Boron neutron capture therapy is based on the nuclear reaction that occurs when a stable isotope, $^{10}$B, is irradiated with low energy (0.025 eV) or thermal neutrons to yield stripped down helium nuclei ($\alpha$-particles) and $^7$Li nuclei.

\begin{equation}
^{10}\text{B} + n_{\text{neutron}} \rightarrow ^{[\alpha]\text{B}} - 2^{\text{He}} + ^7\text{Li} + 2.79 \text{ MeV (6%)}
\end{equation}

\begin{equation}
^{10}\text{B} + ^7\text{Li} + 0.48 \text{ MeV} \gamma + 2.31 \text{ MeV (94%)}
\end{equation}

The therapeutic potential of this reaction was recognized by Locher over 50 years ago (1), but it was Sweet (2-4), who first suggested that BNCT might be useful for the treatment of brain tumors. Shortly thereafter, a clinical trial was initiated at the Brookhaven National Laboratory in cooperation with Sweet and others at the Massachusetts General Hospital utilizing borax as the capture agent (5, 6). The objective at that time was to use BNCT as an adjunct to surgery for the treatment of patients with the most highly malignant and therapeutically refractory of all brain tumors, glioblastoma multiforme. Further trials were carried out in the early 1960s, but as will be described in more detail later on, these failed to show any evidence of therapeutic efficacy (5-7) and were associated with adverse effects in normal tissues (7). Stimulated by the more encouraging clinical studies of Hatanaka et al. (8, 9) for the treatment of malignant gliomas and those of Mishima et al. (10) for melanoma, there has been renewed national and international interest in BNCT. The theoretical advantage of BNCT is that it is a two component or binary system, consisting of $^{10}$B and thermal neutrons, which when combined together generate high LET radiation capable of selectively destroying tumor cells without significant damage to normal tissues. In order for BNCT to succeed a critical amount of $^{10}$B and a sufficient number of thermal neutrons must be delivered to individual tumor cells. Over the past few years the Department of Energy and the NIH have renewed funding for BNCT-related research, and this has supported a growing number of investigators in many different fields. Advances in BNCT in the areas of compound distribution and pharmacokinetics compare favorably with other emerging modalities such as photon activation therapy, photodynamic therapy, and the use of radiolabeled antibodies for cancer treatment in which physiological targeting is used.

There are a number of nuclides that have a high propensity for absorbing low energy or thermal neutrons (Table 1), and this property, referred to as the neutron capture cross-section ($\sigma$), is measured in barns ($1 \text{ barn} = 10^{-24} \text{ cm}^2$). Of the various nuclides that have high neutron capture cross-sections, $^{10}$B is the most attractive for the following reasons: (a) it is nonradioactive and readily available, comprising approximately 20% of naturally occurring boron; (b) the particles emitted by the capture reaction $^{10}\text{B}(n,\alpha)^7\text{Li}$ are largely high LET; (c) their path lengths are approximately 1 cell diameter (10-14 \text{ m}), theoretically limiting the radiation effect to those tumor cells that have taken up a sufficient amount of $^{10}$B and simultaneously sparing normal cells and (d) the extensive chemistry of boron is such that it can be incorporated into a multitude of different chemical structures. Although the neutron capture cross-sections for the elements in normal tissues (Table 2) are several orders of magnitude lower than boron, two of these, hydrogen and nitrogen, are present in such high concentrations that their capture of neutrons contributes significantly to the total radiation absorbed dose. In order to reduce this it is essential that the tumor have high $^{10}$B concentrations so that the neutron dose or fluence (ncm$^{-2}$) can be held to a minimum, thereby maximizing the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction and minimizing the $\text{p}$-reaction with nitrogen [$^{14}\text{N}(n,p)^{14}\text{C}$] and the $\gamma$-reaction with hydrogen [$^{1}\text{H}(\gamma,\gamma)^{1}\text{H}$]. It has been estimated that with a tumor $^{10}$B concentration of 50 \text{ µg/g, 86% of the total radiation dose would result from the capture reaction (2).}

$^7$Li and $\alpha$-particles are the primary fission product of the neutron capture reaction with $^{10}$B. $\alpha$-Particles are relatively slow and give rise to closely spaced ionizing events that consist of tracks of sharply defined columns. They have a path length of approximately 10 \text{ m}, are high LET, and destroy a wide variety of biologically active molecules including DNA, RNA, and proteins. For these reasons there is little, if any, cellular repair from $\alpha$-particle-induced radiation injury. Since the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction will produce a significant biological effect only when there is a sufficient fluence of thermal neutrons and a critical amount of $^{10}$B localized around, on, or within the cell, the $\alpha$ particles will be absorbed by a distance substantially less than the LET path length in the tumor cell. The number of $\alpha$-particles that can be produced per unit neutron fluence is inversely related to the number of thermal neutrons. Thus, the higher the neutron capture cross-section of a given nuclide, the less the number of $\alpha$-particles that can be produced per neutron fluence, and the neutron fluence that can be delivered must be increased.

### Table 1 Thermal neutron capture cross-section values of potential nuclides for neutron capture therapy

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Cross-section (a)</th>
<th>Nuclide</th>
<th>Cross-section (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^3\text{He}$</td>
<td>5,500</td>
<td>$^{165}\text{Gd}$</td>
<td>58,000</td>
</tr>
<tr>
<td>$^4\text{Li}$</td>
<td>953</td>
<td>$^{167}\text{Gd}$</td>
<td>240,000</td>
</tr>
<tr>
<td>$^{10}\text{B}$</td>
<td>3,387</td>
<td>$^{167}\text{Hf}$</td>
<td>400</td>
</tr>
<tr>
<td>$^{113}\text{Cd}$</td>
<td>20,000</td>
<td>$^{169}\text{Hg}$</td>
<td>2,000</td>
</tr>
<tr>
<td>$^{125}\text{Xe}$</td>
<td>2,720,000</td>
<td>$^{231}\text{U}$</td>
<td>678</td>
</tr>
<tr>
<td>$^{148}\text{Sm}$</td>
<td>41,500</td>
<td>$^{241}\text{Pu}$</td>
<td>1,375</td>
</tr>
<tr>
<td>$^{199}\text{Eu}$</td>
<td>5,900</td>
<td>$^{241}\text{Am}$</td>
<td>8,000</td>
</tr>
</tbody>
</table>

* Asterisk (*) indicates that the nuclides are radioactive.

