directed neutrons (0° to 50°) are the most energetic and require the higher moderating power of D_2O, whereas the 50° to 90° neutrons require less moderation and more reflection by the graphite and bismuth that they encounter. The low energy gamma radiation emanating from the lithium-7 target and reaching the patient is reduced by a factor of 20 by adding 1.6 cm of bismuth between the target and the patient.

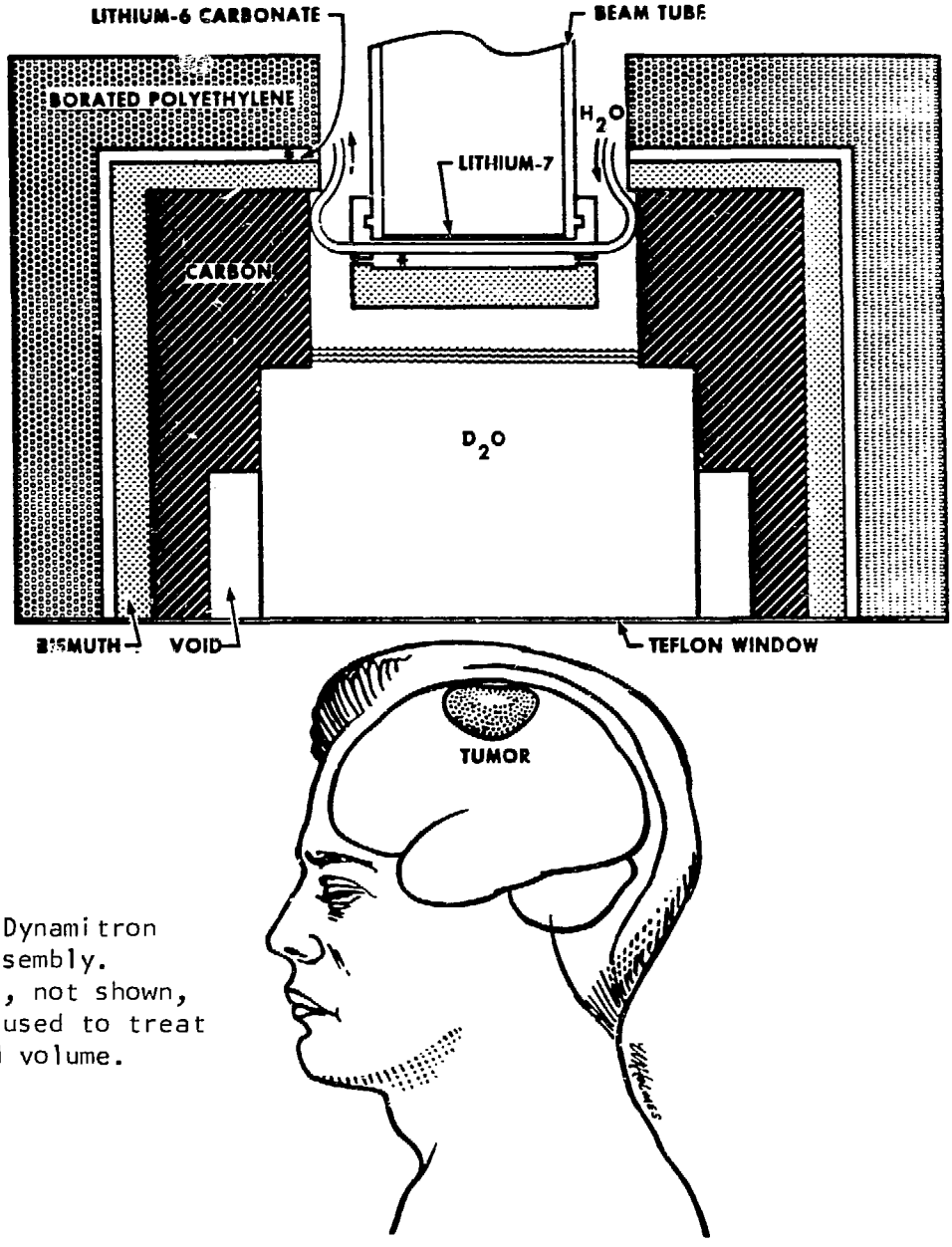

Fig. 6. Dynamitron target assembly. ^6Li tiles, not shown, would be used to treat a defined volume.

Light water will be used to remove the 5 kW of beam heating produced by the anticipated 2 mA of beam current. The beam current will be defocused to cover the 7.5-cm-diameter lithium metal target. An alternative and more flexible arrangement would be to use a focused beam of protons and to sweep this beam spot with magnetic deflection. Thermal neutron shielding between the D_2O moderator and the light water is used to reduce the intensity of the 2.2-MeV capture gamma ray.

To predict the performance of this target, Monte Carlo calculations will be made which take into account the variable D_2O level, the different moderator materials, and the coupling of the neutrons to the patient, i.e., the neutrons that go from the target assembly to the patient and then are scattered back to the target assembly. At present, the calculations of neutron spectra have been for a simplified model in which only the neutrons emitted in the forward cone (0° to 50°) are considered. These neutrons are interacted with the D_2O in a straight-ahead approximation. Spectra of these neutrons, emerging from the target, are shown in Figure 7 for a 10-cm and a 12-cm level of D_2O. This model does not properly predict the low energy end of the spectra because the 50° to 90° neutron group is not included and neutrons were followed through no more than five collisions. This calculation is intended only to show the degree of control that can be achieved by control of the amount of D_2O in the target assembly.

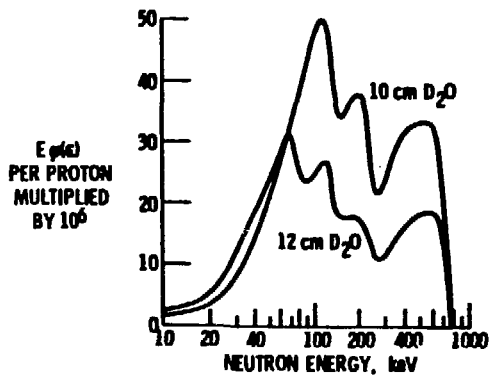

Fig. 7. Energy spectra of forward-directed neutrons moderated by D_2O.

This target is estimated to produce 1.6×10^{12} neutrons/sec and give an emerging flux of 1.6×10^{9} cm^{-2} sec^{-1}. The emerging gamma dose rate from the 430- and 478-keV photons arising from the ^{7}Li reactions is estimated to be 0.15 Gy/h. The uncertainty in the gamma dose rate is due to neutron capture in trace elements in the materials of the target, for example, ^{1}H contamination of the D_2O. Brenner and Zaider's Monte Carlo calculation, scaled for the Dynamitron target, predicts a gamma dose rate of 0.2 Gy/h. For a given neutron energy flux, the time required for BNCT depends on the ^{10}B concentration, the tumor depth, and the amount of the patient's body available to moderate the neutrons. The calculations of others, summarized at the previous conference (5), provide data from which patient irradiation times are estimated to be 2 to 3 hours. Though this is too long for most patients to endure as a single fraction, it is about the same as the total time required for a course of fast neutron therapy administered over 12 fractions.

The use of a Dynamitron as a BNCT facility is considered to be a temporary arrangement because the use of a hospital-based accelerator with a factor of ten larger beam current would be more desirable. This second generation accelerator would have a beam current of 20 mA of 2.5-MeV protons, which would result in a power dissipation in the target of 50 kW. Such an accelerator is not now commercially available, but the principle (6) of operation is established, and a number of successful machines have been constructed (7,8). It has been estimated that a linear accelerator employing the radio-frequency quadrupole (RFQ) concept can be built for about $\$2 \times 10^6$ (9). Figure 8 shows a schematic arrangement of a BNCT facility employing an RFQ to accelerate protons. A 30-kV ion source would inject protons continuously into the linear accelerator, which would be fed with a klystron operating at 425 MHz and delivering 1 MW of power. The idea of using an RFQ and the $^7Li(p,n)^7Be$ reaction as a source of low energy neutrons was advanced several years ago by Lone et al. (10), who were suggesting the application of the device as a source of thermal neutrons for neutron radiography and other industrial applications.

An approach to the problem of removing the 50 kW of beam heating from the thin layer of lithium-7 metal is suggested by the technology developed for heat pipes. Figure 9 shows a conceptual design in which the beam heating is removed from the target by evaporation of liquid lithium. The temperature of the lithium will rise to about 600°K and the vapor pressure to 9 Pa (10^{-4} atm). At this temperature about 2 g/sec of lithium is vaporized to be condensed on the cooler walls above the liquid layer and is then returned by gravity to the target region. An important consideration is to keep ^7Li vapor from diffusing back into the accelerator, because the copper surfaces would become contaminated and the work function reduced to the point that the high electric fields required for acceleration could not be achieved.

SUMMARY

A method of achieving a neutron source for neutron capture therapy using the NASA Lewis Research Center Dynamitron has been described. This facility will be used to study physics and biology problems of BNCT, and if these studies are promising patient treatment can be undertaken because the neutron output appears to be adequate. The Dynamitron can also be used to study the target cooling problem which will arise if an RFQ accelerator is used for hospital-based BNCT treatments.

During the two years since the First International Conference on BNCT, in several clinical comparisons (11,12,13) fast neutron therapy as a high-LET modality has shown results superior to those of conventional low-LET therapy. This is viewed as encouraging for BNCT, since BNCT also is a high-LET modality.

A combination of fast neutron therapy and BNCT with low-energy neutrons may be the best way to approach high-LET therapy. It has the advantages of targeting the high-LET dose to the tumor cells, which BNCT can offer, and of delivering a high-LET dose with fast neutrons to the poorly vascularized component of the tumor, which would not take up an adequate amount of boron. Combining fast neutron therapy and BNCT is an old idea that has

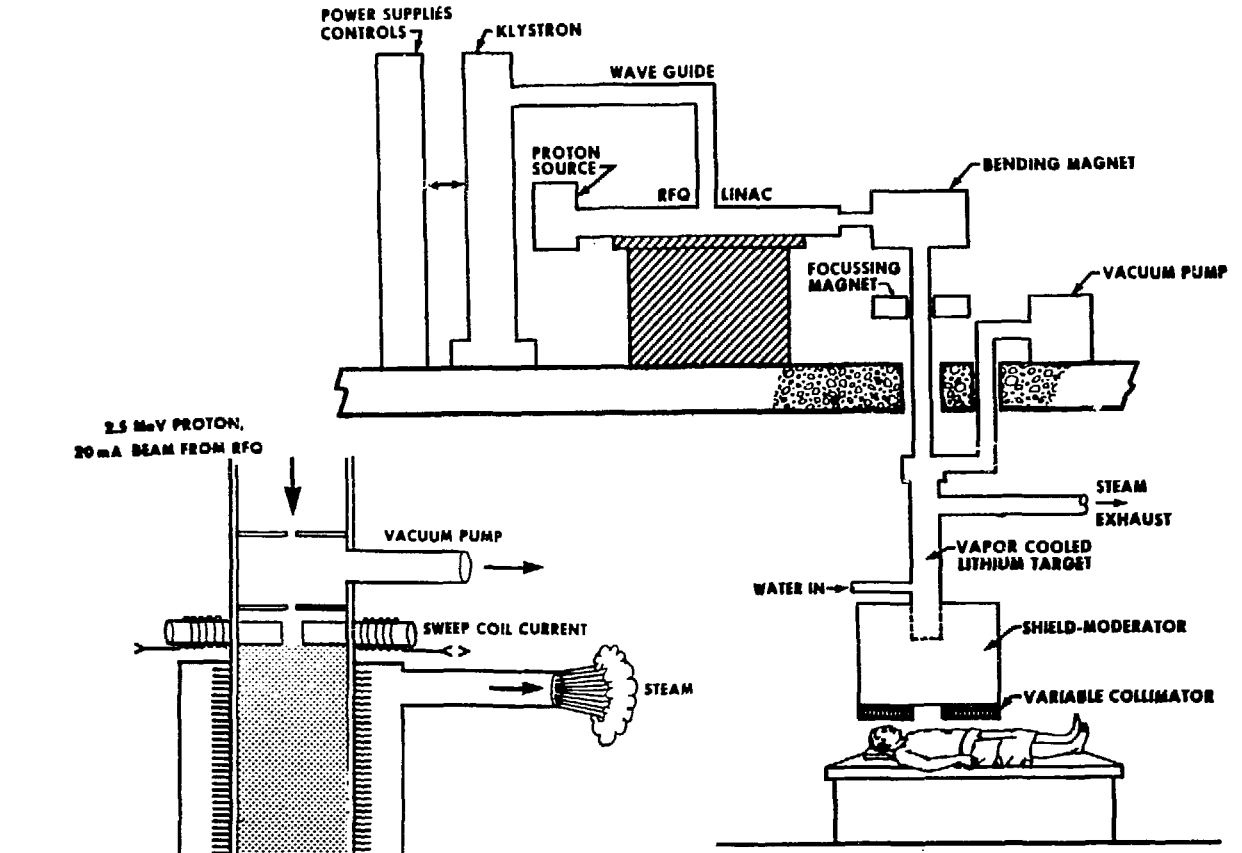

Fig. 8. Schematic of RFQ-Linac BNCT treatment facility.

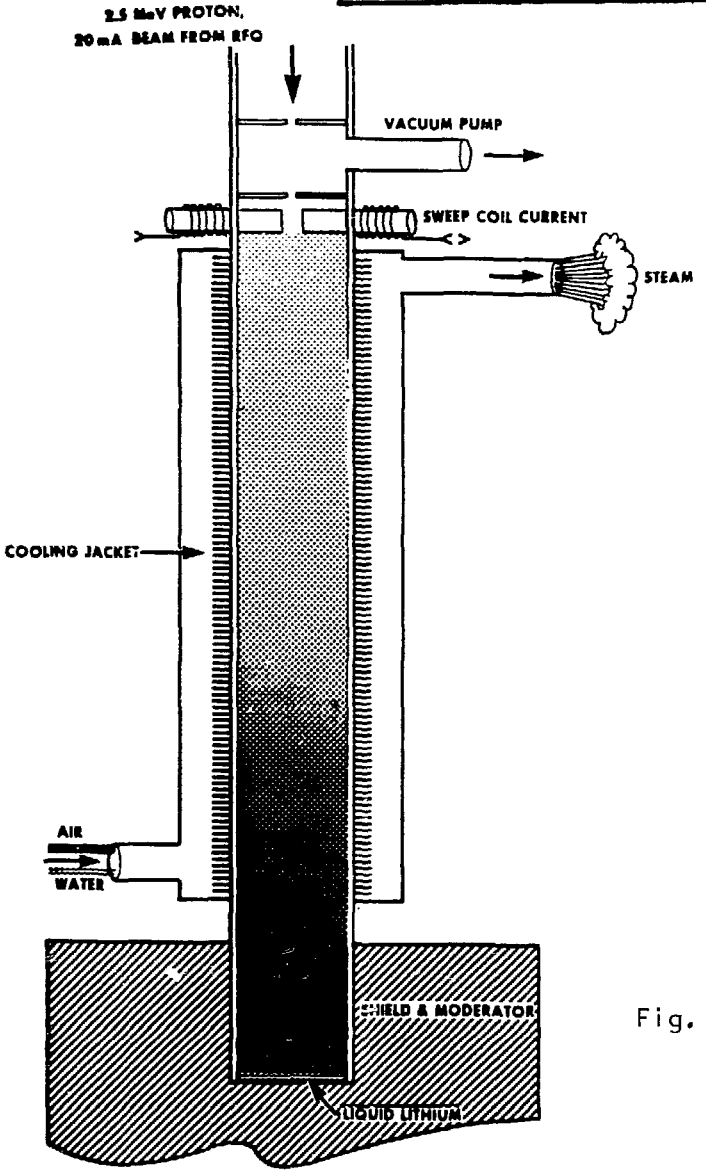

Fig. 9. Schematic of liquid lithium vapor-cooled target.

been referred to as fast neutron dose augmentation and was discussed at the First Conference by Larsson (14). Combining them in the manner suggested here, with two independent accelerators, adds greatly to the flexibility of treatment. The ratio of BNCT dose to fast neutron dose is not a treatment variable (above a limit set by the maximum tumor boron loading) in fast neutron therapy augmented with boron. Also, the two therapies could be spatially separated, with fast neutron therapy being given to the tumor mass and the low energy neutrons being used to cover a larger volume, encompassing regions where microscopic disease might be expected.

In speculating on the future and the possible widespread use of high-LET therapy, if this should be indicated by clinical studies, it seems unlikely that pion therapy or energetic heavy ions will be able to contribute in any significant way because of the high cost and extreme complexity of such facilities. It is easier to imagine that a major medical center might have for fast neutron therapy a superconducting cyclotron of the type being developed for Harper-Grace Hospital in Detroit. This type of cyclotron (Figure 10) will cost about $\$2.5 \times 10^6$. In addition, the same medical center could have an RFQ accelerator as a source of low energy neutrons for BNCT. The two accelerators together would cost much less and take less space than recently commissioned fast neutron therapy facilities using conventional cyclotrons. Also, BNCT would be forever freed of connection with a nuclear reactor.

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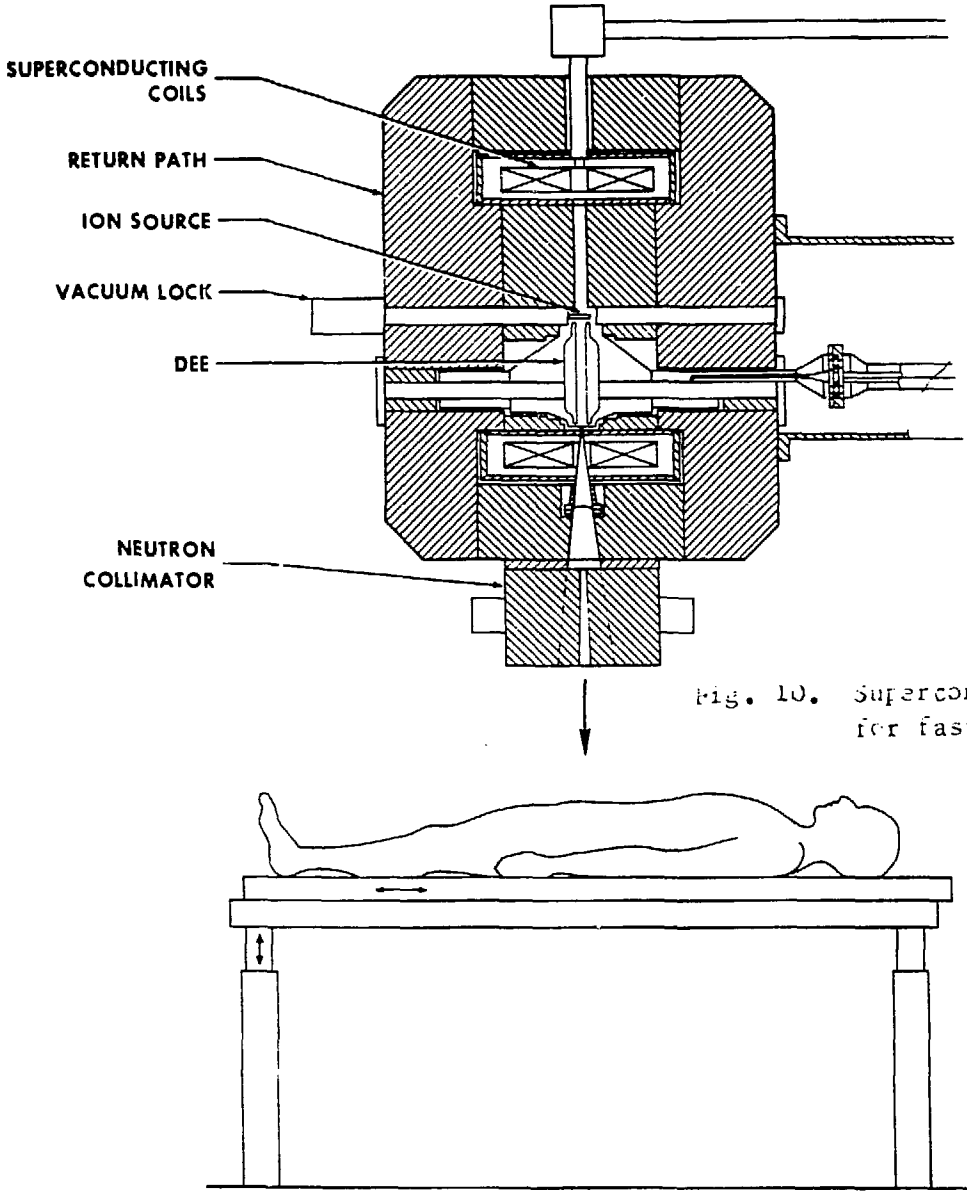

Fig. 10. Superconducting cyclotron for fast neutron therapy.

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Aspects of Implementation of NCT

John L. Russell, Jr.
Nuclear Medicine, Inc.
900 Atlantic Drive, N.W.
Atlanta, GA 30332

ABSTRACT

The organizations and systems which will be required to implement NCT on a practical scale are identified and briefly described.

1. INTRODUCTION

The successful application of Neutron Capture Therapy probably demands as wide a range of technology as any other therapy ever seriously proposed. If NCT is to be used to treat some 13,000 brain tumors each year in the US, to say nothing of other types of cancer being proposed, such as melanoma and lung cancer, a variety of institutional, regulatory, organizational and economic aspects must be dealt with in order to bring each technical, scientific and medical descipline to bear on the patient at the proper time and under circumstances the patient can tolerate. This paper briefly addresses this aspect of NCT since these practical considerations will have considerable impact on what technology can eventually be transferred from the laboratory to the clinical setting where it can actually benefit a patient.

NCT already has been applied to some 30 patients in the US and some 70 in Japan. There are other examples of therapies utilizing nuclear facilities. For example, the cyclotron at the NASA Lewis Laboratory is used by the Cleveland Clinic in a trial of fast neutron therapy. If it is so simple, what is the problem being addressed in this paper? This question is perhaps best answered with an ancedote.

A noted British neurosurgeon visited Dr. Hatanaka in Tokyo to see firsthand the techniques of NCT. He was met at the airport and immediately taken to the bedside of a patient scheduled for therapy that day. He participated in the boron compound infusion, a last minute bit of brain surgery, transportation to the reactor, patient preparation, anesthesia, irradiation and patient recovery. Twenty hours after landing he collapsed exhausted into bed. The next day he left, explaining to his surprised host that the technique might work just fine, but it would never be used anywhere else in the world because Hatanaka was obviously the only physician alive with the physical stamina required to carry out the procedure.

Of course more complex procedures are currently performed such as organ transplants. These would not be possible without a team approach which sub-divides the necessary tasks. However, a complicating factor is that for NCT the nuclear reactor and all that it entails is not currently imbedded in the medical infrastructure. Also, it is not practical to consider supplying hospitals with such facilities. The five or so reactors in the US capable of producing a suitable beam become a very real constraint upon what will be possible.

In order to highlight the types of organizations and interfaces which must be addressed, a hypothetical patient is followed from diagnosis through follow-up in the year 1990 when these systems could be in place.

2. THE PATIENT

Consider such a hypothetical patient in Omaha, Nebraska who is checked in to a hospital operated by one of two or three major U.S. health care corporations. After CT scans, NMR scans and possibly a biopsy the diagnosis is confirmed as glioblastoma multiforme. The decision is made to transfer the patient to a hospital operated by the health care corporation in Atlanta, one of the five cities in the US with access to a reactor equipped for NCT. Following further batteries of tests, surgery is performed to debulk the tumor to reduce pressure and brain deformation.

After a few days to a week or so the boron compound is administered, possibly slowly by IV over a period of another week. Toxicity, boron uptake and distribution are monitored. A treatment time is scheduled at the reactor.

A specially trained ambulance team transfers the patient and his doctor or doctors to the patient holding area of the reactor facility.

Blood and skin samples are taken from the patient and boron concentrations are determined. Pre-calculated irradiation schedules are corrected for actual boron concentration. If conscious and cooperative, the patient is familiarized with the positioning equipment and radiation shielding into which he must be rigidly held for some period of time. If the patient is not able to cooperate he must be anesthetized and remotely monitored during irradiation, requiring an anesthesiologist skilled in remote monitoring and control of a patient.

The patient is irradiated while being remotely monitored both for neutron dose received as well as certain medical parameters. On completion of irradiation the patient is transferred back to the hospital by the specially equipped ambulance and crew.

At the hospital the patient is placed in a special ward for caring for radioactive patients.

Depending upon the state of health of the patient, he should be ready for release from the hospital in about one to four weeks.

Follow-up and drug therapy at a medical facility near the patient's home will be required for some months as the brain recovers from the surgical and radiological insults as the necrotic tumor tissue disolves and the brain redistributes itself in the healing process.

3. SYSTEMS AND SERVICES

The above scenario presupposes at least the following list of syste and services:

1. Patient referral network
2. Specially equipped hospitals near nuclear facilities
3. Drug manufacturor
4. Physicians trained in the entire procedure
5. Specially equipped and trained ambulance service
6. Nuclear Reactor facility with:
   (a) modest emergency room witn a registered nurse on duty
   (b) rapid boron analysis service
   (c) staff nuclear physicist/radiologist
   (d) health physics staff for monitoring activities other than those concerned with reactor operations
   (e) management and coordinating staff
   (f) beam treatment room equipped for remote monitoring of patient and beam and remote anesthesiology
   (g) patient holding areas
7. Procedure for payment of the various services
8. Liability protection

The complex patient support systems of a modern hospital will not be addressed because they currently exist and will be an implicit part of the therapy system. To this must be added one or more organizations which provide those services unique to NCT. One representation of the relationship between these organizations is shown in figure 1, which diagrams the interfaces between the organizations providing the various required services. In this particular representation, all of the non-hospital services are coordinated through a single "Nuclear Service". The purpose of this arrangement is to make possible the functional relationships shown in figure 2, which are designed to facilitate the coordination task of the primary physician in treating his patient.

Figure 1, Interfaces

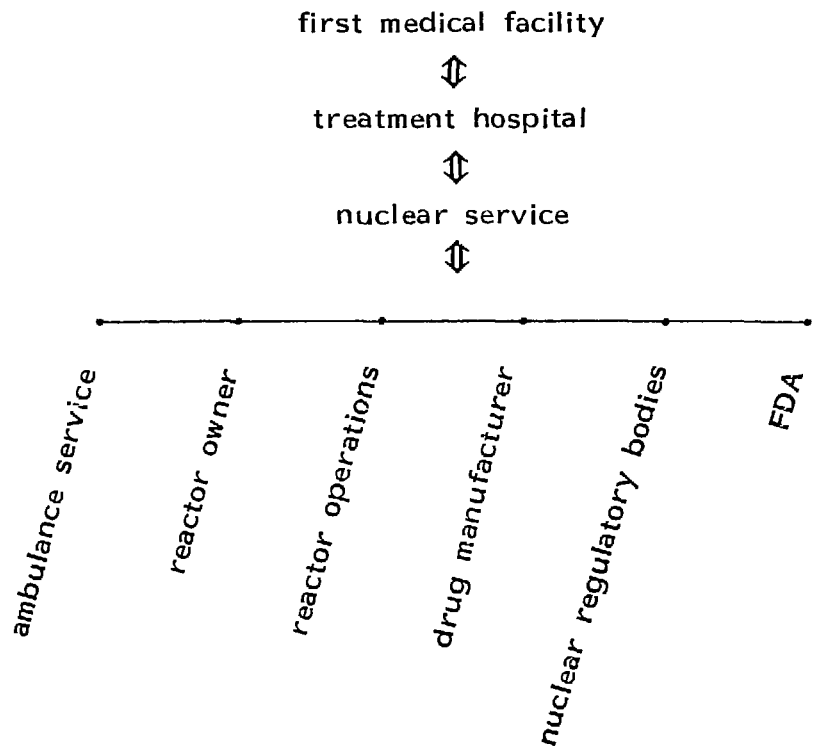
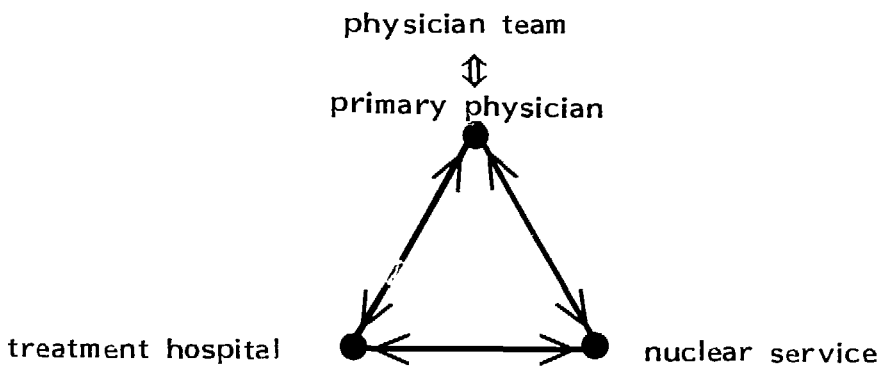


Figure 2, Interfaces



4. DISCUSSION

Clearly, much of the required infrastructure is now in place and the rest does not appear to involve any insurmountable barriers. There remain, however, several organizations, systems and interfaces to be created before a significant number of patients can receive the benefits of NCT. These are discussed in the following.

1. Patient Referral Network. Patients and physicians across the country do not automatically know that the thing to do with a brain tumor is to fly to a distant city for treatment. I have discussed this problem at some depth with Dr. Charles Redman, President of HCA Research Corporation, a division of Hospital Corporation of America. He has assured me, and authorized me to state here, that at the appropriate time HCA would put in place a patient referral network for referring patients to facilities in "treatment cities". Since HCA operates hospitals in most of the prospective treatment cities, this will be a fairly straightforward process, even though transport of severely ill patients is not a trivial problem.

I would envision more than one referral network. Certainly other patient care corporations could form them. However, the more conventional regional networks around major cities in which special cases are referred from the surrounding towns to the large teaching hospitals would still apply.

2. Special Hospital Facilities. To understand the size of the patient care problem it is useful to reflect on a few numbers. If 13,000 U.S. brain tumors are to be treated in 5 facilities, that amounts to 50 per week per facility. If the average hospital stay is 4 weeks, that means 200 hospital beds are continually occupied with patients undergoing therapy at a single treatment center. Only about 15% of those beds need to be in wards equipped to handle radioactive patients because of the rapid decay (15-hour half-life) of Na-24, the principal activated isotope. These needs will probably be served by 5 to 10 hospitals in the metropolitan area around the treatment center.

This level of hospital support is not a large perturbation of a large metropolitan area, but might present a problem for an isolated facility.

The key to smoothly integrating the hospital support lies in the interfacings between the nuclear service, the treatment hospital and the primary physician.

3. Drug Manufacturer. Making commercially available the boron compounds to be used in therapy presents significant technical hurdles to be overcome. These include the maze of non-exclusivity and FDA approval, as well as the fairly formidable technology of compounding boron cages using isotopically enriched materials. Fortunately, Callery Chemical Company has developed and maintained production capability for $Na_2B_{12}H_{11}SH$ and certain derivatives. This capability has been maintained in spite of the dismal outlook to date for a profitable return on its investment. It would be normally assumed that once a market is demonstrated there would be several suppliers eager to move into the market. However, I would suggest that this glib assumption may not be warranted. Most of the compounds being considered fall into the category of "specialty products" and do not follow the market rules of commodities. The costs, time and trouble of dealing with the FDA, of working with a complex market place and questionable exclusivity (patent protection) do not present an attractive picture to a commercial entity looking for a place to make a profit. It is only an occasional company which, because of special circumstances, can fit into and potentially profit from, these kinds of specialty markets. For very selfish reasons it is important that we all encourage, and seek ways to protect the market of, our potential supplier.

4. Physicians. In order to meet reasonably the patients' needs, a pool of a few dozen physicians covering all of the required specialties must have working relationships with the relevant institutions in each treatment city. The training of these physicians in the details of NCT must not be overlooked.

5. Ambulance Service. A dedicated ambulance service will be required primarily because the vehicles unavoidably will become contaminated by radioactive sodium from the irradiated patients. While the levels will not be hazardous they will prevent the routine use of the vehicles for other purposes.

6. Nuclear Reactor. The facilities and services itemized under this item in the previous section are largely self-evident and do not warrant embellishment in this brief document. There is one very important practical consideration which must be addressed. The U.S. reactors which are suited for, or can reasonably be modified to be suited for, NCT belong either to the US government or to a university. Neither type of institution is well suited to operating a "radiation-for-hire" business treating hundreds of patients per week. Arrangements must be made for legally and operationally separating the reactor operations functions from the patient irradiation functions. This is not a trivial problem and solutions will not be suggested here, although this is a problem that can be solved.

7. Payment. The nuclear services present an additional cost over and above the normal medical costs, which must be paid by the patient or his insurance company. Billing procedures and rates are developed in conjunction with the major insurance carriers and government health care agencies. Consideration must be given to adequate compensation to the reactor owners, ambulance services, liability insurance, etc. The procedure involves a very complex series of negotiations which cannot be undertaken until we are much closer to practical implementation.

8. Liability. In today's insurance climate, in contrast with only two years ago, it is virtually impossible to buy product liability insurance for a new high risk medical product. A saving grace for NCT is that the Price-Anderson Act setting up insurance pools for the nuclear industry specifically requires the pool to be responsible for any radiation caused liabilities incurred on a nuclear site. The effect is that NCT is probably automatically covered. Rate adjustments have been discussed with the carriers and they do not appear to be unreasonable.

On that optimistic note I will conclude by affirming that I personally believe the problems of implementation, while non-trivial, can indeed be overcome, and that NCT can be made available to the hundreds of thousands of Americans who will otherwise have their lives unnecessarily shortened by several varieties of currently incurable cancer.

Future Boronated Molecules for Neutron Capture Therapy

A.H. Soloway, F. Alam, and R.F. Barth
The Ohio State University
Columbus, Ohio 43210

1. INTRODUCTION

The intrinsic attractiveness of Neutron Capture Therapy (NCT) for the treatment of cancer utilizing boron-10 has been significantly limited by the boron compounds available and their ability to localize specifically in neoplasms. The rationale for concentrating on using boron-10, vis-à-vis other nuclides with high cross-section capture for thermal neutrons, stems from several factors. First, the capture reaction involving boron-10 yields predominantly two high-LET particles which are confined to a radius of 10-14 microns and therefore this destructive radiation will be limited largely to those cells which contain boron. Second, boron-10 is not radioactive and is only activated when the capture reaction occurs. Third and very importantly, there is a great range of choice for different boron compounds due to the chemistry of boron per se; in many regards it rivals the diversity observed with carbon. Finally, its cross-section capture of approximately 4,000 barns would permit useful destruction if 10^9 boron-10 atoms could be confined largely to each cancer cell. Such a concentration level is essential in order to minimize the background radiation dose from those elements normally found in tissue. Though they have low neutron capture cross-sections, their high concentrations can contribute significantly to the background radiation dose. It is for this reason that achieving high selective boron concentrations in tumor cells is an absolute prerequisite for the successful clinical development of NCT.

2. EARLY BORON COMPOUNDS IN BNCT

Before considering the present and future boron compounds that may be ultimately used for NCT, it is very pertinent to examine briefly the compounds which were used in clinical trials. Initial research concentrated on the use of inorganic boron compounds, especially those which are related to boric acid and its derivatives. The basis for their use was their ready availability in B-10-enriched form and the greater knowledge of their biological action and toxicology in man. As a consequence, boric acid derivatives such as borax and sodium pentaborate were evaluated in brain-tumor-bearing animals. Though the initial tumor:normal boron ratios were encouraging, the differential was very transient and disappeared within several hours. Clinical studies demonstrated severe radiation damage, especially to normal tissues in the path of the neutron beam. These results spawned efforts to develop boron compounds

which would show a longer concentration differential between tumor and normal tissue. Among the compounds which were considered were boric acid esters and aliphatic, aromatic and heterocyclic boronic and borinic acid. A correlation of physicochemical parameters of various aromatic boronic acids with their concentration ratios in tumor-bearing mice is shown in Table 1.

These results demonstrated the apparent importance of the hydrophilic nature of the boron compounds to be used in brain tumor treatment by BNCT. An important limitation of such compounds was the relatively low percentage of boron. Since therapy was directly dependent upon achieving a critical level of boron-10 within the tumor (10-50 mg/kg), chemical toxicity posed a major problem. The significant synthetic progress and remarkable chemical stability of certain boron hydrides, namely, the B_{10} and B_{12} anions of the polyhedral boranes and of the carboranes, opened new vistas to BNCT. Chemical toxicity was no longer an impediment since some of these structures, based upon boron content, were less toxic than boric acid. Two compounds, one an aromatic boronic acid (p-carboxybenzeneboronic acid) and the other a polyhedral borane salt ($Na_2B_{10}H_{10}$), showed useful tumor-localizing properties in a murine ependymoblastoma (Figure 1) and in human glioblastomas (Figure 2). Chemical toxicity was sufficiently low so that clinical trials were initiated in man using boron-10-enriched compounds.