### Table 2 Thermal neutron capture cross-section values of normal tissue elements

<table>
<thead>
<tr>
<th>Element</th>
<th>Cross-section (a)</th>
<th>Element</th>
<th>Cross-section (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}$</td>
<td>0.332</td>
<td>$\text{N}$</td>
<td>1.75</td>
</tr>
<tr>
<td>$\text{Na}$</td>
<td>0.536</td>
<td>$\text{P}$</td>
<td>0.19</td>
</tr>
<tr>
<td>$\text{K}$</td>
<td>2.07</td>
<td>$\text{O}$</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>$\text{Mg}$</td>
<td>0.069</td>
<td>$\text{S}$</td>
<td>0.52</td>
</tr>
<tr>
<td>$\text{Ca}$</td>
<td>0.44</td>
<td>$\text{Cl}$</td>
<td>31.8</td>
</tr>
<tr>
<td>$\text{C}$</td>
<td>0.0037</td>
<td>$\text{Fe}$</td>
<td>2.62</td>
</tr>
</tbody>
</table>

* Capture cross-sections (ε) are given in barns, where 1 barn = 10$^{-24}$ cm$^2$.
the radiation produced can be extremely localized thereby sparing normal tissue components. Thus, selectivity is simultaneously one of the advantages and disadvantages of BNCT, since it requires delivery of boron-10 to tumor cells in greater amounts than normal cells. In contrast to the ionizing radiation produced by radionuclides, little or no radiation is delivered to bystander cells by the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction, if the $^{10}\text{B}$ is selectively localized on or within tumor cells. Otherwise, adverse effects may be produced in surrounding normal tissues (11–13).

A major advantage of a binary system is that each component can be manipulated independently of the other. With BNCT one can adjust the interval between administration of the capture agent and neutron irradiation to an optimum time when there is the highest differential between normal tissues and the tumor. Furthermore, the neutron beam itself can be collimated so that the field of irradiation is circumscribed and normal tissues with high $^{10}\text{B}$ concentration can be excluded from the treatment volume. Protection of normal tissues near and within the treatment volume can be achieved by selective targeting of $^{10}\text{B}$ to the tumor. Following the early clinical trials at the Massachusetts General Hospital and the Brookhaven National Laboratory it became apparent that there were two major reasons for their lack of success. (a) Thermal neutrons are attenuated rapidly in tissue due to absorption and scattering, and their effective depth of penetration is limited to 3–4 cm. This means that only superficial tumors would be destroyed by the capture reaction. (b) The boron compounds that were used were freely diffusible, low molecular weight substances that did not achieve selective localization in the tumor. Those which did had high blood values, and this explains why so much radiation was delivered to adjacent normal brain.

**Boron Chemistry and Compound Development**

Ideally, boron compounds to be used for BNCT (Fig. 1) should have a high specificity for malignant cells with concomitantly low concentrations in adjacent normal tissues and blood. Since it is desirable to confine the radiation solely to these cells, an intracellular and optimally intranuclear localization of boron would be preferred. Initially, boron compounds were not specifically designed for use in BNCT but, rather, were selected because of their ready availability, known pharmacology, and lack of toxicity (13). Because of these considerations, sodium borate, boric acid, and their derivatives were chosen for evaluation. Time course studies in mice that had been inoculated either s.c. or i.c. with a transplantable epedymoblastoma were used to evaluate the clinical potential of a compound for BNCT (14). It was postulated that these inorganic boron compounds would not penetrate normal brain tissue to the same degree as brain tumors, where the blood-brain barrier was absent or severely compromised. Differences in the concentration of boron in tumor and brain were detected, but these were transient and not very large, and within a period of 1 to 2 h had decreased to unity (2, 4, 15). This limitation prompted a major effort in compound development prior to further clinical trials. From more than 100 compounds that were screened, p-carboxybenzenboronic acid and sodium decahydrodecaborate (Na$_2$B$_{10}$H$_{14}$) were selected. These attained tumor:brain boron ratios of 5–8:1 which persisted for 2–3 h (16). Subsequently these were synthesized at a $^{10}\text{B}$ enrichment level of 92–94% (16) and used for another clinical trial, the results of which were disappointing (7).

In the 1960s the basis for achieving selective delivery of boron compounds was unknown, since by their very nature they were not naturally occurring. The clinical results of Sweet et al. provided the impetus for a pragmatic approach to compound development. Following the cessation of clinical trials in 1961, new compounds were developed and screened. These were administered several times daily, followed by a 2-day interval in order to allow blood boron values to fall. From the many compounds tested, two sulfhydryl-containing boron hydride anions, B$_2$H$_4$H$_2$SH$^{-}$ and B$_6$Cl$_6$(SH)$_4$SH$^-$, initially synthesized at E. I. duPont de Nemours Co., were chosen for further study. These had tumor: blood boron ratios in mice that ranged from 1.7–20:1 (17).

In retrospect, based upon the methods of synthesis that were used at that time, it is likely that the initial preparations contained mixtures of the disulfide analogues as well as the mercapto compounds. There are major biological differences between the B$_2$H$_4$H$_2$^+ anion and its mercapto counterpart, B$_2$H$_4$H$_2$SH$^-$, which has the potential to form mixed disulfides with disulfide groups on various plasma proteins (18).

Such covalent linkage of sulfur-containing polyhedral boranes bound to proteins has been demonstrated by their cleavage with dithiothreitol. It remains to be determined whether the incorporation of mercapto compounds into proteins of tumor cells is the basis for their selective uptake. There also has been increasing interest in the disulfide and its further oxidation product: B$_2$H$_4$H$_2$S–SB$_2$H$_4$H$_2$^+ and B$_2$H$_4$H$_2$S(O)SB$_2$H$_4$H$_2$^+ (19). The disulfide attained higher concentrations in gliomas than did the parent mercaptoborane, but at the same time the liver enzyme levels were elevated suggesting hepatotoxicity. The mechanism for the increased uptake of the dimer is also unknown. One possibility is the facile generation of stable free radicals by homolytic cleavage of disulfide groups (20) and their subsequent incorporation into proteins. Alternatively, the disulfide may react directly with sulfhydryl-containing constituents of tissue. The mechanism by which sulfur-containing compounds achieve greater selectivity for brain tumors and possibly other malignancies is not only important per se but may also provide the rationale for the design and development of other capture agents for BNCT.

Because of high and persistent boron concentrations in tumor and low systemic toxicity, Na$_2$B$_2$H$_4$H$_2$SH appeared to be a particularly attractive compound for BNCT. For these reasons Hatanaka (8) initiated a clinical trial in the late 1960s prior to the standard requirement of in depth pharmacokinetic studies in humans. Nevertheless, boron uptake data have been accumulated in 57 patients with surgically resected brain tumors who received Na$_2$B$_2$H$_4$H$_2$SH at doses ranging from 30–80 mg of $^{10}\text{B}$ enriched Na$_2$B$_2$H$_4$H$_2$SH/kg of body weight by intracarotid infusion approximately 12 h prior to neutron irradiation. The average concentration was 26.3 $\mu\text{g/g}$ tumor and 18.2 $\mu\text{g/g}$ blood, and the mean tumor: blood ratio obtained from 48 patients was 1.69 (21). The lack of toxicity of this compound in nearly 100 patients, together with a suggestion of therapeutic efficacy, has provided the impetus for more detailed pharmacokinetic and tissue distribution studies, which will be initiated shortly at several institutions.

Malignant melanoma is another tumor that is a candidate for treatment by means of BNCT. Although melanoma cells are variably resistant to photon irradiation (22), they are highly sensitive to $\alpha$-particles (23). Mishima (24) in Japan first proposed the incorporation of boron into chlorpromazine as a capture agent for the treatment of melanomas. Fairchild et al. (25) have shown that this compound is selectively accumulated in murine and hamster melanomas in amounts exceeding 100 $\mu\text{g/g}$ of tumor. Based on these data several boron-containing derivatives of this drug have been synthesized (26, 27) and are...
Fig. 1. Boron compounds that either are being used or potentially could be used as capture agents are shown above. Compound 1, a sulfhydryl-containing polyhedral borane (Na₂B₁₂H₁₀SH), was first shown by Soloway et al. (17) to have tumor-localizing properties and currently is being used by Hatanaka in Japan as a capture agent to treat patients with glioblastoma (8, 9). Compounds 2 and 3 are derivatives of alanine and phenylalanine, respectively. Based on their selective incorporation into melanin, Mishima in Japan first suggested that phenylalanine derivatives might be useful in the treatment of melanomas (28). Compounds 4 and 5 are promazines and the rationale for their use is based on the observations of Mishima (24) and Fairchild et al. (25) that chlorpromazine exhibits a significant degree of localization in melanoma. Compound 6 is a carboranylporphyrin. Hematoporphyrin has an affinity for tumors, which has led to its use in photodynamic therapy. Kahl in the United States has synthesized boron-containing analogues (36), such as the one shown here. Compound 7 is a boron-containing nucleoside synthesized by Schinazi and Prusoff (41). Such analogues of nucleic acid precursors may be incorporated into rapidly dividing malignant cells.

being evaluated for their in vivo tumor localizing properties. p-Boronophenylalanine is another compound that is being studied as a potential capture agent for the treatment of melanoma. The rationale for its use is the avidity of melanomas for aromatic amino acids and their subsequent incorporation into melanin (28, 29). Tumor localization has been demonstrated following i.g. administration by means of whole body autoradiography (30) and in several patients with cutaneous melanoma following perilesional injection (31). A clinical trial of this compound is currently underway in Japan under the direction of Mishima and his promising results (10) will be discussed in more detail later in this review. Stimulated by Mishima’s experience, a number of other boron-containing amino acids have been synthesized that potentially could be incorporated in larger amounts into proteins of malignant cells (32). Another approach to the selective targeting of boron to melanomas is based on the observation that thiouracil is preferentially incorporated into melanotic melanomas during melanogenesis (33). This observation provided the impetus for the synthesis of several boron-containing thiouracils (34), and these currently are being evaluated in animals.

Two other classes of compounds with a propensity for localizing in malignant tumors are the porphyrins and the related phthalocyanines. The biochemical basis by which these compounds achieve elevated concentration in malignant tumors is unknown, but this observation has served as the rationale for the use of hematoporphyrin derivative in the photodynamic therapy of cancer (35). The high concentration of these compounds in tumors and their intracellular localization and persistence have stimulated several groups of investigators to synthesize boronated porphyrins (36) and phthalocyanines (37) as potential capture agents. Boronated porphyrins appear to be 3–4 times more effective per unit dose in cell culture than the monomeric or dimeric form of Na₂B₁₂H₁₀SH (38). Although liver concentrations of these compounds are also high (36) this would not limit their use as a capture agent for the treatment of brain tumors. Key questions that must be answered for all of these compounds include: (a) the biochemical and physiological mechanisms by which they concentrate in tumors; (b) their toxicity; and (c) their photosensitizing potential in humans.