Figure 1. Tumor/Brain Boron Ratios in Mice

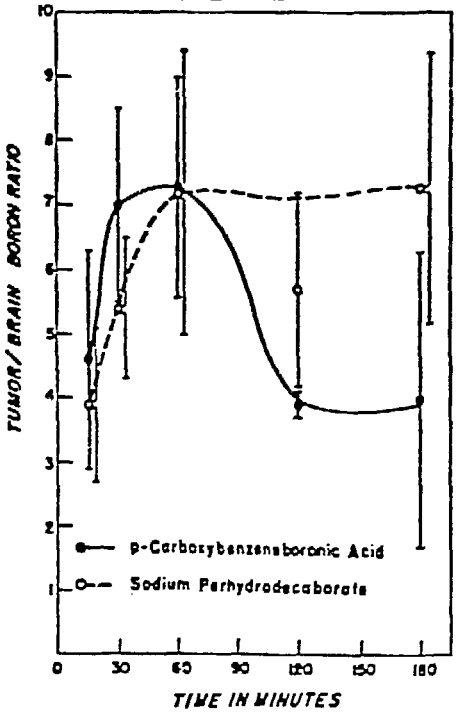
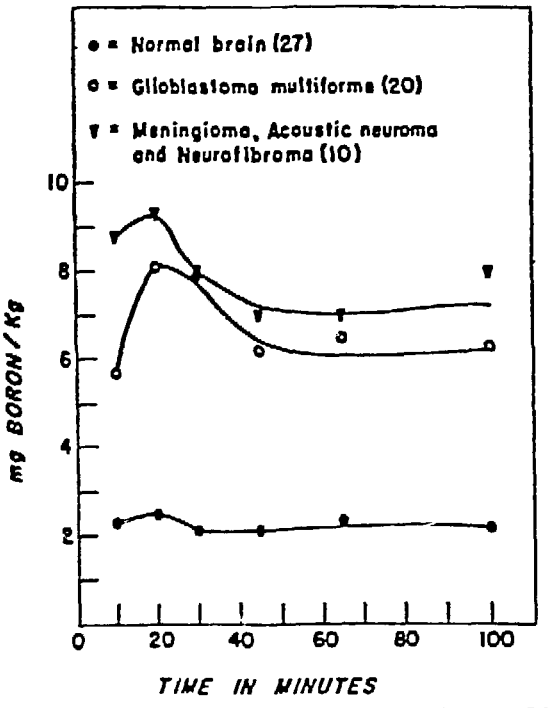


Figure 2. Boron Concentrations in Human Brain Tumors



Unfortunately, these clinical trials were unsuccessful with these first-generation compounds. This stemmed from the non-uniform distribution of the compounds in the tumor, uptake by surrounding brain tissue, and lastly but more importantly, high blood concentrations. The latter resulted in exposure of vessel walls to high doses of alpha radiation, thereby producing severe necrosis of the vascular endothelium and thrombosis of blood vessels.

Table 1. Tumor/Brain Ratios of Various Boronic Acids

Substituted Benzeneboronic Acid X—Ph—$B(OH)_2$	Aqueous/Benzene Partition Coefficients	Tumor/Brain Boron Ratios
4-$Si(CH_3)_3$	0.03	0.1*
2,4,6-tri-CH_3	0.4	0.2*
3-CF_3	0.4	0.2*
2-CH_2OH (anhydride)	0.6	---*
4-SCH_3	0.7	0.2*
4-Br	0.8	0.2*
4-OC_2H_5	1	0.6
4-Cl	1	0.4
2-CH_3	2	0.4
3-CH_3	2	0.3
4-CH_3	2	0.3
4-OCH_3	3	0.7
4-F	3	0.3
4-H	6	0.7
2-NO_2	7	0.6
3-NO_2	12	0.4
3-$NHCOOC_2H_5$	14	0.6
4-CHO	29	0.6
3-CO_2-4-CH_2	29	0.5
3-NO_2-4-COOH	51	2.5
3-NH_2-4-CH_3	67	0.9
4-COOH	67	4.8
3-NO_2-5-NH_2	170	1.8
4-$B(OH)_2$	200	2.3
3-NH_3	200	1.2
4-$N(CH_3)_2$	200	1.4
3-$NHCOC_6H_5$-5-COOH	200	4.0
2-NO_2-4-NH_2	200	2.6
3-COOH	200	5.7
4-CH_2CHCOO^- NH_3^+	200	8.5
3-OH	200	1.5
4-OH	200	1.6
2-NO_2-4-COOH	200	7.7
3-NH_2-4-COOH	200	6.4
3-$NHCOCH_2CH_2COOH$	200	6.9
3-$NHCONH_2$	200	7.5
3,5-di-NH_2	200	7.5
2-CH_3-3,5-di-NH_2	200	4.8
2-CH_2-4-COOH	200	7.3

*Animals died at low doses of the compound.

3. SECOND-GENERATION BORON COMPOUNDS

This failure directly led to the development of second-generation compounds, many of which possessed a biochemical rationale for their selective incorporation into tumor cells. Even prior to these clinical studies, boron compounds were being synthesized with the objective that they might be incorporated into more rapidly dividing neoplastic cells. The clinical failures provided additional impetus for these studies. Boron-containing potential anti-metabolites and other tumoriostatic compounds were synthesized, including amino acids, steroids, purines, and various alkylating agents. Examples of structures that were synthesized are shown in Figure 3.

While such compounds were being synthesized, a screening program was initiated in tumor-bearing mice to evaluate various polyhedral boranes for their ability to leave the vascular compartment and to achieve a differential concentration between tumor and blood as well as contiguous normal tissues and those in the beam pathway. Two compounds that displayed such useful properties were $Na_2B_{12}H_{11}SH$ and $Na_2B_{10}Cl_8(SH)_2$. Promising initial results in animals, which are summarized in Table 2, ultimately led Hatanaka and his associates in Japan to use ^{10}B-enriched $Na_2B_{12}H_{11}SH$ for the treatment of patients with malignant brain tumors. The results obtained in treating patients with glioblastoma, treated by a combination of surgery and BNCT, have stimulated considerable interest in this compound.

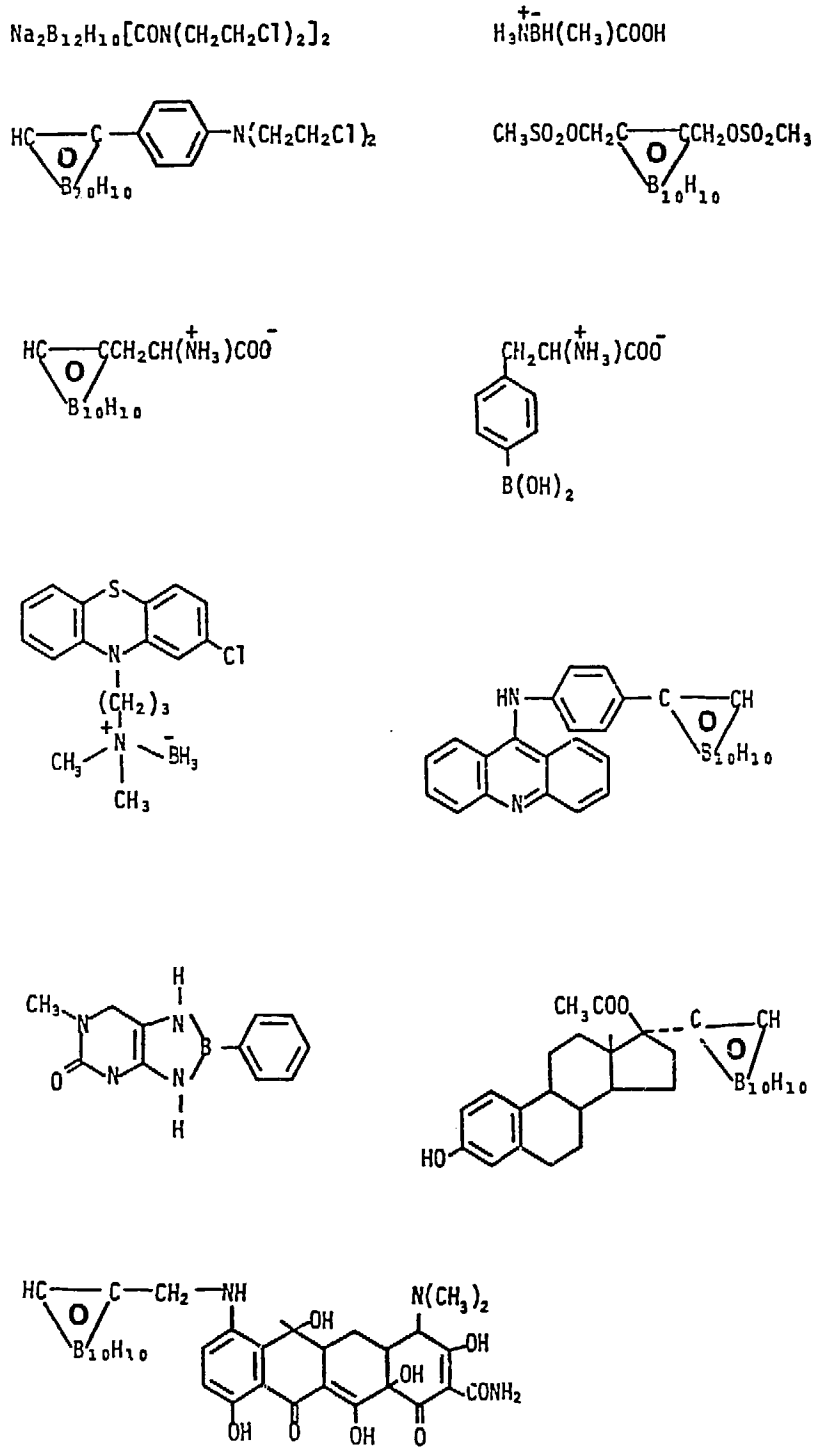
Table 2. Tumor and Blood Distribution of $B_{12}H_{11}SH^{2-}$

Micrograms of Boron/g		Tumor:Blood Ratio
Tumor	Blood	
17.2	4.4	3.9
21.8	5.0	4.4
6.5	1.7	3.8
4.4	2.1	2.1
33.0	6.2	5.3
6.0	2.2	2.7
37.6	2.1	17.9
19.9	3.9	5.1
4.2	1.1	3.8
5.0	1.8	2.8
13.3	2.0	6.6
7.5	0.9	8.3
23.4	3.4	6.9
18.7	3.5	5.7
	Average:	5.7

Dose: 35 μg Boron/g mouse/day
Total Dose: 175 μg Boron/g

The material used in Table 2 was probably a mixture of the sulfhydryl compound and its oxidized disulfide. This dimer, $[B_{24}H_{22}S_2]^{-4}$, and the disulfide monoxide were considered by Tolpin and Wellum and by Slatkin and his

Figure 3. Examples of Boron Compounds with a Biochemical Rationale



associates at Brookhaven National Laboratory to be derivatives of the sulfhydryl compound which may possess more favorable tumor-localizing properties. Key questions which must be answered relate to the relative toxicity of these three species and the mechanisms involved in their localization in tumors. Certainly, the sulfur-containing polyhedral borane anions behave differently biologically from the unsubstituted parent anions. The mechanism by which the former provides neoplastic selectivity remains to be elucidated, but at this juncture such compounds remain an attractive possibility for use clinically with BNCT.

One of the compounds in Figure 3 which is being actively considered for clinical use in BNCT is p-boronophenylalanine. The basis for using this boron-containing amino acid is its potentiality for being incorporated into tumor proteins and serving in this location as a radiation source following the capture reaction. Active research is underway at Brookhaven National Laboratory to assess its potential.

4. THIRD-GENERATION BORON COMPOUNDS

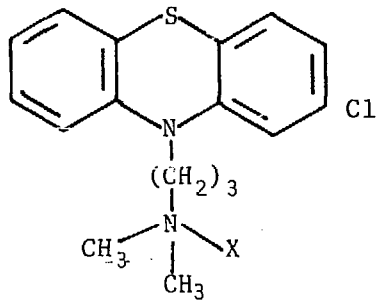
The foregoing have generally not been synthesized specifically for their ability to localize selectively in neoplasms. The third-generation boron compounds do possess such a biological rationale. This category can be divided into two broad classes of boron-containing compounds: (1) those organic compounds with a proven predilection for tumor cells, and (2) tumor-seeking macromolecules (i.e. antibodies against tumor-associated antigens). Developments in both areas are proceeding in several laboratories at this time.

a) Tumor-seeking Organic Compounds

Among the organic structures with a propensity to localize selectively in neoplasms are the porphyrins and certain phenothiazines. The former, such as derivatives of hematoporphyrins, have been shown to achieve high concentrations in a variety of tumors. This is the basis for their utilization clinically in another binary system, namely, photoradiation therapy. If boronated porphyrins localize in a comparable manner in malignancies, such as melanoma, then they also might have clinical applicability for BNCT. Stephen Kahl at the University of California, San Francisco, has been engaged in the synthesis of boronated tetraphenyl porphyrins by the incorporation of the carboranyl moiety into anilidoporphyrins. Such structures and their nido derivatives are now being evaluated at Brookhaven National Laboratory in order to determine their specific localization in malignancies, their toxicity, and their clinical potential in BNCT. At this time, boronated porphyrins appear to be a most attractive class of compounds for BNCT.

Another compound, chlorpromazine (CPZ), demonstrated a high degree of localization in melanomas and other melanin-containing tissues. A recent study in melanoma-containing animals showed tumor concentrations in excess of 100 μg/gram; tumor/normal tissue ratios greater than 15; and a biological half-life of approximately ten days.

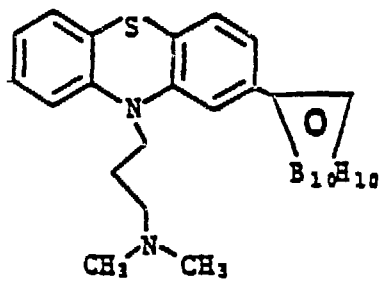
If boronated analogues of CPZ contained a single carborane or polyhedral borane moiety and showed similar biological properties as CPZ, then boron concentrations of 30 μg ^{10}B/g tumor would be achievable. Such levels would be entirely adequate for BNCT. Three boronated analogues of CPZ have been reported, and studies of these compounds by Mishima and his colleagues in Japan in Greene's hamster melanoma have demonstrated an enhancement of neutron irradiation destruction by BNCT.

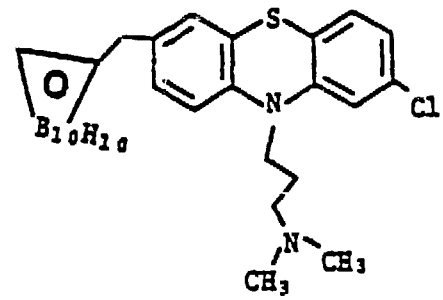


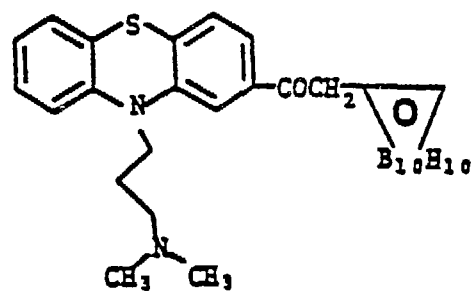
a. X = BH_3
b. X = $B_{12}H_{11}^-$
c. X = $B_{10}H_9^-$

Since binding of CPZ to melanoma is considered to involve a charge transfer complex between CPZ and the indole nucleus of melain, the aliphatic tertiary amine in the side-chain is crucial to the binding process. The basis for this statement is the fact that phenothiazine itself did not exhibit any strong proclivity for pigmented cells. Attachment of the boron moiety to the tertiary aliphatic amine would certainly interfere with the charge transfer complex between this substituted CPZ and melanin. This would account for some apparent loss in selectivity.

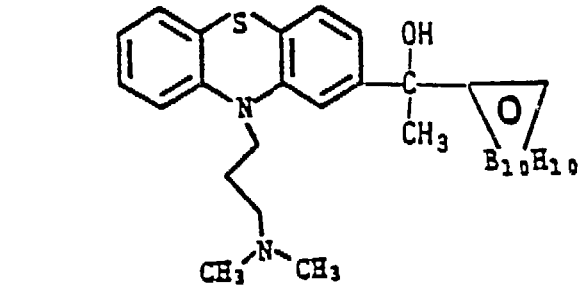
In order to synthesize substituted CPZ compounds which would be expected to mimic CPZ biologically with respect to melanin binding, the following compounds have been considered:

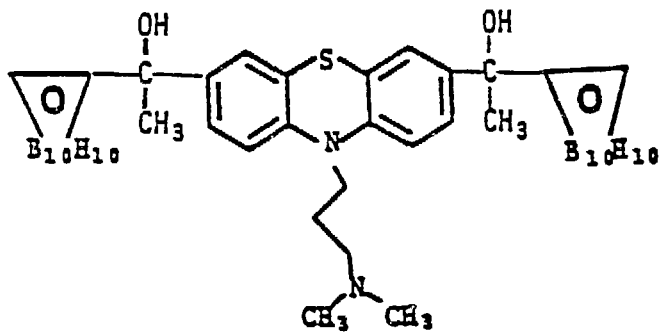






The primary factor in the selection of these boronated promazine structures is to incorporate the boron cage at a position which would be less likely to interfere with the binding of the promazine structure to the melanoma receptor. For this reason, attachment of the carborane moiety to the phenyl rings and distant from the S-N-N axis, which is involved in the pharmacological activity of the promazine, is the basis for presenting such target compounds. In order to determine the validity of this rationale, we have recently synthesized the following carborane-containing promazines:





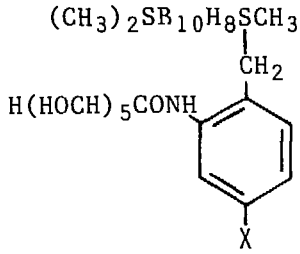
They were simply prepared from the corresponding promazine methyl ketones and lithiocarborane. Their evaluation in tumor-bearing animals is a first prerequisite in determining their potential clinical utility.

b) Boronated Monoclonal Antibodies

The foregoing studies have concentrated on the use of relatively small molecules for attaining high concentrations of boron compounds in tumors. This is certainly one approach; however, the use of macromolecules such as antibodies is clearly another.

An early suggestion was made that antibodies directed against tumor-associated antigens could be used for the delivery of boron-10 for neutron capture therapy. Initially, the focus was on whether proteins and polyclonal antibodies could be boronated with a sufficient percentage of boron and yet retain their water solubility and specificity. Some of these compounds and the early results on their covalent attachment to gamma globulin and other protein molecules are shown in Figure 4 and Table 3.