One final category of low molecular weight boron compounds that should be mentioned are boron-containing purines and pyrimidines and their nucleosides. The rationale for their development is that such compounds may be selectively incorporated into rapidly proliferating tumor cells and trapped within the cell following their conversion to the corresponding nucleotide. Alternatively, these bases and their nucleosides may function as analogues of naturally occurring precursors of nucleic acids and become incorporated into nuclear DNA. Cytoplasmic or preferably a nuclear localization of all of these boron compounds would be advantageous since the heavy particles resulting from the capture reaction would deliver a greater proportion of their energy to intranuclear targets, thereby permitting lower boron concentrations than would have been required if the compounds were located extracellularly (39, 40). Schinazi and Prusoff (41) have synthesized the first boron-containing nucleoside, 5-dihydroxyboryl-2′-deoxyuridine, an analogue of thymidine, and have shown that it was not cytotoxic to African green monkey (Vero) cells at a concentration level of 1600 μM (42). In vitro neutron radiation studies of cells grown in the
presence of 5-dihydroxy-2'-deoxyuridine produced a biological
effect that was equivalent to a concentration of ~6 μg 10B/g,
which, if attainable in vivo, would be sufficient for BNCT.
All of the compounds described in the preceding section are
low molecular weight substances, but in most instances, it is
unclear whether these compounds remain unchanged in vivo. It
is conceivable that these structures could interact with other
molecular species such as serum or cellular proteins through
the formation of ionic, hydrophobic, or covalent linkages to
yield conjugates that would alter either the transport or cellular
uptake of the capture agent. To date, very little has been done
to determine whether such reactions occur and what effects, if
any, they may have on their selective concentration in tumors.

Antibodies and Other Macromolecular Species

During the 1960s and early 1970s interest developed in the
potential use of polyclonal antibodies directed against tumor-
associated antigens for the delivery of drugs and radioisotopes
to tumors (43-45). In 1964 Soloway suggested that antibodies
might be used for the selective targeting of 10B to tumors (15).
Hawthorne et al. (46) reported on the incorporation of the
diazonium salt from 1-(4-aminophenyl)-1,2-dicarbo-closododecaborate
into antibodies directed against bovine serum albumin and polyclonal antibodies directed against human
and mouse histocompatibility antigens (46). It was claimed from in vitro experiments that these immunoconjugates were capable of delivering enough boron to human and murine lymphocytes
to sustain a lethal 10B(n,α)7Li reaction, as evidenced by reduced viability following neutron irradiation. However, the immunoconjugates contained only 0.2% natural boron by weight, which
was equal to 6 atoms of 10B/molecule of antibody. In retrospect, it appears that there must have been some other explanation for the reduced cell viability that was observed. Sneath et al. (47) showed that water-solubilizing groups had to be incorporated into protein-binding polyhedral boranes if protein solubility in aqueous systems was to be maintained. Subsequently, a group of polyhedral borane derivatives containing protein-binding functional groups were linked to IgG molecules by
means of the carbodiimide reaction without evidence of precip-
itation (48).

With the advent of hybridoma technology and the development
of monoclonal antibodies directed against a wide variety of
tumor-associated antigens, new possibilities opened up for
the targeting of 10B. Our own studies initially focused on the
linkage of the polyhedral borane disodium mercaptoundeca-
hydro-closododecaborate (Na2B12H12S) to antibodies either
by thiol disulfide exchange (49) or by means of the heterobi-
functional reagent N,N'-succinimidyl-3-(2-pyridyldithio)propionate and N-maleimidobenzo-
yl JVA-hydroxysuccinimide ester (59, 60). More than 1000
boron atoms have been incorporated per antibody molecule
weight and up to 2000 boron atoms/molecule of
lysine and the resulting macromolecule contained 21 to 28%
atom of boron by weight and up to 2000 boron atoms/molecule of
polymer (58). This in turn has been linked to monoclonal antibodies 17-1A and IB16-6, which is directed against the B16 melanoma, utilizing two heterobifunctional reagents, N,N'-succinimidyl-3-(2-pyridyldithio)propionate and N-maleimidobenzoyl
N-hydroxy succinimide ester (59, 60). More than 1000
atoms of boron have been incorporated per antibody molecule
by modifying only one site and the resulting immunoconjugates
retained 40-90% of the immunoreactivity of the native antibody (60). The in vitro cellular uptake of the boronated 17-1A was
studied by means of electron energy loss spectroscopy utilizing a Zeiss 902 microscope. This instrument can detect elemental
boron with a high degree of sensitivity and spatial resolution (61).

Preliminary observations suggest that there is intracellular
uptake of boron by colorectal cancer cells exposed in vitro to
the immunoconjugate (60). These observations have important
dosimetric implications, since intracellular uptake of 10B would
increase the selective therapeutic effect achieved as a result of the 10B(n,α)Li reaction (39, 62). This is illustrated by Monte
Carlo calculations for hamster V-79 cells, which show that 10B
located external to the cell will produce ~10% of the dose
delivered by a uniform distribution while cytoplasmic and nu-
clear locations would each deliver 2.5× the dose from a uniform
distribution (39). If boronated antibodies are not internalized, this
clearly would be a disadvantage.

In vivo distribution studies have shown that there was a
marked reduction in the amount of boronated 17-1A localized
in human colon cancer tumors that have been implanted s.c.
into nude mice and a corresponding increase in the amount in
the liver compared to the native antibody (60). The problem of
altered distribution is one that has been encountered with a
variety of immunoconjugates including immunotoxins, radio-
labeled antibodies, and drug-antibody conjugates, and meth-
ology will have to be developed that produces less modifica-

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tion of the antibody molecule. New developments in hybridoma technology such as the production of recombinant antibodies that have two combining sites, one specific for the tumor-associated antigen and the other for the tumoricidal agent, potentially might have applicability to BNCT; if the boronated species itself were immunogenic and reactive with one of the combining sites on the hybrid molecule. Advances in the chemistry of immunoconjugation, especially the ability to increase the distance between the combining site for the tumor-associated antigen and the tumoricidal moiety, also might have applicability to developing better boronated immunoconjugates. The boronated polylsine that we have synthesized has a high negative charge, and this may have adversely affected its tumor-localizing properties and increased its clearance by the reticuloendothelial system. The production of antibodies directed against more universally expressed tumor-associated antigens that have two combining sites, one specific for the tumor-associ-ated antigen and the other for the tumoricidal agent, might have applicability to developing better boronated immunoconjugates.

One final category of macromolecular species that potentially may be useful for the delivery of 10B is what may be termed "encapsulating complexes," such as liposomes, microspheres, and low density lipoproteins (63). Theoretically large amounts of 10B could be encapsulated, and if these encapsulating complexes could be targeted to the tumor by linkage to a monoclonal antibody using existing methodology or targeting an endog-enously expressed cell surface receptor, they might be powerful delivery systems. Again, there may be preferential localization in the reticuloendothelial system, and methodology would have to be developed to minimize this and maximize tumor uptake.

Neutron Sources

Nuclear Reactors. It is thought that a fluence of 5 x 10^{12} n_{th} / cm^{2} will be needed for successful NCT. At the present time only nuclear reactors are capable of generating such beams, although accelerator-based neutron sources are being investigated as less expensive and more practical for hospital environments. Approximately 35 research and test reactors with powers of ~1 MW now exist in the United States that potentially could produce beams of therapeutic intensity (64). In particular, the Brookhaven Medical Research Reactor, the MIT Research Reactor, and the Georgia Institute of Technology Research Reactor have irradiation facilities that were designed for medical and biological research. In addition, extensive work has been done on the design of a proposed clinical facility for NCT at the Power Burst Facility at the Idaho National Engineering Laboratory. This reactor, with a steady state of power of 20 MW, would provide a beam of greater intensity than any other currently available. The patient irradiation ports of all of these reactors have a geometry that reduces fast neutron and y-photon contamination of the neutron beam thereby enhancing its clinical potential.

Beam Types. Neutrons with an energy of ~1 MeV are "born" in the fission reaction within the reactor core. Low energy or thermal beams (0.025 eV), epithermal beams (1–10,000 eV) or fast neutron beams (>10,000 keV) may be extracted from nuclear reactors for use in radiation therapy, by varying the amount of slowing down or "moderation" that occurs. Fast neutrons can be obtained by extracting a beam of neutrons that has little or no moderation. Scattering media such as light (H_{2}O) or heavy (D_{2}O) water or graphite can slow down or "moderate" fast neutrons so that they lose energy and become thermalized (64–66). The latter "thermal" or room temperature neutrons are the ones that are utilized in the 10B(n,\alpha)\alpha Li reaction. Thermal neutrons are rapidly attenuated by tissue with a half-value layer (distance to reduce beam intensity by a factor of 2) of ~1.5 cm (40), and consequently it is difficult to obtain sufficient neutron fluence rates at increasing depth without heavily irradiating surface tissues. Alternatively, an "epithermal" neutron beam (1–10,000 eV) can be produced by using moderators or filters that slow the fast neutrons into the intermediate or epithermal neutron energy region. By filtering out residual thermal neutrons with absorbers such as boron or cadmium, a relatively pure epithermal beam can be produced (40). This beam produces 10B-absorbing thermal neutrons, which are the ones that interact with 10B, as it penetrates tissue because of the moderating effects of hydrogen. Thermal neutrons generated in tissue by such a beam actually "peak" at a 2–3 cm depth thereby circumventing problems associated with the poor penetration of incident thermal beams. As an example, the various beam components from the epithermal beam at the BMRR are shown in Fig. 2. The thermal flux density generated by the epithermal beam follows the curve for "30 ppm 10B," as the 10B(n,\alpha)\alpha Li reaction is produced by the thermal neutrons (65). If the incident beams were a thermal beam, the falloff or attenuation of the thermal flux would be rapid and similar to the attenuation of the fast neutron dose (H) shown in Fig. 2.