Figure 4. Structures of the Protein-Binding Polyhedral Borane Derivatives



a. X = NH_2
b. X = NCS
c. X = COOH

Table 3. Molar Concentrations of Boron and Protein and Their Mole Ratios in the Coupling Reaction Mixtures and in the Purified Conjugate

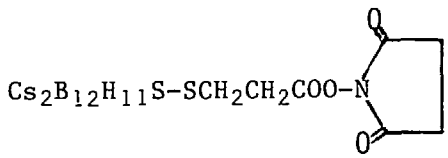
Compound	Reaction mixture			Conjugate
	[Boron]* ($M \times 10^3$)	[Protein] ($M \times 10^6$)	Boron / protein (molar ratio)	Boron / protein (molar ratio)
1a	3.96	6.50	610	26
	5.28	6.50	810	82
	7.92	6.50	1200	99
1b	3.90	6.50	600	410
	5.20	6.50	800	590
	7.80	6.50	1200	1100
1c	3.75	6.70	500	85
	5.00	6.70	1100	260

* Calculated as gram-formula weights of the element per liter of solution.

With the advent of hybridoma technology, a new avenue of approach has opened up for the targeting of ^{10}B by means of monoclonal antibodies directed against tumor-associated antigens. Drugs and radionuclides also have been linked to monoclonal antibodies, and although in vitro tumoricidal activity has been demonstrated, the in vivo therapeutic effectiveness of these conjugates has been modest. One of the problems encountered relates to an alteration of antibody specificity in linking any entity to a monoclonal antibody and also an inability of the antibodies to localize in sufficient concentration on each and every tumor cell.

It is likely that the problems associated with the in vivo use of murine monoclonal antibodies in humans ultimately will be solved by using human monoclonals either as intact molecules or $F(ab')_2$ fragments. It is on the basis that these antibodies eventually will provide a powerful modality for the targeting of tumoricidal agents that we have focused on the linkage of polyhedral boranes to antibody molecules.

Using protein-binding polyhedral borane derivatives to boronate antibodies directly, we have been able to incorporate up to 1300 boron-10 atoms per antibody molecule. This level of boronation appears adequate for therapy where suitable antigen site densities are available. However, linking individual boron cages containing 10 or 12 boron atoms to antibodies directly to achieve that level of boronation results in considerable loss of antibody reactivity due to an extensive modification in the antibody's conformation. Even under the very mild conditions employed with n-succinimidyl-3-(undecahydro-closo-dodecaboranyldithio)propionate (SBDP),



SBDP

there was an 80-90% reduction in reactivity following conjugation of 500-1300 boron atoms. We have concluded that in order to attain the required degree of boronation ($>10^3$ boron atoms per antibody) without an unacceptable loss of antibody reactivity, macromolecules containing a large number of boron atoms ($>10^2$) must be linked to a few sites on the antibody surface. These macromolecules would have to be soluble in aqueous buffers, possess high boron content, and be capable of conjugation to antibodies.

By reacting $B_{12}H_{11}NCO^{2-}$ with proteins (BSA, Concanavalin A, and IgG), we have been able to prepare boronated, water-soluble macromolecules containing 4-7% boron by weight. Macromolecules with up to 28% boron were obtained by the reaction of $B_{12}H_{11}NCO^{2-}$ with polylysine. Although this boronated polymer is highly water soluble, attempts to link this species to antibodies resulted in immediate precipitation of the protein just by mixing. Possibly the high anionic charge on the boronated macromolecule or the composition of the buffer were contributing factors to such denaturation. In order to reduce this charge, another new isocyanate derivative $Me_3NB_{10}H_8NCO^-$ with a lower negative charge was used to boronate polylysine. The resulting boronated polylysine contains on an average, more than 1500 boron atoms per molecule. This boronated macromolecule did not precipitate antibody molecules in certain buffers and within certain pH ranges, depending on the particular antibody. Conjugation of this macromolecule to antibodies has been carried out.

In the attachment of polyhedral boranes to preformed polymers, the clear objective is to achieve a high boron loading density. Reaction conditions must be developed in order to achieve a consistently high degree of boronation in such polymers. Utilizing $NaMe_3NB_{10}H_8NCO$, for example, we have prepared boronated polylysine where more than 90% of the ε-NH_2 groups reacted, resulting in a macromolecule that contains 24% boron by weight and over 1500 boron atoms per molecule. Other boronated macromolecules have been prepared using other polyhedral borane isocyanates and a boron-containing heterobifunctional reagent. the extent of incorporation into such polymers is based upon reaction time, temperature, and the boronating agent:polymer ratio. These conditions can be manipulated to obtain high boron loading densities.

Work is currently underway with both monoclonal antibodies and Fab' fragments together with heterobifunctional linker molecules so that the

incorporation of boronated polymers into such tumor-specific antibodies results in minimal alteration of the antibody. It would be optimal to have a single point of attachment to the antibody, since the fewer the number of sites altered on the antibody, the greater the possibility that its antigen-binding properties will not be compromised. However, even incorporation of a single group does not guarantee that the antibody will retain activity, since conformational changes can occur with a single incorporated group. Subsequent linkage of a boronated macromolecule could result in a mixture of different species with loss of affinity for target antigens in some of those species. However, with the high tumor:blood ratios obtainable with antibodies, it may be possible to use such a mixture provided unboronated antibodies and unconjugated macromolecules were separated from the boronated antibodies.

It would, of course, be preferable to isolate only the active boronated antibodies from the mixture. The possibility of such purification by affinity chromatography of the boronated antibody utilizing immobilized antigens is an important possibility. Such a procedure will be dependent upon the isolation and immobilization of the tumor-associated antigen.

The development of tumor-specific monoclonal antibodies for use in BNCT is only in its beginning stages but there is promise that such targeting of neoplastic cells has clear potential for their selective eradication. Certainly the various third-generation structures are designed to accomplish that objective.

Distribution of Sulfhydryl Boranes in Mice and Rats

D.N. Slatkin, P.L. Micca, B.H. Laster and R.G. Fairchild
Medical Department, Brookhaven National Laboratory
Upton, New York 11973

The sulfhydryl borane $Na_2B_{12}H_{11}SH$ (monomer) was developed by Soloway et al. for use in boron neutron capture therapy (BNCT) about twenty years ago (1). Monomer has been used for the treatment of human brain tumors in Japan by BNCT, with some reported success (2).

In 1984, we began to compare boron distributions in mice bearing transplanted Harding-Passey melanomas after rapid and slow administration of monomer. Therapeutic concentrations of boron (>15 μgB/g) in tumors were observed in only one of the early slow administration experiments. Thin-layer chromatographic (TLC) analysis of the corresponding infusion solution, nominally a solution of monomer, revealed a slow-moving principal band that was later shown to correspond to $Na_4B_{24}H_{22}S_2$, the dimer (3) of $Na_2B_{12}H_{11}SH$. It was surmised that the monomer had undergone spontaneous oxidation during storage prior to infusion into mice. It was found thereafter that, while monomer and chemically synthesized dimer yielded similar boron concentrations when they were given rapidly intraperitoneally to mice, the dimer yielded higher boron concentrations in mouse melanoma and higher melanoma-blood boron concentration differences than did the monomer when each was infused slowly intraperitoneally for 8-9 days (4). When administered slowly this way, dimer also yielded therapeutic concentrations of boron in mouse mammary carcinoma (5). Table 1 is a summary of some boron distribution data to be published in reference 4.

Table 1: Average boron concentrations (μgB/g) in Harding-Passey melanoma and blood of female BALB/cJ (15-20g) mice at various indicates times after start of an 8-9 day intraperitoneal infusion of a sulfhydryl borane monomer or dimer. Concentrations are extrapolated to a total dose of 200 μg B per gram of body weight. Numbers of mice are in brackets.

Time after start of infusion (days)	Monomer ($Na_2B_{12}H_{11}SH$)			Dimer ($Na_4B_{24}H_{22}S_2$)		
	Melanoma	Blood	Cerebrum	Melanoma	Blood	Cerebrum
6	9 [5]	8 [5]	1 [5]	16 [5]	6 [5]	1 [5]
9	9 [14]	6 [14]	1 [4]	15 [8]	3 [9]	2 [9]
10	10 [3]	6 [4]	2 [4]	18 [4]	3 [4]	4 [4]
12	6 [5]	0 [5]	2 [5]	13 [5]	0 [5]	3 [5]

Studies have been started on the uptake of dimer into an intracerebrally implanted rat glioma (6). Boron levels in the rat glioma and in the mouse melanoma from slow intraperitoneal infusion of proportionately comparable amounts of dimer, are similar. However, after these slow infusions boron levels in rat blood are about as high as boron levels in rat brain tumor (Table 2).

Table 2: Boron concentrations in tissues of eight 2-3 month old male CDF rats after 7-9 days of continuous intraperitoneal infusion of sulfhydryl borane dimer, $Na_4B_{24}H_{22}S_2$. The average concentrations are extrapolated to the mean boron dose, that is, to 214 μg B per gram of body weight (gbw).

Rat No.	1	2	3	4	5	6	7	8	Average
Time (days)	9	9	9	9	7	9	9	9	8.8
Boron dose (μg B/gbw)	26	242	228	253	188	155	210	212	214
	Boron concentration (μg B per gram)								
Brain tumor	-	28	-	-	26	-	15	16	[21]
Whole blood	22	24	9	12	23	41	13	22	[22]
Blood plasma	42	41	16	24	46	-	24	45	[33]
Blood cells	7	7	3	1	11	4	2	5	[5]
Cerebrum	3	3	2	-	4	2	4	6	[3]
Liver	97	132	35	74	150	64	90	92	[94]
Kidney	53	283	176	255	250	220	247	185	[237]
Spleen	62	78	23	57	92	31	41	43	[54]
Heart	12	16	8	11	14	15	13	16	[13]
Skeletal muscle	6	8	3	5	9	6	5	6	[6]
Testis	18	20	9	11	16	-	13	14	[14]

Our observations on rat blood (Table 3) indicate that after ~9 days of slow infusion of dimer, most of the boron in blood is bound to plasma proteins. Electrophoresis of rat plasma proteins after prolonged intraperitoneal infusion of dimer, followed by detection of boron in the electrophoresis strip using a contiguous cellulose nitrate ionizing particle detector, shows little or no boron in alpha or gamma globulins, some boron in beta globulins, and much boron in albumin (Fig. 1). These results indicate that plasma exchange may be useful for lowering the blood boron concentration artificially prior to BNCT, to lessen damage to endothelial cells in normal brain tissue. Knowledge of the biochemical basis for the affinity of dimer to liver, plasma proteins, and tumors may eventually enable one to assess clinically the limits of acceptable toxicity from $Na_4B_{24}H_{22}S_2$ to patients with malignant brain tumors.

Table 3: Boron concentrations in various fractions of the blood of rats that had been killed immediately after 9 days of steady intraperitoneal infusion of $Na_4B_{24}H_{22}S_2$ to a cumulative dose of about 215 μg B per gram of body weight.

Boron concentration (μg B/g)	Rat		
	A	B	C
Whole blood	21.7	8.5	12.2
Blood cells	6.7	2.7	1.1
Blood plasma	42.4	15.5	23.8
TCA-precipitated plasma*	98.6	36.6	49.5
Non TCA-precipitated plasma*	0.7	1.0	1.1

*TCA = trichloroacetic acid

Observations of the behavior of mice during infusions suggest that the dimer may be more toxic than the monomer. Boron concentrations in mouse liver, but not in other mouse tissues, are about five times greater after 18-24 hours of intravenous infusion of dimer than of monomer (Table 4). Whether the affinity of dimer to tumor is related to its affinity to liver and whether dimer accumulation in the liver is the cause of its apparent toxicity, are questions that are under study at Brookhaven.

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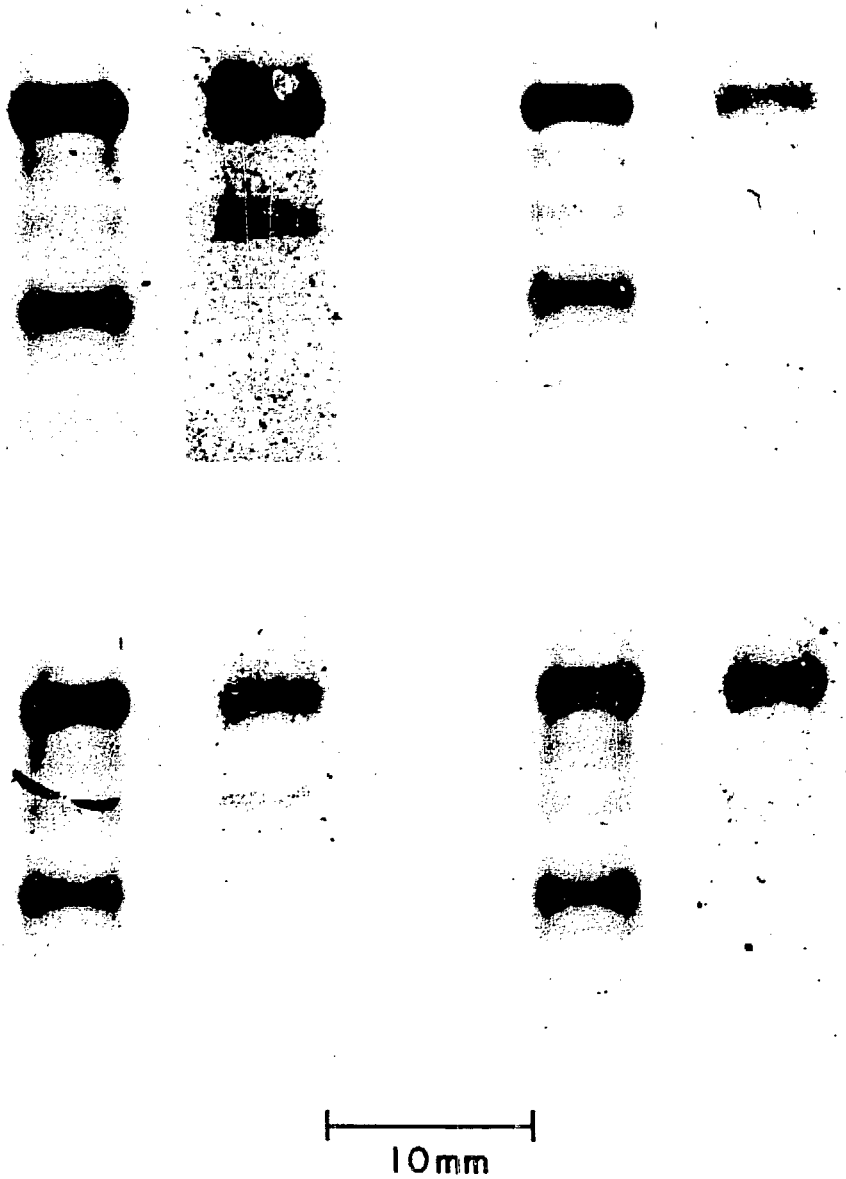

Fig. 1: Four pairs of matched plasma protein electrophoresis (left) and neutron-induced ionizing particle track detector (right) patterns. About 1 µl of plasma was applied to each cellulose acetate plate prior to electrophoretic separation of proteins at pH 8.8 in Tris-barbital buffer (Quick Quant, Helena Laboratories, Beaumont, Texas). The curved lines in the electrophoresis pattern, lower left, are cracks in the plate due to drying. Plasma samples were from four different rats after ~9 days of slow intraperitoneal infusion of dimer to a nominal total boron dose of ~200 µg B per gram of body weight.

Table 4: Average boron concentrations (μgB/g) in various tissues of BALB/cJ female mice bearing transplanted Harding-Passey melanoma after 18-24 hours of continuous intravenous infusion of sulfhydryl borane monomer or dimer. Concentrations are extrapolated to a total dose of 50 μg B/gram of body weight. Numbers of mice are in brackets.

Tissue	Monomer ($Na_2B_{12}H_{11}SH$)		Dimer ($Na_4B_{24}H_{22}S_2$)	
Melanoma tumor	9	[4]	9	[6]
Blood	18	[4]	13	[6]
Cerebrum	2	[4]	1	[6]
Liver	17	[4]	85	[6]
Kidney	18	[4]	17	[6]
Spleen	5	[4]	7	[6]
Skeletal muscle	5	[4]	2	[6]

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Medical and Biological Requirements for Boron Neutron Capture Therapy

R. Gahbauer, M.D.
Department of Radiology/Division of Radiation Oncology

J.H. Goodman, M.D.
Department of Surgery/Division of Neurologic Surgery

C. Kanellitsas, Ph.D.
Department of Radiology
and
N. Clendenon, Ph.D.
Department of Neurology
The Ohio State University Hospitals
410 West 10th Avenue, N-082A Doan Hall
Columbus, OH 43210
and
J. Blue, Ph.D.
NASA-CCF Cyclotron, Cleveland, OH 44135

In conventional radiation therapy, tumor doses applied to most solid tumors are limited by the tolerance of normal tissues. The promise of Boron Neutron Capture Therapy lies in its potential to deposit high doses of radiation very specifically to tumor tissue. Theoretically ratios of tumor to normal tissue doses can be achieved significantly higher than conventional radiotherapeutic techniques would allow. Effective dose distributions obtainable are a complex function of the neutron beam characteristics and the macro and micro distributions of boron in tumor and normal tissues.

Doses are constituted by the boron dose ^{10}B (n,alpha)^{7}Li, fast neutron dose, the $^{14}N(n,p)^{14}C$ reaction, and the H(n,gamma)D reaction as well as contributions due to radiation from the incident beam.

For the purpose of this discussion, the doses were divided into the boron dose contribution, high-LET contribution (fast neutron and proton), and the gamma contribution. Only effective doses are used whereby the physical dose was multiplied by the appropriate RBE [fast neutron RBE = 2, $^{14}N(n,p)^{14}C$ RBE = 2, ^{10}B (n,alpha)^{7}Li RBE = 2.5].

To relate the dose distributions with their high- and low-LET constituents to the experience of clinical radiation therapy and biology, I have attempted to replot the data as presented by Dr. Fairchild in a format more similar to what radiation oncologists and biologists are used to interpret.