Beam Requirements and Optimization. There is slightly in-

![Fig. 2. Dose distribution in a phantom head from the various components of the mixed radiation field produced by the "optimized" epithermal neutron beam at the Brookhaven medical research reactor. The beam has been "optimized" by enhancing beam intensity, while minimizing fast neutron (H recoil) and y contamination in the incident beam. The 14N(n,p)14C and 14N(y,14C) components in Fig. 2 are generated in tissue by the optithermal beam and cannot be reduced. Tumor would receive a dose given by the total dose + 30 ppm boron curve (65). Time for therapy in a single dose would be ~45 min.](image-url)
creased penetration of tissues by epithermal neutrons with increasing neutron energy so that the lowest energy fast neutrons or the highest energy epithermal neutrons would be optimum. For example, iron-filtered neutron beams produce fairly pure 24-keV neutrons, but both experimental determinations and calculations have shown that the normal tissue dose produced by hydrogen recoils from 24-keV neutrons is significant and produces ~3 times the normal tissue dose than that of an optimal epithermal neutron beam (65, 67). If, however, neutrons with energies <1 keV are used, this harmful dose is reduced to negligible levels (67). The acceptable level of fast neutrons is generally believed to be ~2 x 10^{-10} cGy per epithermal neutron, i.e. that dose that would be delivered by a monoenergetic 2-keV beam (65). Current research efforts are directed towards the production of epithermal neutron beams, which when filtered or moderated, have a preponderance of neutrons in the 1-1000-eV range. Since the distribution of thermal neutrons generated at depth is only moderately affected by the energy of the incident epithermal neutrons, it would be best to maximize intensity by using the entire epithermal energy region, rather than reduce intensity via a filtered monoenergetic beam (68). When the whole reactor core is used as a source of neutrons, suitable epithermal neutron beam intensities >10^7 n/cm^2 sec^{-1} should be available with reactor powers of 1-3 MW or more. Thus a single irradiation of 5 x 10^{12} n/cm^2 would take 80 min assuming that one thermal neutron was generated per epithermal neutron (65). Reactors with this power output include the BNL Medical Research Reactor, the Massachusetts Institute of Technology reactor, the Georgia Institute of Technology, and the Power Burst Facility at the Idaho National Engineering Laboratory.

Approximately 35 μg/g of 10B/g of tumor would be necessary in order to raise the n,α tumor dose to levels significantly above that delivered to normal tissues by the unavoidable n,p and n,γ reactions with nitrogen and hydrogen, respectively. With this "optimized" epithermal neutron beam, the therapeutic gain, or ratio of tumor dose to maximum normal tissue dose, would approach 4 (40). It is a tenet of radiation therapy that the tumor dose is limited by normal tissue tolerance. A therapeutic effect could be achieved with an epithermal neutron beam delivering 5 x 10^{12} (peak) n/cm^2. The reason for this is evident from calculated and measured dose distributions generated in a phantom head, from "pure" epithermal neutrons. Approximately 900 cGy (rads x RBE) would be produced by gammas and protons from the 1H(n,γ)2H and 14N(n,p)14C reactions (40, 65, 67). When this is added to 400 cGy (rads x RBE) from a hypothetical 3.5 μg 10B/g present in normal tissue assuming one-tenth of the 35-μg 10B tumor, the normal tissue dose would be ~1300 cGy, which approximates the normal tissue tolerance for single dose whole brain irradiation (69).

Current efforts directed towards the modification of existing reactors for clinical trials in the United States include those at: (a) BNL, using the Al2O3-moderated epithermal beam at the BMRR; (b) MIT, using a proposed aluminum-sulfur-moderated epithermal beam; and (c) PBF at Idaho National Engineering Laboratory, using a proposed and yet to be installed and tested aluminum-D2O-moderated beam. Of the three, the BMRR beam, as shown in Fig. 2, is the only one the parameters of which have been measured and reported. The PBF, at a power of 20 MW, would theoretically be able to deliver therapy in a single dose in 6 min while ~45 min would be needed for the BMRR. Calculated parameters for the MIT reactor are promising and an experimental filter is currently being installed and tested. It is anticipated, however, that because of radiobiological considerations such as selective repair of low LET damage in normal tissues and redistribution of boron compounds in the tumor, neutron irradiations will be delivered in 4-6 fractions (70). Such fractionation would reduce the effective normal tissue dose significantly, due to repair of the low LET component. Tissues damaged by the 10B(n,α)7Li reaction should not repair, due to the high LET character and the α and 7Li particles.

Alternative Neutron Sources

If BNCT is shown to have therapeutic efficacy in initial clinical trials, then alternative neutron sources become attractive, due to the relative expense and paucity of suitable nuclear reactors, as well as public concern about the siting of reactors in metropolitan areas. Neutron sources such as Cf-252, 7Li(p,n)7Be, and spallation neutron sources are all being investigated as alternatives to nuclear reactors. While ultimately such sources may prove to be capable of providing a sufficiently high flux of neutrons for NCT, they have not as yet been shown to have the required intensity and purity (40, 65, 71-76).

Isotopic Sources

252Cf would be the most suitable of the various isotopic sources that have been considered and used for neutron production (71). Neutron spectra and beam characteristics are similar to those of reactor fission sources with a model energy of 1 MeV. Gram amounts of 252Cf, which emits 2.34 x 10^6 n/s/μg would be necessary for beams that could be used for therapy. The t½ of 2.65 years would provide a simple and reliable source, which could be used in localities where no suitable nuclear reactor is available.

Low Energy Proton Accelerators

Epithermal neutrons for BNCT also can be produced in low energy proton accelerators (72-74) by irradiating lithium targets. Proton beam currents in the range of 1-10 mA would be required, and additional neutron moderation with materials such as D2O would be necessary in order to obtain suitable epithermal neutrons. Although the availability of such beams has not been demonstrated experimentally, mA beam currents are technically feasible and preliminary design studies have been carried out (74).

High Energy Proton (Spallation) Sources

Neutrons of various energies are produced by irradiating heavy elements such as copper, lead, and uranium with high energy protons. The spectra include neutrons with energies higher than those in fission spectra, but these can be moderated to produce epithermal beams suitable for BNCT (75). Measurements carried out with 72-MeV neutrons on copper indicate that irradiation times in the order of hours will be required (76).