Table I gives effective doses (cGy x RBE) normalized to 2000 cGy in tumor for the thermal, epithermal, and the 2-KeV beam, whereby for each beam doses were calculated separately for a tumor presumed to be at 4cm to

Table I. Effective RBE Doses Normalized to 2000 cGy in Tumor

	Tumor (B 35μg)		Normal Tissue (B 3.5μg)	
Thermal				
4cm	2000	1529 Boron 149 High-LET 322 gamma	1680	662 Boron 545 High-LET 472 gamma
7cm	2000	1361 Boron 136 High-LET 503 gamma	5032	1985 Boron 1632 High-LET 1414 gamma
Epithermal				
4cm	2000	1332 Boron 422 High-LET 246 gamma	1262	132 Boron 880 High-LET 250 gamma
7cm	2000	1351 Boron 345 High-LET 304 gamma	2073	203 Boron 1450 High-LET 420 gamma
Bilateral Ports				
7cm	2000	1351 Boron 345 High-LET 304 gamma	1052	99 Boron 756 High-LET 200 gamma
2-KeV Beam				
4cm	2000	1612 Boron 97 High-LET 291 gamma	573	171 Boron 97 High-LET 301 gamma
7cm	2000	1565 Boron 80 High-LET 355 gamma	1067	250 Boron 142 High-LET 440 gamma
Bilateral Ports				
7cm	2000	1565 Boron 80 High-LET 355 gamma	568	133 Boron 75 High-LET 233 gamma

Maximum normal tissue doses were calculated for tumor doses at 4cm and 7cm depth respectively for both tumor and normal tissues doses. The contribution of the boron dose, high-LET, and gamma doses were given for epithermal and 2-KeV beams - calculations were also performed for treatments given through bilateral ports. Doses are estimates based on Dr. Fairchild's data (1).

7cm depth. Boron ratios of 10:1 were assumed, and the dose to the tumor was to be 2000 cGy x RBE total. The maximum total dose occurring anywhere in normal tissue was then calculated, and for both tumor doses and normal tissue doses the constituent boron, high-LET, and gamma doses were given. It is apparent that a tumor at 7cm can not be treated with the thermal beam. However with epithermal and 2-KeV beams the treatment can be delivered by parallel opposing ports, which would further reduce the maximum normal tissue dose significantly with therapeutic gain factors close to 4 obtainable for the 2-KeV beam using parallel opposing portals. Figures 1, 2, and 3 display these results in graphic form. From Table I the following conclusions can be drawn. The treatment of deep tumors is not possible with thermal beams, whereas for both epithermal and 2-KeV beams impressive therapeutic gain factors can be obtained for both superficial and deep tumors if parallel opposing fields are used. The therapeutic gain for the 2-KeV beam approaches 4, which has to be compared to gain factors in conventional therapy of around one. The effective dose to normal tissues can further be reduced by fractionated therapy. Since the high-LET component in the epithermal beam is rather high, fractionation will be less yielding than in the 2-KeV beam, where fractionation may be of quite considerable advantage due to the rather high gamma contribution to the total dose. One may further anticipate that with epithermal and 2-KeV beams the irradiation will not require scalp reflection at the time of irradiation, which would significantly facilitate the clinical applicability of the technique.

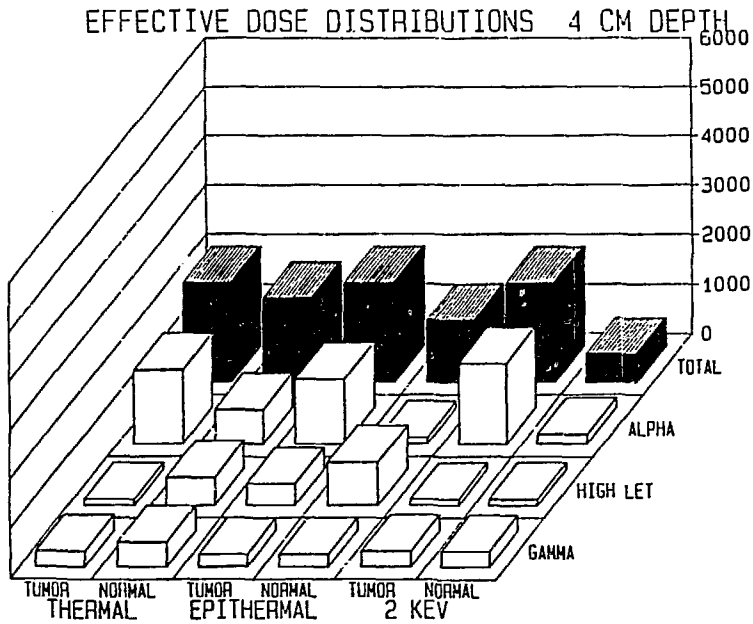

Fig. 1. Graphic demonstration of data in Table I normalized to a 2000 cGy X RBE tumor dose at 4cm depth.

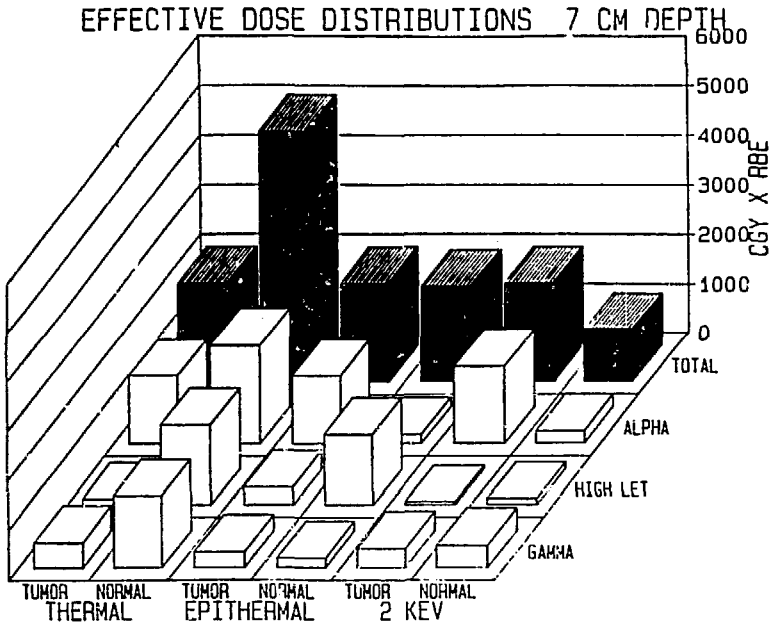

Fig. 2. Graphic demonstration of data in Table I normalized to a 2000 cGy x RBE tumor dose at 7cm depth.

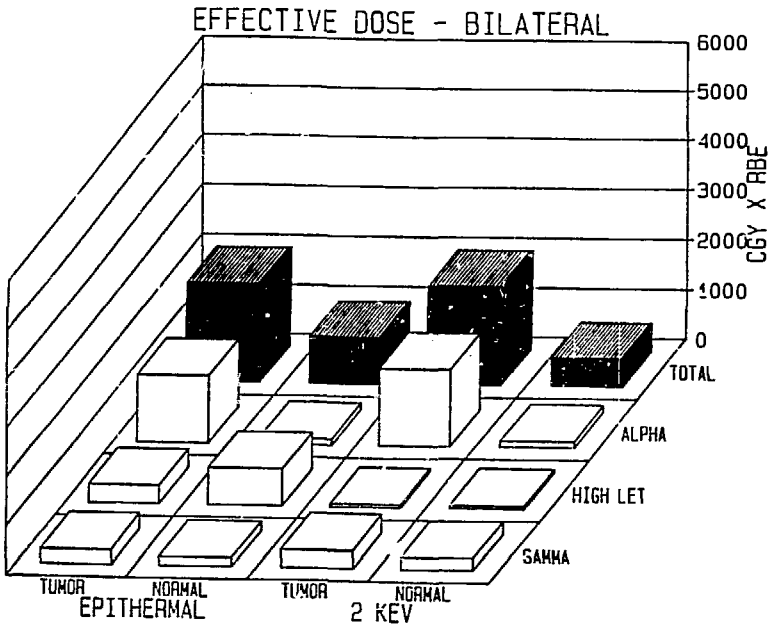

Fig. 3. Graphic demonstration of data in Table I normalized to a 2000 cGy x RBE tumor dose using bilateral radiation portals.

From these theoretical calculations, it may appear that Boron Neutron Capture Therapy may be a uniquely effective treatment modality for high-grade astrocytomas on its own. If we consider the mechanisms of failure of treatment methods as I understand them (Table II), the limitation of external radiation therapy is due to the limited normal tissue tolerance. The mechanism of failure for interstitial radiation therapy is probably primarily due to micro-extension of the tumor not appreciated at the time of the procedure or again in our ability to deliver high enough a dose into the normal brain tissues where such micro-extensions may penetrate. The success of Boron Neutron Capture Therapy on the other hand depends very critically on the micro-distribution of boron in tumor tissue due to the cellular concentration of the boron dose. One might speculate that due to the very selective deposition of dose to tumor cells with BNCT, combinations of interstitial radiation and Boron Neutron Capture Therapy may be worth considering.

Table II. Mechanisms of Failure

External Radiation:	Normal tissue tolerance
Interstitial Radiation:	Microextensions of tumor
Boron Neutron Capture:	Microdistrubution in tumor

In order to utilize Boron Neutron Capture Therapy alone or in combination with other radiations, the radiation tolerances have to be determined very carefully to arrive at maximum benefit. The beams have to be optimized to reduce normal tissue radiation, whereby the reduction of high-LET components is more important than the reduction of low-LET components. The tolerance of normal tissues can be improved by fractionation, particularly where the high-LET components are sufficiently low. Unique problems may be further encountered in Boron Neutron Capture Therapy should the treatment be delivered in just one single fraction. The intense dose deposition and destruction of tumors may lead to unforseen problems and may require a fractionated approach. As Dr. Soloway had pointed out previously, the simultaneous use of different classes of boronated compounds for better micro-distribution should be investigated.

Similarly, the use of combinations with other radiations (interstitial ?) could be considered since the high dose volume in BNCT is so uniquely concentrated in tumor cells with some margin of normal tissue tolerance. There are important further questions remaining such as the advisability of tumor debulking before or after radiation which need to be addressed by the working groups.

Boron Neutron Capture Therapy remains a fascinating concept with the potential of providing a single and uniquely effective treatment method. However, we must not lose sight of the fact that the ultimate goal is the better treatment of glioblastoma multiforme, which may require the combination of various treatment approaches to eliminate the possible mechanisms of failure of the individual components.

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CLINICAL ASPECTS OF BORON NEUTRON CAPTURE THERAPY

J.H. Goodman, M.D.
Department of Surgery
Division of Neurologic Surgery

R. Gahbauer, M.D.
Department of Radiology
Division of Radiation Oncology
and
N. Clendenon, Ph.D.
Department of Neurology
The Ohio State University Hospitals
410 W. 10th Avenue, N-950 Doan Hall
Columbus, OH 43210

The concept of selective tumor sensitization followed by cytodestruction using external energy sources offers a method of controlling malignant brain neoplasms. Clinical applications to date have resulted in inconclusive results regarding real benefits of boron neutron capture therapy (BNCT) (6). Recent advances in neutron beam technology and development of third-generation boron-containing compounds provide a basis for continued investigation as to the actual potential of BNCT for clinical applications. Several factors must be considered in developing clinical protocols, and clinical implementations will depend on what best combination of treatment modalities is forthcoming.

A sequence of investigations to confirm proof of concept, satisfy safety and toxicity considerations, and establish feasibility of treating large numbers of patients is in order.

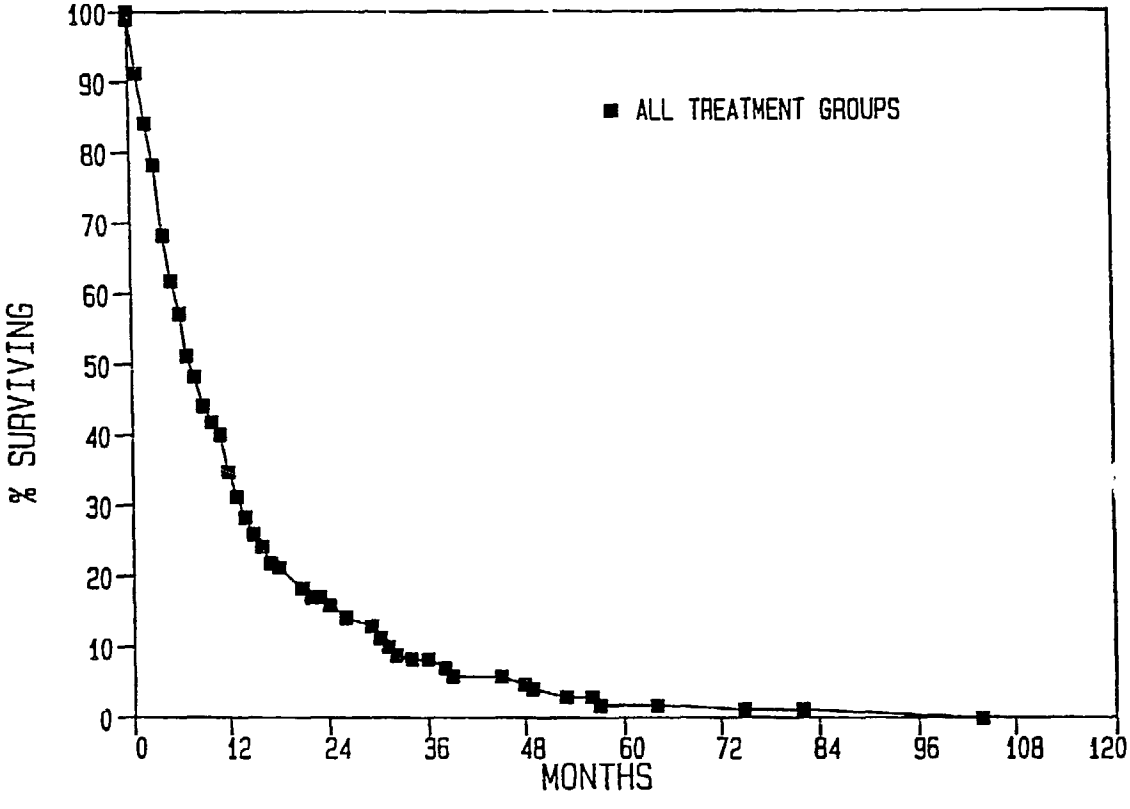
Presently available boron-containing compounds show an affinity for proliferating tissues and may selectively bind to tumor. The mechanism of this binding is unclear. Regardless of the mechanisms involved, treatment effectiveness depends on tissue responses following neutron irradiation. Favorable results are claimed in a series of patients treated by Hatanaka with several long-term survivors (3). Careful consideration of this data is in order and additional in vitro and in vivo testing is advisable before embarking on extensive clinical trials. Several animal brain tumor models are available for testing localization of capture agents that will assist in selecting treatment parameters (2,4,5,7). Even though these models may not be directly comparable to a human glioblastoma, the information derived from such testing is essential in determining dosimetry. The ultimate proof of concept will be in clinical testing and optimum parameters need to be established for this phase of investigation.

Toxicity testing of treatment modalities is complicated by the binary nature of this technique, conventional assessment of systemic toxicities and maximum normal tissue tolerances need to be established for each

treatment component as well as their combined effect. Neuropathologic studies of 14 patients following BNCT have been reported (1). Of particular importance is the coagulation necrosis of all parenchymal central nervous system elements and blood vessel changes, which become more prominent with the passage of time. The progressive endothelial damage noted warrants investigation in large animals, including primates, to establish upper limits of normal tissue tolerances to prevent potentially harmful side effects of BNCT.

Patients with malignant astrocytomas (glioblastoma multiforme, Grade III astrocytoma) have a uniformly fatal outcome. The natural history of this disease is established. There have been only limited improvements in survival statistics with present-day therapies consisting of surgery, radiation, and chemotherapy (8). Long-term follow-up is available in a series of 187 patients treated between 1969 and 1980 at Ohio State University Hospitals with surgery followed by a randomized protocol of radiation and chemotherapy. Admission criteria for this study were established by the National Brain Tumor Study Group and required histologic confirmation of a malignant primary tumor of the central nervous system. From the time of initial diagnosis 178 patients expired within 10 years. (Figure 1).

Fig. 1. 178 Patients - all fatalities.



Nine patients are currently living and of this group all have survived more than 5 years and 3 have survived greater than 10 years. (Table I)

Table I. Patients with diagnosed CNS malignancies surviving at the time of this report. Months are from time of initial diagnosis. Age is current age.

PATIENT	AGE	DIAGNOSIS	MONTHS
DS	26	Anaplastic astrocytoma	65
DI	52	Anaplastic astrocytoma	68
FP	36	Glioblastoma	69
LS	36	Anaplastic astrocytoma	74
BW	36	Malignant glioma	78
GM	27	Anaplastic astrocytoma	110
LZ	35	Astrocytoma, Grade III	134
ED	67	Pleomorphic glioblastoma	140
KT	33	Astrocytoma, Grade IV	153

This series represents 13 greater than 5-year survivals and 3 greater than 10-year survivals out of 187 patients.

This tumor category needs improved treatment techniques and, if the potential for significant palliation can be established experimentally with BNCT, Phase I and Phase II clinical trials are justified. Treatment protocols will depend on data presently being generated. A clinical facility in close proximity to a suitable neutron source is desirable to improve logistics related to transportation. Epithermal beams capable of delivering adequate fluences through intact scalp and skull may negate the need for craniotomy and should be considered in developing treatment plans. Conventional tumor therapy which includes tissue diagnosis and debulking by craniotomy are consistent with boron neutron capture therapy. Imaging technology and stereotactic surgical techniques are providing means of early diagnosis of small tumors, often in surgically inaccessible areas which favor development of treatment techniques not requiring craniotomy. It is likely a number of patients with small surgically inaccessible tumors will meet histologic inclusion criteria and should be allowed for. Surgical manipulations in a reactor area may increase morbidity and should be avoided if possible. If a determination is made that craniotomy is essential for effective neutron dose delivery, whatever means necessary to achieve this can be carried out including multiple craniotomies and prolonged anesthetic times as needed. Risk-benefit ratios will be established based on results. Neurodiagnostic imaging to monitor

clinical progression includes computed axial tomographic (CAT) and magnetic resonance imaging (MRI) scans. The Karnofsky performance scale defines a numerical functional level which is also useful. Prolongation of useful survival is the ultimate goal, and statistical analysis of mortality data as compared to historical controls will determine effectiveness during initial clinical studies.

SUMMARY

Boron neutron capture therapy is potentially useful in treating malignant tumors of the central nervous system and is technically possible. Additional in vitro and in vivo testing is required to determine toxicities, normal tissue tolerances and tissue responses to treatment parameters. Adequate tumor uptake of the capture agent can be evaluated clinically prior to implementation of a finalized treatment protocol. Phase I and Phase II protocol development depends on results of ongoing laboratory testing, new compound development, clinical pharmacokinetic studies and neutron beam development.

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II. COMMITTEE PRESENTATIONS AND DISCUSSIONS

V.P. Bond: First Dr. Wambersie will summarize his overall views of the Workshop, and include some results of the deliberations of the three Committees. The Chairman of each Committee will then comment, following which the floor will be open for discussion, which we highly encourage.