Clinical Beam Requirements

There is a consensus that the increased penetration afforded by epithermal beams is superior to the thermal neutron beams that currently are being used clinically in Japan. Attempts are being made at four United States reactor facilities (BMRR, MIT reactor, Georgia Institute of Technology research reactor, and PBF at Idaho National Engineering Laboratory) to
produce beams with a preponderance of neutrons in the region between 1 and 1000 eV using aluminum-D₂O, Al₂O₃ and aluminum-sulfur moderators and filters. The alternative of using scandium as a filter is being considered in the Soviet Union (77). Clinical irradiations in Japan have been carried out with a thermal neutron beam having an incident flux density of 10⁹ ncm⁻² s⁻¹. With an incident epithermal neutron beam flux density of 10⁷ ncm⁻² s⁻¹ producing the same thermal neutron flux densities throughout the tumor the epithermal beam installed at the BMRR should be sufficient to produce a therapeutic dose within ~1 h, either as a single exposure or as the sum of a number of fractionated exposures (65, 78). While flux levels 10 times higher (10¹⁰ ncm⁻² s⁻¹) might be convenient for therapeutic dose within ~1 h, either as a single exposure or as the sum of a number of fractionated exposures (65, 78). While flux levels 10 times higher (10¹⁰ ncm⁻² s⁻¹) might be convenient for delivery of a single therapeutic exposure in a few minutes, especially if a large number of patients are to be treated in a short time, there is no known radiobiological advantage to this, and, in fact, the reverse may be true.

Experimental Animal Studies

Soloway et al. initially reported that tumor-bearing mice given sodium decahydrodecaborate (Na₂B₁₀H₁₀) and irradiated with 3.0–3.3 × 10¹² ncm⁻² had a survival time of 62 days compared to 23 days for reactor-irradiated and 18 days for nonirradiated controls (79). Subsequently it was shown that a related compound, Na₂B₁₂H₁₀S₂, preferentially localized in s.c. implanted, transplantable murine ependymoblastomas (17) and glioblastoma-like tumors (80).

Using the latter compound as a capture agent we have carried out extensive studies with a rat brain tumor model for human glioblastoma (81), the F98 anaplastic glioma, which has a biological behavior similar to that of human glioblastoma multiforme (82). F98 cells were implanted intracerebrally into syngeneic CD Fischer rats and 7 to 13 days later ¹⁰B-enriched Na₂B₁₂H₁₀S₂ was administered at a dose of 50 mg of compound/kg of body weight. At varying time intervals thereafter ranging from 3 to 27 h, animals were irradiated at the BNL Medical Research Reactor. The best results were seen in rats given the capture agent 16 h prior to irradiation with 4 × 10¹² ncm⁻² (429 cGy) delivered to the center of the tumor. These studies together with our own provide additional experimental evidence for the therapeutic efficacy of BNCT.

Clinical Studies

Following Sweet’s initial suggestion that BNCT might be useful for the treatment of brain tumor (3), Sweet and Javid studied the distribution of sodium tetraborate (borax) following i.v. administration to a group of 58 patients who were undergoing neurological biopsy or resection of their brain tumors (4). It was observed that 3 times as much borax concentrated in rapidly growing tumors as in surrounding normal brain tissue. Based on these studies, a clinical trial of BNCT was initiated in 1951 at the Brookhaven National Laboratory by Farr and Sweet (5). A total of 10 patients with glioblastoma multiforme were treated using borax (Na₂B₁₄O₁₄·10H₂O) as the capture agent, followed by neutron irradiation at the BNRL reactor. Five patients received a single irradiation and 5 patients received multiple irradiations. There was no statistically significant prolongation of life or evidence of therapeutic efficacy. In May 1959 the BNL Medical Research Reactor became critical and between then and May 1961 an additional group of 16 patients were treated using either sodium tetraborate (borax) or sodium pentaborate (Na₂B₁₄O₁₄·10H₂O) as the capture agent (85, 86). Similarly, there was no increase in survival time or histological evidence of α-particle-induced radiation injury in the brains of these patients. In the next study, carried out in 1961–1962 by Sweet at the Massachusetts General Hospital, a series of 18 patients were treated (6). In contrast to the Brookhaven study where there was no surgery, as much of the tumor as possible was surgically excised, including a margin beyond grossly identifiable tumor. Sixteen of the patients received an i.v. injection of p-carboxybenzeneboronic acid and two received sodium decahydrodecaborate (Na₂B₁₀H₁₀) via intracarotid injection. Patients were irradiated at the MIT reactor following reopening of the craniotomy wound with reflection of the scalp and dura. Patient deaths occurred from 10 days to 11.5 months following irradiation. Neuropathological examination at the time of autopsy revealed extensive radiation necrosis with prominent vascular lesions of different types in the brains of 9 of 14 patients (7). These effects were attributed to the high blood boron concentrations at the time of neutron irradiation. These studies led to the conclusion that it was essential to have a boron-containing capture agent that was largely cleared from the blood by the time neutron irradiations were carried out. A search for more suitable boron-containing, tumor-localizing compounds was intensified, and as described earlier in this review, a sulfhydril-containing polyhedral borane, Na₂B₁₂H₁₀S₂, was identified.

In 1968 Hiroshi Hatanaka, who had spent several years at the Massachusetts General Hospital working with Sweet, initiated a clinical trial in Japan utilizing Na₂B₁₂H₁₀S₂ as the capture agent. The procedure used was similar in many respects to that used by Sweet (17). The majority of patients had glioblastoma multiforme, and in many instances the tumors were recurrent. As much of the tumor as possible was surgically removed (“debulking”), and at varying time intervals ranging from 1 to 2 weeks following surgery the patients were given an intracarotid infusion of ¹⁰B-enriched Na₂B₁₂H₁₀S₂ at concentrations ranging from 30 to 80 mg ¹⁰B/kg body weight over a
be used to treat large, bulky tumors. Residual tumor that could
result from the use of an epithermal neutron beam that would have a
large penetration depth, thereby precluding adequate treatment of
more deep seated tumors. Hatanaka's results have been described in a
number of reports (8, 9, 86–88) and are noteworthy in several respects.
First and foremost, there was no radiation necrosis of normal
brain except in one patient who had several craniotomies and an
extraordinarily large dose of neutrons (87). This indicates
that the capture agents had been adequately cleared from the
blood. Second, of a total of approximately 77 patients who have
been treated, 38 of whom had glioblastoma multiforme, and 12
of whom had tumors located in the cerebral mantle (i.e., less
than 6 cm from the cortical surface), the reported mean survival
time was 44 months, and the median was 25.6 months. These
include several long-term survivors. One of them is a 65-year-
old man who was treated in 1972 and 17 years later is alive and
well with no evidence of tumor or neurological deficit. At least
taxe least two patients also seem to have been cured, a 70-year-old
woman and a 13-year-old girl.