A. Wambersie: First of all, I would like to thank Drs. Bond and Fairchild for their invitation to participate in this very stimulating Workshop on neutron capture therapy (NCT) and to present the summary of the deliberations. Since my personal involvement is not in the field of neutron capture therapy but mainly in fast neutron therapy, my information may be incomplete and, beforehand, I would like to ask your indulgence for any inaccuracy or misinterpretation in my concluding remarks.

The main objectives of this Workshop, as Dr. Fairchild has indicated, can be summarized in the following way. Neutron capture therapy was initiated in the United States, in the early 1950s and 1960s, at Brookhaven and at the MIT, about 20 patients being treated at each facility. The results were considered disappointing (especially because of severe complications) and the clinical programs were stopped. Nevertheless, some research continued in the U.S. On the other hand, more recently (about 1965), exciting results obained with NCT were reported, from Japan, by Dr. Hatanaka. These results, which were presented yesterday by Dr. Sweet, are by far the best ever obtained for glioblastomas. The dilemma that we have to face is the following: do we have today new data and new technical possibilities which could explain the present success of the Japanese physicians compared with the relative failure of the U.S. programs 20 years ago? Do these new data provide a sufficient guarantee and ethical justification for initiating new clinical programs in the U.S.? In addition to this main aspect of the problem, there is another one that we have to consider. Existing reactors, at least those in the U.S., could rather easily be used for NCT if a clinical program were to be adopted. Furthermore, a large amount of work has been done in physics, technology, and chemistry (new compounds) in order to be prepared to start, eventually, NCT programs under better technical conditions. I will start with some general considerations and briefly discuss the relative position of NCT with respect to the other radiation therapy techniques. I think it is important in the present Workshop not to focus only on a single technique but to compare constantly the relative merits and weaknesses of the various radiotherapy techniques.

Neutron Capture Therapy and Other Radiotherapy Techniques. One of the reasons which contribute to making NCT so attractive in its rationale is that it deals with the problem of physical selectivity at the cellular level. With conventional external-beam therapy techniques, one tries to achieve the best physical selectivity, or the best dose distributions, at the "gross tissue" level. That is, one tries to maximize the dose inside the target volume relative to the dose to the normal tissues outside the target volume. The target volume (ICRU Report 29) contains the tumor volume, which consists mainly of tumor cells, and the security margin, which consists (by definition) of normal cells and blood vessels and only a small proportion of cancer

cells (i.e. "subclinical disease"). Therefore, even in a perfectly planned external-beam treatment, the normal cells within the target volume receive a dose equal to the dose to the cancer cell population. If, in the present context, one defines the physical gain factor (PGF) as the ratio between the dose to the cancer cells and the maximum dose to the normal cells, the PGF cannot be higher than unity in external-beam therapy. Other approaches then have to be used to improve the therapeutic efficiency, such as fractionation, sensitizers, etc., except of course in the infrequent cases where the intrinsic radiosensitivity of the cancer cells is higher than that of the surrounding normal cells (e.g. seminomas).

With NCT, a physical gain factor, at the cellular level, higher than 1 can be achieved to the extent that one could administer a boronated compound with a specific affinity for the cancer cells, whatever the mechanism involved. The maximum PGF for a given boron compound is then the ratio of the boron concentration in the cancer cell and that in the normal cell population. However, since the dose to the cell population depends not only on the boron concentration but also on the thermal neutron flux density at the point of interest, part of the PGF could be lost if the neutron irradiation is not optimal. This is the justification for the great efforts made by physicists and engineers to improve the neutron irradiation characteristics. As an example to illustrate this point, let us consider a tumor extending from 2 to 6 cm in depth. For a single thermal neutron beam, if the thermal neutron flux is normalized to 1.00 at 6 cm depth, it will be 2.5 at 4 cm depth (center of the tumor volume), 5 at 2 cm depth, and more than 9 at the surface (Fig. 1). Therefore, with a boronated compound for which the ^{10}B concentration is 3 times as high in cancer cells as in normal cells, the PGF will no longer be 3 but less than 1/3, and the highest dose will be reached at the surface (scalp). In the first NCT clinical applications, the poor depth doses with thermal neutrons (Fig. 1), combined with the rather low specific affinity (<1?) of the first-generation boronated compounds for cancer cells, would logically explain, a posteriori, the clinical failures and complications.

There are of course other techniques which aim at achieving selectivity at the cellular level: In radiation therapy, one of the best examples is the use of iodine-131 in the treatment of thyroid misfunction or cancer; and chemotherapy techniques in general try to use chemical compounds which selectively seek the cancer cells and either are toxic themselves or carry a toxic agent. In that respect, the research carried out within the NCT programs to improve the boronated compounds could have interesting applications in cancer therapy in general. Conversely (and this is probably more realistic), the large amount of work performed within the field of chemotherapy could have applications in NCT. Much energy, as well as financial investment, has been put into that field (see e.g. the area of monoclonal antibodies).

NCT, however, keeps two specific advantages since it consists of two parts, injection of the boronated compound and neutron irradiation, which are independent and can be improved separately and combined in different ways. First of all, one need not care about the uptake of the boron compound in organs or sites that will not be included in the neutron irradiated volume (e.g. bone marrow, intestine, but also in some cases liver, kidney). The boronated compounds are in general not toxic by themselves. Second, the

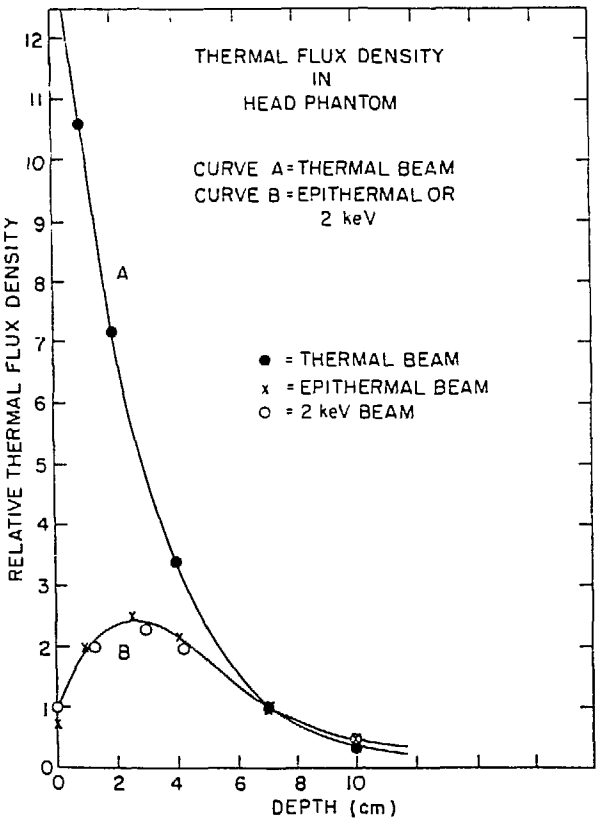

Figure 1.
Relative thermal neutron flux density generated in tissue-equivalent phantom head by a thermal beam, an epithermal beam, and a 2-keV beam (normalization is made at 7 cm depth). As clearly illustrated, it is difficult to treat, with a single thermal neutron beam, a tumor located at a depth of more than about 4 cm. (From Fairchild and Bond, 1985.)

optimal time schedule can be selected, i.e. the time interval between administration of the boronated conpound and neutron irradiation. As a matter of fact, the boron concentration does not vary in parallel in cancer cells and in blood or normal cells.

The Boronated Compounds. It is trivial to say that any NCT program rests on the assumption that it is possible to incorporate ^{10}B selectively into cancer cells compared with normal cells. I purposely do not say into tumor tissue compared with normal tissues. The boronated compounds must be incorporated into all the cancer cells, and if 1%, 0.1%, or even a smaller proportion of the clonogenic cancer cells do not incorporate boron, local tumor control could not be achieved. Incorporation of boron into all the cancer cells is then really a key problem, and all the efforts to improve, e.g. the technique of neutron irradiation, or the dosimetry, become meaningless if the problem of uniform boron incorporation is not adequately solved. One should at this point distinguish brain glioblastomas and other tumor sites or types.

Glioblastomas. As far as glioblastomas are concerned, they present a unique treatment opportunity related to the well-known fact that the blood-brain barrier is destroyed at the level of the tumor. In this particular -- and unique -- situation, some assum tions seem reasonable:

(a) The dose to the skin, subcutaneous tissue, and even the bone is not excessive (see below and Figures 1 and 3) if boron activation is done with epithermal neutrons (or 2-keV neutrons).

(b) The ^{10}B concentration in the normal brain cells is low (close to zero?).

(c) The tissue at risk (critical normal tissue) is the endothelial cell population. This could be deduced from the presentation of Dr. Sweet during this Workshop and from the histopathological observations he reported.

(d) Knowing the ^{10}B concentration in the blood, and taking into account the track length of the alpha particles, one can assume that the average dose to the nuclei of the endothelial cells is about 1/3 (30%) of the absorbed dose inside the blood (see the presentations of Drs. Brownell and Zamenhof).

The last set of information needed is the boron concentration in the individual cancer cells, and this information seems to a large extent to be missing. In several laboratories "average" boron concentrations have been measured, e.g. in blood, brain, tumor, and other tissues. It is of course interesting to compare the relative distribution of various boronated compounds at a macroscopical scale (e.g. in μg ^{10}B per g tissue, see Table I below). As a matter of fact, this type of research helps in selecting the most promising compounds. However, the most relevant information remains the boron distribution at the cellular level. To illustrate this point, a comparison with the problem raised by hypoxic cells in radiation therapy may be of interest. It is well known that if a small proportion (1%, 0.1%, or less) of viable cancer cells remain hypoxic, they will cause local failure. If one measured the oxygen concentration in the tumor tissue with an oxygen probe (e.g. 1 mm size), one would get a kind of "average O_2 concentration," but it would be impossible to detect 1% or 0.1% hypoxic cells.

As far as NCT is concerned, several methods have been developed and applied to study the boron distribution. In particular, the potential benefit of new methods such as CT and NMR has been discussed during this Workshop. Autoradiographic methods have been used and have produced interesting data but, although they can provide information not obtainable by other methods, for the present purpose they suffer from the same weaknesses as histological methods in general: only samples of the tumor are analyzed, and because even in a given section it is difficult to check each cell, 1% of them could easily escape even a careful screening. One must keep in mind that 1 mm^3 of tumor tissue contains about 10^6 cells, that about 1% of them can be considered as clonogenic cells, and that a few surviving cells could produce a recurrence.

There is at present no definite evidence of uniform boron uptake by all individual cancer cells. Since appropriate techniques for obtaining this information are not likely to be available in the near future, one has to search for indirect evidence, and investigations on animal tumors appear to be necessary before initiating new clinical programs. As pointed out by Dr. Bond, animal tumors are often very poor models for simulating human tumors. However, several tumor types could be studied and the conclusions combined. In addition, the study of different tumor sizes could be useful: small tumors with little necrosis, large tumors with vast necrotic areas, etc.

One possible approach to checking the hypothesis of uniform boron distribution is for example to compare the TCD-50 (tumor control dose for 50% of

tumors) actually observed with that expected assuming uniform ^{10}B uptake. A second type of experimental check to perform before going into the clinical program is to evaluate the tolerance to the proposed treatment: this implies the toxicity of the boronated compounds, the effect of the neutron irradiation, and mainly the combination of both. In this respect, past experience can help to identify the tissues or cell populations at risk (such as endothelial cells) and to orient the tolerance studies. These are the two main types of experiments that should be done before initiating a new NCT clinical program.

If the experimental data indicated a lack of uniform distribution of the boronated compounds into the clonogenic cancer cells, only palliative results could be expected, and the improvement in survival or in quality of life would then depend on the proliferation rate of the surviving cells (probably modified by the irradiation) or the doubling time of the tumor.

Regarding the choice of boronated compounds, as indicated by Dr. Fairchild, a tumor to blood ratio of 6 has been measured for the second-generation compounds. From this value, a dose ratio of more than 10 could be derived between the tumor cells and the endothelial cells ("average values," as discussed above). Sodium mercapatoundecahydrododecaborate ($Na_2B_{12}H_{11}SH$), preferably the dimer form, seems to be today the best compound to use.

Tumors Other Than Glioblastomas. The problem is still more fascinating from a theoretical point of view, since it implies the introduction of boronated compounds into the cancer cells through specific metabolic pathways, or the use of carriers with a specific affinity for some types of cancer cells. For example (see Table I):

(a) p-Boronophenylalanine could be used for the treatment of melanomas, as reported by Dr. Mishima.

(b) Porphyrins appear to be incorporated specifically by many tumors and therefore are at present very promising.

(c) Antibodies (monoclonal or polyclonal) could be used as carriers of a boronated compound. As appeared during the discussion, some problems still remain but, as indicated above, NCT can take profit from the huge amount of effort and investment made in this field.

Table I. The Boronated Compounds
(From R.G. Fairchild, Recent Advances in Neutron Capture Therapy)

Second-generation	Third-generation
$Na_2B_{12}H_{11}SH$	p-boronophenylalanine (BPA)†
dimer form: $Na_4B_{24}H_{22}S_2$*	porphyrins antibodies

*Tumor uptake: up to 25 μg ^{10}B per g tissue; tumor/blood ratio: up to about 6.
†Tumor uptake: up to 30 μg ^{10}B per g tissue; tumor/blood ratio: up to about 10.

Different boronated compounds could be combined with the aim of adding the positive effects while diluting the toxic effects. This approach is probably less promising in theory than a combination of drugs in chemotherapy (different normal tissues at risk), but little has been done in that direction up to now.

In summary, although the field is most promising, some work has still to be done before clinical applications could be started. This implies that clinical applications of NCT for tumors other than glioblastomas can not be expected in the near future.

The Neutron Irradiation. With regard to the neutron irradiation, two main problems have to be considered: dose distribution and time factor.

Dose Distribution. The absorbed dose with NCT depends on the boron concentration, but also on the thermal neutron flux at a given point. From simple analysis of the depth-dose curve, it appears difficult to treat, with a single thermal neutron beam, a tumor located at a depth of more than about 4 cm (Fig. 1). For a more deeply seated tumor, a more penetrating beam is needed, and general agreement seems to have been reached to recommend epithermal or 2-keV neutrons (Figs. 1 and 2). In addition, for deep-seated tumors, the use of more than one field should be considered, and parallel opposed fields (Fig. 3) provide better thermal neutron flux distributions (eventually the contributions of each field could be unequally weighted). The use of a large single field is perhaps too simple a technique, although it is recognized that the situations are not identical in NCT and in conventional external photon beam therapy.

More generally, as rightly pointed out by Dr. Gahbauer, all possible approaches should be tried in order to improve or optimize the thermal neutron flux distribution throughout the brain (i.e. selection of the best combination of the number, orientation, size, shape, and relative weight of the irradiation beams depending on the size, depth, and location of the tumor). As a matter of fact, as has been proven in conventional radiation therapy, even a modest improvement in the dose distribution can, in some situations, bring a measurable clinical benefit.

In NCT, irradiation consists of (i) the dose produced from boron activitation which is high-LET radiation and is absorbed selectively by the cancer cells that have incorporated the boronated compounds, and (ii) a rather uniform dose distribution throughout the target volume and surrounding normal tissues which cannot be avoided and consists of a high-LET and a gamma component. The existence of the gamma component has raised some concern. However, one must keep in mind that it is accepted practice, in treating glioblastomas, to perform whole-brain gamma irradiation, at least as part of the treatment. One of the practical consequences of the presence of the gamma component is that it could influence the fractionation scheme (see below).

Time Factor. Since the main part of the dose to the cancer cells is delivered with high-LET radiation, a treatment consisting of a single fraction could be considered, as pointed out by Dr. Bond. The advantages are obvious both from a practical point of view (cost, comfort of patients, etc.) and from a radiobiological point of view (proliferation of cancer cells during protracted irradiation). The advantages of fractionated (or protracted) irradiation are obvious as far as the gamma component is concerned (but this

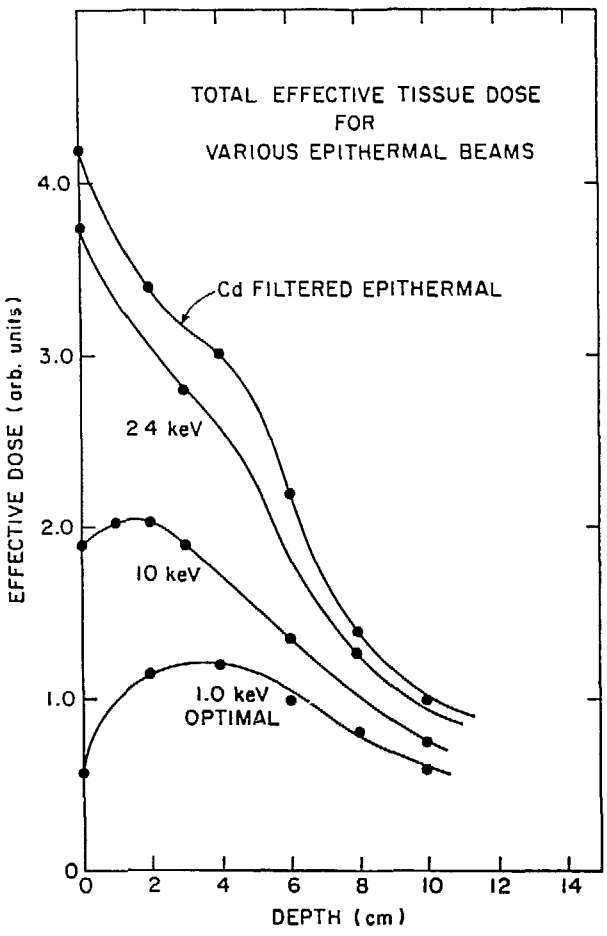

Figure 2.
Study of the relative merits of different epithermal beams for NCT. Comparison of the depth-dose curves for Cd-filtered epithermal and 24-, 10-, and 1.0-keV neutrons. The "effective dose" (ordinate) is obtained by multiplying the absorbed dose by the appropriate RBE values: 2 for fast neutrons and the $^{14}N(n,p)^{14}C$ reaction, and 2.5 for the $^{10}B(n,\alpha)^{7}Li$ reaction. (From Fairchild, this Workshop.)

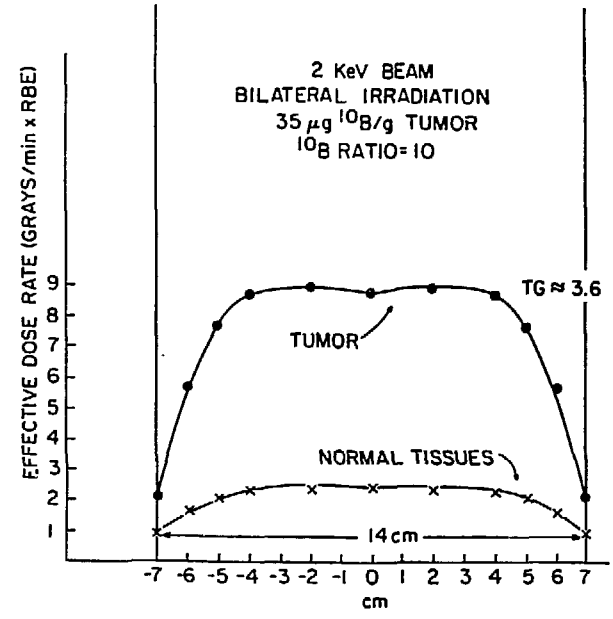

Figure 3.
Effective dose rate distribution, throughout the brain, for an irradiation consisting of two parallel opposed fields (14-cm separation, 2-keV neutrons). This representation is probably more meaningful, from a radiation therapy point of view, than a single-beam depth-dose curve. A therapeutic gain of about 3.6 is achieved for a boron concentration ratio of 10, which is probably a rather optimistic hypothesis. However, with a pessimistic hypothesis of a boron concentration ratio of 3 for glioblastomas, the therapeutic gain is still 1.5 to 2 (depending on the situation and the method of evaluation). (From Fairchild, this Workshop.)

is only a rather small part of the total dose). However, there could be an additional argument which is specific to NCT: fractionated irradiation could reduce the risk of non-uniform boron distribution. As a matter of fact, the blood supply in the tumor is usually insufficient, it varies with time from one part of the tumor to another, some cells are too far from the capillaries, etc.

This evokes some similarity with the problem encountered in attempts at selective killing of hypoxic cancer cells. For example, with Misonidazole used as a sensitizer, the gain factor can reach about 3 for cells irradiated in vitro and is still as high as 1.8 in animal tumors. Nevertheless, the results of most of the clinical trials are not convincing (except maybe the recent data from Overgaard). Regarding hyperbaric oxygen (HBO), the clinical trials conducted in the United Kingdom indicate that the best results were obtained when combining HBO with conventional fractionation: 20 fractions in Glasgow, 27 in Mount Vernon (although HBO results in the highest difference when a small number of large fractions are used, but the control group of patients irradiated "in air" has the worst results).

In conclusion, there seems to be agreement (mainly from radiobiological agruments) in favor of fractionated irradiation, but there is, at present, little information about the optimal fractionation modality (several fractions separated by a few hours?).

In Conclusion: The situation we have to face today in neutron capture therapy (NCT) has some similarity to the situation encountered several decades ago with fast neutron therapy. Between 1938 and 1943, external beams of fast neutrons were applied in cancer therapy, by Stone at Berkeley. The results of these first applications were considered to be disappointing, mainly because of the late complications, and the technique was abandoned (Stone, 1948). Later, careful radiobiological investigation, carried out especially in the United Kingdom (Gray, Thomlinson, and others), led to the conclusion that fast neutrons (and in general high-LET radiations) could be of interest in cancer therapy. The rationale was initially the existence of hypoxic cells and the "oxygen effect" (OER). However, because of the negative results reported by Stone, it appeared to be essential, before starting a new neutron therapy program,

(a) to identify the reasons for the initial failure;

(b) to be sure that all factors or parameters responsible for the initial failure had been improved and could be controlled; and

(c) to investigate as carefully as possible the tolerance of the new treatment modality.

In fact, after a long and systematic radiobiological program, neutron therapy was started at the Hammersmith Hospital in 1970, and a few years later at several other centers. Some technical problems (e.g. need for increasing neutron energy for better beam penetration) were progressively solved, and at present fast neutron therapy has been used at about 20 centers throughout the world. It is now accepted among the other radiotherapy techniques.

Coming back to neutron capture therapy, several factors that could explain the previous failure have been identified and have now been improved: i.e. the poor penetration of the thermal neutrons and the poor selectivity of the first generation of boronated compounds for the cancer cells. Today epithermal neutron beams are available and their depth doses are quite

satisfactory. New boronated compounds have been evaluated and have sufficient selectivity for the glioblastoma cancer cells. In addition, active research is being carried out in that direction, and new compounds are continuously being investigated.

Therefore, there is no scientific or ethical reason for delaying a new clinical program on NCT for glioblastomas, provided that the two series of pretherapeutic radiobiological experiments mentioned above give positive conclusions. They should indicate (i) that the boronated compounds have uniform distribution in all the cancer cells in experimental tumors, and (ii) that the planned therapeutic modality does not exceed the tolerance of the normal brain in animals. In addition, it is self-evident that all the information that could be derived from past clinical experience in the U.S. and Japan should be used for improving the treatment conditions.

Nevertheless, several problems remain to be solved:

(a) Should NCT be delivered in a single session or in several fractions (selection of the optimal fractionation scheme)?

(b) Should NCT be used alone or in combination with chemotherapy or with another radiotherapy technique? (In fast neutron therapy encouraging results have been obtained with neutron beams used as booster only.)

(c) Suggestions were made for combining NCT with "low dose rate" interstitial therapy (using iodine-125 seeds).

Only clinical experience could answer these questions, since the available biological systems are poor models for solving these types of problems. However, as pointed out on several occasions during this Workshop, the historical series on glioblastoma gave such poor results, whatever the technique used (average survival about 18 months), that any improvement in the results would be quickly detected.

It is the hope of such improvements that we would like to formulate at the end of this Workshop.

V.P. Bond: As I interpret what you say, Dr. Wambersie, if the appropriate animal experiments are carried out to test toxicity, efficacy, and fractionation schedules, and these are favorable, you would then be in favor of a clinical trail.

A. Wambersie: Pilot studies have to be performed before randomized clinical trials could be initiated.

V.P. Bond: I now call on the Chairman of the Medical Committee, Dr. Gahbauer.

R. Gahbauer: I would like to express my thanks for the input from the members in our working crew. I have no major points to add to Dr. Wambersie's summary of our discussions.

V.P. Bond: Next we hear from the Chairman of the Radiobiology Committee, Dr. Rockwell.

S. Rockwell: I, too, have very little to add. Dr. Wambersie has covered very well the things said in the Radiobiology Committee meeting,

probably reflecting the fact that he is as good a radiobiologist as he is a radiotherapist. I think we all agreed on the need for some more good animal data, showing the efficacy of current compounds in improving the cure of a variety of tumors over that achievable by neutrons alone, and on the need for some good pharmacology studies of the current compounds in animals and people, and on the need for studies of normal tissue tolerance. I would thoroughly expect, on the basis of what we have seen here, that the results of these studies would be most encouraging and that we would see clinical trials of this modality in the future.

V.P. Bond: We now hear from Dr. Brugger, the Chairman of the Neutron Source Committee.

R.M. Brugger: From what we have heard at this meeting, our Neutron Source Committee concludes one would like to have available at the cancer a fluence of about 2.5 to 5 x 10^{12} neutrons/cm^2. This should be delivered in 30 to 60 minutes, and it might be fractionated. The beams should be of intermediate energy neutrons, low in fast neutrons, thermal neutrons, and gamma rays. Our Committee feels that such beams can be made available; that the technology and several neutron sources are in hand to produce such beams. We have several recommendations for the intermediate beam. We feel that both moderators and filters are possible ways of producing these intermediate beams, and that enough engineering and preliminary tests have been done. Now what is needed is to go ahead and design and test moderators of aluminum or aluminum plus D_2O, and design and test filters of aluminum plus sulfur, or iron, or several newly proposed filters. However, we did hear that the iron filter, which passes 24-keV neutrons, may give neutrons at too high an energy, which is undesirable. This point should be evaluated. In addition, the Committee feels that detailed engineering analyses should be made of the accelerators that have been suggested as sources of neutrons and, if these detailed analyses confirm the promise of the preliminary predictions, tests should be made with existing accelerators to see whether they could deliver the fluences in the times that had been recommended. To duplicate the Japanese procedures, to treat near-surface cancers or to irradiate cultures, there may be a need for thermal beams. Several thermal beams are already available in the U.S. and others could be built at the existing neutron sources if they are needed. One final recommendation is that the reactors that are available now not be compromised by the agencies that own or regulate them, because in the future these facilities may be needed for treatment of a large number of patients. This future need should be taken into consideration, and none of these should be compromised by being shut down without careful evaluation of future needs.

V.P. Bond: The meeting is now open to questions from anyone who wishes to ask one.

R.F. Barth: Dr. Wambersie, you mentioned pilot studies. Could you amplify that and tell us what you had in mind specifically. Were these to precede some clinical trial? What would be the details, as you now see it, of such pilot studies?

A. Wambersie: I refer your questions to the Committee Chairmen.

R. Gahbauer: Several aspects were discussed with almost unanimous agreement in the Radiobiology Committee and in the Medical Committee. The general thrust of the argument was that the data to date are very promising, but the data, as we have them today, need to be reconfirmed and need to be established in animal models as thoroughly as can be done. The neutron experience and the neutron biology that has been done need to serve us as a guideline in establishing the assumptions of BNCT in animal models as to its effectiveness and as to the tolerance of the tissues irradiated. So very careful studies are needed. Once these studies confirm the present optimistic situation, I think one can anticipate human pilot data, for which one probably would first like to see some pharmacology data on the human brain before actual radiation would be undertaken. If these data are again confirmatory, pilot studies would be initiated which of course would be Phase 1 studies. The situation is rather complicated because basically we have Phase 1 studies for the pharmacology compound and we have Phase 1 studies for the radiation part, and we could say we need a Phase 1 study for the combination of the two. Once we have established the toxicity, Phase 2 studies can proceed. I would like to reemphasize what Dr. Goodman said this morning. We hope that in our initial studies a big effect will be seen because if we are talking about a very marginal effect that needs to be demonstrated in hundreds and hundreds of patients to reach statistical significance, in a uniformly lethal tumor, it may not justify the expense of the technique that we are talking about.

V.P. Bond: Extrapolating from what Dr. Wambersie has said, I think he was referring to the fact that we actually have no data to guide us in fractionation. We have no experience with the particular pattern that we get in NCT, namely high-LET radiation of the tumor and low-LET radiation to the normal tissues. Needed are animal tumor data to give us some indication of the effects of fractionation, before pilot clinical trials are undertaken. Dr. Rockwell, have you any further comments on this subject?

S. Rockwell: Yes. I think one of the things that came out of the Radiobiology Committee discussions was the feeling that there are severe limitations to the animal models. And I think this is inherent in Dr. Wambersie's and Dr. Gahbauer's comments about preliminary clinical studies in that we know that the distribution of the compounds into the tumor and normal brain of people who have had a debulking of the tumor, a craniotomy, and so on, may not be the same as that in the animal models. The Committee therefore discussed at length the fact that detailed studies of the distribution of the current boron compounds, throughout the tumor, in the margins of the tumor, and in the brain near the tumor, both in the malignant cells and in the normal cells, would be necessary in order to plan optimal clinical trials with the agents.

V.P. Bond: Very good. Dr. Sweet has some comments.

W.H. Sweet: I am a little chagrined that there is a strong sentiment, I gather, in favor of treating effectively some animal model of glioma before

one proceeds to human radiation. I am frequently asked what to do about a patient with a glioblastoma. These calls come to me from all over the country, and my recommendation at present is that they go to Tokyo. If I had a glioblastoma diagnosed on me today, that is what I would do. It seems to me that the logical gesture for us is to establish as promptly as we can, from data obtained on human patients, what the optimal time is in the average individual with a glioblastoma to treat the patient, and to have the best reactor we can find to do so in this country. I think we are omitting, in our cogitations, the fact that if you turn out with a glioblastoma today, you will not be very happy with the recommenation "Well, we will be all set to handle you in about three years." It seems to me there is an urgency about the problem here, relating to the fact the current modes of management are extremely unsatisfactory.

V.P. Bond: I do not think many here would really disagree with you, Dr. Sweet. I think what is being said here are two separate things. One is that, in this country, in order to get a drug approved for any kind of use in human beings, certain requirements laid down by Federal agencies, particularly by the FDA, must be addressed. We have to address the questions of toxicity and of efficacy. A large part of what has been discussed here concerns fulfilling those recommendations so that we can use those compounds that we wish to try in the human being. The other is that there are certain scientific questions that we would like to see elucidated a bit, such things as the RBE on the normal tissues of the beam that is actually to be used, and, as I mentioned before, some indication from animal tumors of the necessity for, or the efficacy of, fractionation vs. a single exposure. Perhaps we could get by with a single exposure. So the things being discussed are not for the purpose of delay. They are simply for the purpose of being able to use the compounds safely in human beings. Perhaps someone else might like to add to that.

W.H. Sweet: Well, I'd just like to ask -- if I understand you correctly, I am in full agreement that we must have sound toxicological data, which could be very promptly obtained -- but do I understand that we have to have a good idea as to whether fractionation is superior to single-dose data? Or that we need to have some evidence from killing an animal tumor, with whatever compound we elect with BNCT, that those are prerequisites to trials in man?

V.P. Bond: No, those are not strictly prerequisites. However, the experiments do not require an excessive amount of time, and, I, for one, would like to see some elucidation of these points with animal experiments. I personally would not regard that as a prerequisite for clinical trials, but some others may; there is room for honest difference of opinion. Perhaps some others would comment on this.

A. Wambersie: There is, I guess, some misunderstanding: I did not suggest to delay indefinitely the clinical application of NCT, nor to initiate a huge and time-consuming radiobiological program. My main point was the following. First, we have improved the neutron irradiation technique: with

epithermal neutrons, we can achieve a rather homogeneous thermal neutron flux throughout the brain volume. Second, we have new boronated compounds (second and third generation) for which the ^{10}B concentration in the tumor tissue can reach 25 to 30 µg/g and the tumor/blood ratio 6 to 10. This is a marked improvement compared with the situation we had 20 years ago. However, there are some data which are missing: measured boron concentrations are "average values" (expressed in µg per g tissue) and we have little indication of boron distribution in the individual cells. This is one of the key problems in NCT: this technique, in principle, allows the therapist to heavily irradiate a cancer cell without irradiating the next cell, and this is of course not possible with conventional techniques. This variational dose from cell to cell is one of the specific potential advantages of NCT, but, as far as I heard from the presentations and as far as I know from the literature, there has been no clear evidence of boron uptake in each cancer cell. As I said earlier, if 1% of the clonogenic cancer cells do not incorporate boron, only 99% of the cancer population will be destroyed and a recurrence will occur. I think that the distribution of the boronated compounds at the cellular level is really a key point. This information could be obtained relatively quickly in animal tumors, with a few tumor strains, on large and small tumors, as I said earlier.

S. Rockwell: I think none of us would disagree with many of the things that Dr. Sweet has said, and I do not think we were intending to propose a ten-year radiobiology program to go on before clinical trials. Some things, such as have just been mentioned, probably do need to be done before clinical trials, if only for political reasons. I say that as a radiobiologist who has recently been involved in the design of clinical trial for Stage IV carcinoma of the head and neck, for advanced carcinoma of the cervix, and for glioblastoma. I'm thinking of the problems that we have run into in getting those trials ready to go. Clearly many institutions and many agencies now do require some considerations in the laboratory of antitumor efficacy and of toxicity, including normal-tissue radiation response, before they will permit the beginning of clinical trials. Many of the other things we have talked about would be things that we would view as going on simultaneously with the initial clinical trials, to improve use of the second- and third-generation compounds so that we can do our best in this terrible disease.

V.P. Bond: Some of these things we have to do are required to obtain approval from even our local "human use" Committees, so these requirements are evidently widespread.

R. Gahbauer: I would like to reemphasize my personal enthusiasm for BNCT. My concern is that if we rush into early clinical trials, and fail a second time, then we face the risk of having benefited some patients with a suboptimally applied technique, and consequently jeopardize this benefit for the patients in future years to come. I think a waiting period of, if necessary, one or two years and optimizing what we can optimize may in the long run benefit a greater number of patients then we would benefit by rushing into it this year. So I am very enthusiastic about it, but want to be careful.

V.P. Bond: You mean in this ball game, two strikes and you're out?

W.H. Sweet: I'm anxious because of comments in the last couple of hours. I'm going to give you my reasons for advising major craniotomies in the course of the work that we are discussing. The reason for doing a major craniotomy at the first operation is not only that these tumors tend to be substantial and often near enough the surface that it's in the patient's best interest to remove a significant part of the tumor as soon as possible, but also that in our present state of ignorance we can learn a number of important new facts which in each case will be relevant to the treatment of that particular patient. First of all, we need to understand why some patients appear to derive dramatic benefit from BNCT -- even though the boron levels measured in the few samples of tumors taken by Dr. Hatanaka might be lower than the levels in the blood. Nevertheless the patient may have a good result. The most dramatic example of that is the patient I mentioned this morning, who, at the time of irradiation, had some 27 μg/g of boron in his blood and something like half that in the tumor specimen. Yet he is a dramatic success. Is there, then, some special concentration of the boron-loaded compound in some particularly vulnerable part of the tumor cell? Is the concentration in the nucleus or the Golgi apparatus or some other important organelle? Or is there no clear-cut reason why these phenomena occur?

We need to know, then, from the initial tumor specimens what the alpha-particle distribution is, not only in a single tumor specimen. One thought that Dr. Hatanaka and I have had for a long time is that maybe his patients have done as well as they have done because he removed a great deal of the tumor at the first operation. Then, pressure on the blood vessels by the expanding tumor mass having been eliminated in the original operation, the more open tumor vessels at the time of the radiation permitted more boron to escape into the tumor cells. So what we need to know to test these hypotheses, are the concentrations of boron in individual tumor cells and in tumor-laden blocks, not only at the original craniotomy but also at the time of the radiation procedure. The only way to get these data is by taking samples of significant size. In each sample we need three kinds of data. We need to have a histologic aliquot of the sample in which by standard tumor stains one determines which and how many are tumor cells and which are non-neoplastic cells -- glia, neurons, and so forth. Then we need another aliquot to determine the total boron concentration, and finally a third aliquot for alpha-particle studies of the precise distribution of the boron in subcellular organelles. We would profit by such data not only at the original craniotomy but also at the time of the BNCT because those data, in particular, are directly relevant to the situation of the patient at the time he is receiving his radiation treatment.