As encouraging as these results are, a number of questions
have been raised concerning Hatanaka's studies. These include
a lack of patient randomization, varying combinations of treat-
ment prior to the initiation of BNCT, lack of uniformity in the
histological grading of tumors, varying time intervals between
surgery and the administration of the capture agent and irra-
diation, and most importantly, poor depth of penetration of the
neutron beam. What clearly is required is a controlled clinical
trial of BNCT for the treatment of glioblastoma multiforme
using currently available compounds and the best neutron beams.
At the present time plans are underway at several institutions
to carry out careful pharmacokinetic and brain tumor localiza-
tion studies in patients who are undergoing surgical resection of
their glioblastomas. The capture agent Na2B4H4S will be administered at varying doses and time intervals prior to surgery in order to determine the optimum
time between compound administration and neutron irradiation.
Current interest, as described earlier in this review, focuses
on the use of an epithermal neutron beam that would have a
greater depth of penetration than a thermal beam and the
development of better tumor-localizing boron-containing
compounds. At this point in time it is unlikely that BNCT
would be used to treat large, bulky tumors. Residual tumor that could
not be eradicated by surgery, conventional chemotherapy, or
radiotherapy could best be treated by BNCT. In order to attain
sufficient concentrations of the capture agent within the tumor,
it must have an adequate blood supply, or in the case of micrometastases, these should be in proximity to blood vessels
through which the capture agent can diffuse and reach indi-
vidual tumor cells. Since the oxygen enhancement ratio of alpha-
particles is unity, BNCT would be highly effective against
hypoxic cells.

Turning to the treatment of melanomas by means of BNCT,
Mishima and his associates have carried out pioneering work
in this area. Therapeutic efficacy initially was established in an
animal model using Duroc pigs, which develop spontaneously
occurring melanomas (89). [10B]Boronophenylalanine was in-
jected perilesionally around the cutaneous melanoma followed
by a single neutron irradiation. As early as 2 months there was
evidence of regression and this led to a complete cure, as
evidenced by depigmentation at the melanoma site. This was
followed by a clinical study that currently is in progress. As of
November 1989 six patients with cutaneous melanoma, who
for one or another reason were not candidates for surgery, have
been treated by means of BNCT. Multiple doses of a [10B]-
boronophenylalanine-fructose complex, which is more soluble
in water than [10B]BPA, were injected perilesionally into an 80-
year-old patient with a primary acral lentiginous melanoma
occurring on the sole of the foot. After allowing for sufficient
time for the [10B]BPA to clear from surrounding normal tissues,
the patient's foot was irradiated with a dose of 1.04 × 1013
n/cm². Within 2 weeks the melanoma showed signs of regres-
sion, and this was completed by 9 weeks at which time only a
small pigmented spot remained. Two years later there was no
evidence of recurrence. An additional five patients have been
treated, and most recently the [10B]BPA-fructose complex has
been administered i.v. Mishima et al. clearly have demonstrated
the therapeutic efficacy of BNCT for the treatment of primary
cutaneous melanoma in patients who are not candidates for
other forms of therapy. The challenge that lies ahead is to
extend this form of therapy to melanoma patients who have
disease in extracutaneous sites, which currently cannot be
treated by any available form of therapy. One such group would
be patients with cerebral metastases, and an animal model is
being developed by us to address this problem.

Conclusions

The purpose of the present review was to provide an overview of
a therapeutic modality that until recently has received relatively
little attention in the cancer literature. There are a variety
of reasons for this, not the least of which were the disappointing
results obtained in the original clinical trials that were held in
the 1950s and early 1960s. These have served as a cautionary
note against proceeding onto further clinical trials in the United
States until all of the complex questions upon which the success
of BNCT depends have been adequately addressed. These in-
clude the delivery systems for 10B, the optimization of the
neutron beams to be used, careful dosimetry based on phar-
camokinetic and tissue analytic studies, and the design of neu-
tron sources that takes into account all of the advances that
have been made in neutron physics and nuclear engineering.
Studies in each of these areas are either planned or in progress
and it is anticipated that a carefully controlled, randomized
study could be initiated within the next few years to rigorously
assess the therapeutic efficacy of BNCT. As attractive as the
concept of BNCT is, serious problems can be encountered if all
of the various parameters are not properly optimized. For
example, intracellular distribution of boron compounds that
would be used clinically must be evaluated in order to predict
relative biological efficacy, and their pharmacokinetics must be
carefully studied in order to optimize both the absolute and
differential concentrations in tumor and normal tissues.

The true test of therapeutic efficacy for BNCT will be estab-
lished only by clinical trials that bring together a most diverse
team of experts to address these complex questions. Attempts
to shortcut this process may have disastrous consequences, not
only for the patients treated but also for the future of a thera-
peutic modality that otherwise might find an important place
in the armamentarium of 21st century cancer therapy.
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References
BORON NEUTRON CAPTURE THERAPY


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Boron Neutron Capture Therapy of Cancer

Rolf F. Barth, Albert H. Soloway and Ralph G. Fairchild


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