I can see the point of those who say that application to deep tumors probably will not be fruitful for any of these approaches. I would point out, however, a disadvantage of our present methods of obtaining stereotactic biopsies, i.e. blindly inserting a little metal cannula (as small a metal rod as possible) down into the tumor. Most of these tumors are highly vascular; if one starts bleeding as a result of the blind insertion, there is no satisfactory way to stop the bleeding. This is a hazard of stereotactic biopsy which naturally leads the surgeon to use the most minute device he can to get

some sort of a specimen. Thus, although the pathologist may be able to make a crude diagnosis, there would not be enough specimen to do any of the special studies that I indicated are going to be directly germane to getting more information on the problems still confronting us. I would also emphasize that glioblastoma is a particularly vicious tumor, one of the worst that human beings can have. We shall be very fortunate if we can achieve a significant major advance even if we optimize every aspect of the treatment that we can possibly think of. We have come to realize after a great deal of debate that at present the best way to handle a glioblastoma is to do an open craniotomy removing as much of the tumor as possible, give as much radiation as the individual can possibly stand, and add to that as much chemotherapeutic agent as the patient can stand. However, that tactic still yields grossly unsatisfactory results. Hence I think that at present, if we are to go to BNCT, we want to give this form of radiation every possible chance of success in terms of the maximally beneficial open craniotomy that we can provide for the patient, purely from the standpoint of that patient's immediate greatest benefit.

A.H. Soloway: I would like to report on a Subcommittee that Dr. Fairchild has established on an ad hoc basis to look at the compounds and compound development: Dr. Jeffrey A. Coderre, Dr. Donald C. Borg. Dr. Stephen Kahl, and myself. If you don't agree, I will refer you to the other people on the Committee. The compounds we discussed initially were third-generation compounds, and we broke those down into three categories. (1) Compounds designed for selective uptake and incorporation by certain tumors, based on specific biochemical components and metabolism; among these were boronated phenothiazine, p-boronophenylalanine, and potentially boron-containing thiouracil. (2) Compounds that showed selective uptake and incorporation by tumors generally, that is, the boronated porphyrins, proteins that are absorbed by endocytosis, and various carbohydrates. (3) Compounds specifically targeted for cell surface receptors; among these are monoclonal antibodies. In a fourth, sort of general, category, are liposomes and boron compounds that bind to cell nuclei for nuclear targeting of cells. In discussion, there was the feeling that Brookhaven National Laboratory is an important source for evaluating compounds and for prompt gamma analysis measurements of boron compounds in tissue and that it is an invaluable resource for the continuation of boron compound development.

With respect to the guidelines for evaluating compounds in categories 1, 2, and 4, that is, excluding compounds targeted for cell surface receptors, the feeling was that these compounds were not limited in number or in quantity, and that these should be evaluated in tumor-bearing animals initially. As for the boron-labeled antibodies that are for cell surfaces, these should be evaluated initially in cell cultures, and we need to assess the radiobiology of the cell cultures to be used. If the compounds do not localize in sufficient amounts in tumors, obviously we need not proceed further with those. For the boronated antibodies, there will be an evaluation for toxicity comparable with that in other antibody therapy. For the other compounds, we need a toxicological evaluation in animals followed by efficacy studies in suitable animal tumor models. Success in these studies would prompt a full toxicological evaluation in animals prior to any clincal

studies in man. With respect to the sulfur-containing boranes that have been discussed, under the conditions set out above, the group did not believe that efficacy has been fully established for any of these compounds. And therefore, we strongly recommend that efficacy in animal tumor models be demonstrated prior to any initiation of clinical BNCT trails.

We examined some of the compounds. Among those in the first category, namely those for selective uptake based on biochemical components and metabolism, it was the feeling that the one probably furthest along is p-boronophenylalanine, and perhaps that should be looked at in greater detail from a toxicological standpoint. Among those in category 2, it was felt that the boronated porphyrins appear to be most attractive, and one of these has already demonstrated good localization in tumor. Some of the other compounds are at an earlier stage in their development. Monoclonal antibodies, though in a very early stage of development, offer a great deal of promise for many different types of tumors. Incorporation of sufficient boron levels into such proteins has been obtained, and in some cases antibody specificity has been preserved. It is certainly going to be important to develop those and to be sure that one can separate and retain antibody specificity in compounds in those boronated antibodies that have suitably high levels of boron. Finally I might mention that at a meeting of the American Nuclear Society in the Fall of this year I will be chairing a session on BNCT, and I would encourage any people who wish to present papers to send them to me at The Ohio State University, 500 West 12th Avenue, Columbus, Ohio 43210.

A. Wambersie: I would like to comment on Dr. Soloway's presentation this morning. When you consider the possiblity of combining different compounds to increase the therapeutic benefit, you make a comparison with chemotherapy. I agree it could be true in some aspects, but the situation is not identical because in chemotherapy you aim at adding the effects on the tumor of all the agents, but the toxic side effects are completely different. One drug has neurotoxicity, another one is toxic to the bone marrow, still another to the intestine, and so on: you do not add the toxicities, but only the effects on the tumor. In the case of boronated compounds, one tries to increase the boron content in the cancer cells, but, as far as the side effects are concerned, they would be simply related to the boron concentration in the tissues at risk, in the endothelial cells for example. So it is not by combining different compounds which have a "poor" distribution that you will obtain an improved distribution; you will end up with a kind of "mean" boron distribution arrived at by adding the distributions obtained with the individual compounds.

A. Soloway: I would say that the problem we are seeing with some of the tumors that we are looking at is that, as you were alluding to, not all of the boron compounds are localized in all of the cells. We really do not know the mechanism by which these compounds are localizing in certain cells and not in others, and, if we were able to have different compounds that show different specificity with different types of cells, then we might avoid, with those cells we were talking about, 1% of the cells escaping and not being boronated. Maybe, by having different compounds, we might achieve a greater distribution over all of the tumor cells, rather than just in some.

S.B. Kahl: As one of the members of the Compound Development Committee, I would like to add to, and perhaps emphasize, what Dr. Soloway has said with respect to the usefulness of Brookhaven as a resource center in the evaluation of compounds to those of us working in the clinical area. Since compound development takes a long time, we are looking at third-generation compounds that would be used, we hope, in three, four, or five years. It is absolutely critical that those of us working in that area who do not have facilities to evaluate those compounds -- I speak particularly of prompt gamma and that sort of thing -- have a source such as Brookhaven for that purpose. And I would simply like to make sure funding agencies know that that is critical for all of us.

V.P. Bond: We thank all of you for attending and putting forth your views. With that, the conference is closed.

III. COMMITTEE RECOMMENDATIONS: STEPS REQUISITE FOR THE LOGICAL DEVELOPMENT OF NCT

A. Radiobiology and Medical Committees

The discussions of the Radiobiology and Medical Committees covered similar topics, and the recommendations of the Committees were very similar. We have, therefore, combined these recommendations into a single report.

The Committees limited their discussions to the preclinical studies requisite for the treatment of high-grade brain tumors such as astrocytoma and to discussions of the two compounds closest to potential clinical application; however, there was consensus of both groups that the development of third-generation compounds should be continued, and that the eventual application of BNCT to other tumors and sites should be investigated.

The Committees felt that several areas of preclinical investigation would be necessary before it would be possible to initiate clinical studies. As neither the monomer nor the dimer (of sulfhydryl boron hydride) is unequivocally preferable at this time, studies on both compounds should be continued until one is proven superior. Necessary investigations are the following:

1. The preclinical toxicology studies required by the regulatory agencies.
2. Animal studies evaluating the antineoplastic efficacy of boron neutron capture therapy. These should be performed in multiple tumor-host systems and should demonstrate that the compound in combination with BNCT has efficacy greater than that of the neutrons alone.
3. Animal studies of normal tissue tolerance are needed, with and without the compound, using different fractionation schemes and different beams. These studies should be similar to the preclinical normal tissue tolerance studies performed for fast neutron therapy.
4. Animal studies are needed for the pharmacology and biodistribution of the compounds. Macro- and microdistributions are to be studied since the efficacy of BNCT depends critically on the microdistribution.
5. The compounds should further be tested for any accompanying radiosensitizing or radioprotective effects.
6. It would then be necessary to examine the pharmacology of these compounds in human tumors. These studies should include macroscopic analyses of blood and tissue levels and microscopic analysis of levels in tumor, tumor margins, brain adjacent to tumor, blood, and skin. It will be necessary to determine intra- and interpatient variabilities. These distributions should lead to effective radiation dose ratios of approximately 2 to 1 for tumor cells versus endothelial cells. Further studies should be performed to determine the effective dose distributions of various thermal, epithermal, 2-keV, and other beams. It appears desirable to minimize the high-LET components of the beams.

Additional studies would probably be necessary before the initiation of clinical trials of therapeutic efficacy. These should include the following:

1. Studies of various fractionation and dose levels. These would depend on the choice of beam and the pharmacology and toxicology of the compound to be used.

2. At that time the merits of debulking and scalp reflection at the time of irradiation should be determined on the basis of the accumulated information.

3. The criteria for patient selection in clinical protocols should be established on the basis of the characteristics of the compound and beam and the anticipated quality of life.

B. Physics Committee

In order to improve depth-dose distribution and minimize fast neutron and gamma dose to normal tissues, it is recommended that intermediate energy neutron beams be developed capable of delivering a fluence of about 2.5 to 5 x 10^{12} neutrons/cm^2 in 30 to 60 minutes. It is generally understood that the technology for such beams is in hand.

1. Moderators (aluminum or aluminum plus D_2O) and filters (aluminum plus sulfur, iron, etc.) should be tested in order to determine that adequate thermal neutrons can be generated and that adventitious radiation can be restricted to negligible or tolerable levels. In view of the experience at Harwell, England, with the 24-keV Fe-filtered beam, the possibility should be kept in mind that neutrons in this energy region (or above) may deliver a significant dose from hydrogen recoils.

2. As NCT progresses, the possibility of using accelerators as alternative sources of neutrons should be considered. Engineering analyses can be made to evaluate the potential of such machines to deliver intermediate energy neutrons in the required times (as described above).

In view of the increasingly optimistic outlook for NCT, and the potential geographical as well as beam-time requirements, it is recommended that currently available reactors with power levels capable of delivering beam intensities noted above, should be kept in a retrievable mode.

C. Compound Development Committee

While the above recommendations have been focused on describing a procedure for evaluating the sulfhydryl boron hydrides, the concensus is that the full potential of NCT resides in the development of third-generation compounds which can be selectively targeted to tumor cells via physiological pathways. Therefore it is recommended that such compounds be investigated concomitantly with procedures outlined in A and B above. The classes of boronated compounds which are currently being evaluated and which continue to show promise are the following:

1. Melanin-affinic compounds such as phenothiazine, thiouracil, and phenylalanine.

2. Compounds showing uptake in tumors generally, such as porphyrins, nucleosides, proteins, and carbohydrates.

3. Monoclonal antibodies and other biomolecules targeted to cell surface receptors.

4. Other compounds which may have a boron-carrying potential for various reasons, such as liposomes.

AUTHOR INDEX

Adams, D.M., 42
Alam, F., 42, 162
Bay, J.W., 143
Barth, R.F., 42, 162, 197
Bernard, J.A., 55
Blue, J.W., 143, 178
Blue, T.E., 42, 143
Boesel, C.P., 42
Bond, V.P., 22, 188, 196, 197, 198, 199, 200, 201, 204
Borg, D.C., 106
Brownell, G.L., 49
Brugger, R.M., 32, 83, 197
Carey, W.E., 42
Carney, C., 49
Chou, S., 143
Clendenon, N.R., 42, 178, 184
Coderre, J., 106
Elmore, J.J., 106
Fairchild, R.G., 44, 106, 173
Foster, S., 106
Gabel, D., 106
Gahbauer, R., 42, 143, 178, 184, 196, 198, 200
Girvin, J.R., 42
Glass, J., 106
Goodman, J.H., 42, 178, 184
Greenwood, R.C., 123
Harling, O.K., 55
Goldhaber, M., 1
Kahl, S.B., 204
Kalef-Ezra, J., 106
Kanellitsas, C., 178
Laster, B.H., 106, 173
Less, T.J., 32, 83
Madoc-Jones, H., 55
Mafune, N., 42
Micca, P.L., 106, 173
Moeschberger, M.J., 42
Noonan, D.J., 77
Passmore, G.G., 32, 83
Roberts, T.C., 42
Roberts, W.K., 143
Rockwell, S.C., 196, 198, 200
Russell, J.L., Jr., 155
Slatkin, D.N., 106, 173
Soloway, A.H., 42, 162, 202, 203
Staubus, A.E., 42
Stephens, R.E., 42
Sweet, W.H., 3, 198, 199, 201
Talnagi, J.W., 42
Vincent, J.S., 145
Wambersie, A., 188, 196, 198, 199, 203
Wheeler, F.J., 92
Yates, A.J., 42
Zamenhof, R.G.A., 55

PARTICIPANTS

Dr. H.L. Atkins
Dept. of Radiology,
Health Sciences Center
State U. of New York
Stony Brook, NY 11794

Dr. George Archibald
EG&G Idaho
Idaho National Engineering Lab.
Idaho Falls, ID 83415

Dr. R.B. Aronson
Medical Dept., BNL

Dr. Rolf F. Barth
Dept. of Pathology
Ohio State U.
Columbus, OH 43210

Dr. Michael A. Bender
Medical Dept., BNL

Dr. G.W. Bennett
Medical Dept., BNL

Dr. James W. Blue
NASA/CCF Neutron Therapy Facility
Lewis Research Center
Cleveland, OH 44135

Prof. Thomas Blue
Ohio State U.
Columbus, OH 43210

Dr. Victor P. Bond
Medical Dept., BNL

Dr. Donald C. Borg
Medical Dept., BNL

Dr. Lawrence Borges
c/o Dr. W.H. Sweet
Ambulatory Care Center
Massachusetts General Hospital
Boston, MA 02114

Dr. A.B. Brill
Medical Dept., BNL

Dr. Gordon L. Brownell
Professor of Nuclear Engineering
Massachusetts General Hospital
Boston, MA 02114

Dr. Robert M. Brugger
Research Reactor Facility
U. of Missouri
Columbia, MO 65211

Dr. Nancy Clendenon
Dept. of Radiation Oncology
Ohio State U. Hospital
Columbus, OH 43210

Dr. A.D. Chanana
Medical Dept., BNL

Dr. Jeffrey A. Coderre
Medical Dept., BNL

Dr. E.P. Cronkite
Medical Dept., BNL

Ms. Margaret Dienes
Technical Information Div., BNL

Dr. Charles DeLisi, Assoc. Director
Office of Health & Environ. Research
U.S. Dept. of Energy
Washington, DC 20546

Dr. Kenneth J. Ellis
Medical Dept., BNL

Dr. John Elmore
Medical Dept., BNL

Dr. Ralph G. Fairchild
Medical Dept., BNL

Dr. Sheila Foster
Medical Dept., BNL

Dr. Reinhard Gahbauer
Dept. of Radiation Oncology
Ohio State U. Hospital
Columbus, OH 43210

Dr. John Glass
Medical Dept., BNL

Dr. Gertrude Goldhaber
Physics Dept., BNL

Dr. Maurice Goldhaber
Physics Dept., BNL

Dr. Joseph H. Goodman
Dept. of Radiation Oncology
Ohio State U. Hospital
Columbus, OH 43210

Mr. Dennis Greenberg
Medical Dept., BNL

Dr. Reginald C. Greenwood
EG&G Idaho
Idaho National Engineering Lab.
Idaho Falls, ID 83415

Dr. Merle Griebenow
EG&G Idaho
Idaho National Engineering Lab.
Idaho Falls, ID 83415

Professor Otto Harling
Nuclear Reactor Laboratory
138 Albany St.
Cambridge, MA 02139

Dr. Walter Hughes
Medical Dept., BNL

Dr. Terry Johnson
16 Griffith Drive
Mt. Sinai, NY 11766

Dr. Andre Kalend
Dept. of Radiation Oncology
State U. of New York,
Stony Brook, NY 11794

Dr. Stephen B. Kahl
School of Pharmacy
Dept. of Pharmaceutical Chemistry
U. of California
San Fransisco, CA 94143

Dr. J. Kehayias
Medical Dept., BNL

Dr. H.M. Peter Kuan
Dept. of Radiology
Health Sciences Center
State U. of New York
Stony Brook, NY 11794

Ms. Brenda H. Laster
Medical Dept., BNL

Dr. Tim Less
Research Reactor Facility
U. of Missouri
Columbia, MO 65211

Dr. Samuel McCalmont
Callery Chemical Co.
Callery, PA 16024

Dr. Alan Meek
Dept. of Radiation Oncology
State U. of New York
Stony Brook, NY 11794

Ms. Peggy Micca
Medical Dept., BNL

Dr. Richard Moore
Nuclear Medicine Inc.
Atlanta, GA 30332

Dr. K. Morstin
c/o Dr. V.P. Bond
Medical Dept., BNL

Dr. Stephen V. Musolino
Safety & Env. Prot. Div., BNL

Dr. Denise J. Noonan
Nuclear Medicine Inc.
Atlanta, GA 30332

Dr. Donald Pizzarello
Dept. of Radiology
NYU Medical Center, Bellevue Hosp.
New York, NY 10016

Dr. Edwin A. Popenoe
Medical Dept., BNL

Dr. Richard Radomski
Callery Chemical Co.
Callery, PA 16024

Dr. Larry Reinstein
Dept. of Radiation Oncology
State U. of New York
Stony Brook, NY 11794

Dr. James S. Robertson
Human Health & Assessments Div.
U.S. Dept. of Energy
Washington, DC 20545

Dr. Sara C. Rockwell
Therapeutic Radiology
Yale U. School of Medicine
New Haven, CT 06510

Dr. John L. Russell, Jr.
Nuclear Medicine Inc.
Atlanta, GA 30332

Dr. David Schweller
U.S. Dept. of Energy
Brookhaven Area Office, BNL

Dr. R.B. Setlow, Chairman
Biology Dept., BNL

Dr. C.J. Shellabarger
Medical Dept., BNL

Dr. Daniel N. Slatkin
Medical Dept., BNL

Dr. Albert H. Soloway, Dean
College of Pharmacy
Ohio State U.
Columbus, OH 43210-1291

Dr. John H. Spickard
EG&G Idaho
Idaho National Engineering Lab.
Idaho Falls, ID 83415

Ms. Marie A. Susa
Medical Dept., BNL

Dr. William H. Sweet
Ambulatory Care Center
Massachusetts General Hospital
Boston, MA 02114

Dr. J.W. Thiessen
Deputy Assoc. Director
Office of Health & Environ. Research
U.S. Dept. of Energy
Washington, DC 20545

Dr. A. Wambersie
Catholic U. of Louvain Medical Faculty,
B-1200 Brussels, Belgium

Dr. Lucian Wielopolski
Medical Dept., BNL

Dr. Floyd Wheeler
EG&G Idaho
Idaho National Engineering Lab.
Idaho Falls, ID 83415

Dr. Robert G. Zamenhof
Medical Physics Div.
Tufts-New England Medical Center
Boston, MA 02111