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Report on the Workshop:

The Clinical State of

Boron Neutron Capture Therapy

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Summary

The Department of Energy (DOE) held a workshop on 'The Clinical State of Boron Neutron Capture Therapy (BNCT)' in Charlotte, North Carolina, November 3–5, 1997. The workshop was aimed at assessing the present state of ongoing clinical trials, to guide future planning, and to prepare for decisions. A preceding DOE workshop on BNCT held May 9-12, 1995 in Williamsburg, Virginia, addressed 'Research Needs for Neutron Capture Therapy.'

BNCT uses boron-10 labeled compounds that accumulate preferentially in a selected target such as tumor cells. The target is then exposed *in vivo* to thermal neutrons which induce the $^{10}B(n;\alpha)^{7}Li$ reaction. This instantaneous nuclear reaction deposits about 2.5 meV locally over a range of about 15 μm, i.e., 1-2 cell diameters, and is lethal to the affected cells. Thus BNCT is considered as a unique technique for accomplishing non-invasive 'targeted and timed cell surgery' in the living body.

Thirty-three participants represented the main US research groups engaged in or immediately preparing for BNCT clinical research. Institutions represented included:

- Brookhaven National Laboratory (BNL) with the Memorial Sloan Kettering Cancer Center,
- Various campuses of the University of California with the Lawrence Berkeley Laboratory,
- Idaho National Engineering & Environmental Laboratory (INEEL),
- Massachusetts Institute of Technology with the New England Deaconess-Beth Israel Medical Center of Harvard University (MIT/H) ,
- Ohio State University,
- University of Tennessee Medical Center,
- Washington State University.

One participant from Neutron Therapies Incorporated (California) is presently general secretary of the International Society of Neutron Capture Therapy. Four participants were from the Department of Energy.

The agenda focused on expectations and challenges of BNCT based on the data from the ongoing phase I clinical trials at the Harvard-MIT program (15 patients) and phase I/II clinical trials at Brookhaven National Laboratory (35 patients). Also, the Japanese BNCT experience was reviewed. The presentations and discussion included treatment planning and dosimetry with special focus on normal tissue tolerance and also included consideration of BNCT as an adjuvant to fast neutron therapy. Further discussed were potential new compounds for clinical BNCT with reference to *in-vivo*

assessment of compound biodistribution and to the optimal delivery and targeting of compounds to tumor cells. Potential application of BNCT to malignancies other than glioblastoma multiforme and melanoma and to nonmalignant diseases were identified. Finally optimal criteria for selection and follow-up of patients were addressed.

The summarizing general discussion acknowledged the safety and lack of unusual adverse effects of BNCT at dose levels used with the present protocols for malignant brain tumors (45 patients) and for cutaneous malignant melanoma (5 patients). The continuation of the ongoing trials, therefore, considers escalation in the amount of boron-10 labeled compound (boron-phenylalanine, BPA) and also escalation of tissue dose from the epithermal neutron flux, as approved by the Institutional Review Boards and the Food and Drug Administration. The maximum absorbed dose of 12.5 Gy-equivalent to the normal total brain should not be exceeded. The ratio of doses to tumor and normal brain is expected to exceed 4. Also, the potential of BNCT as adjuvant to fast neutron therapy was considered promising.

The mean survival times of the patients with glioblastoma multiforme treated at Brookhaven were 15 months in protocol group 1, and more than 10 months to date in groups 2 and 3; the corresponding times for conventional therapy are 10.5 months in group 1 and similar to those seen so far in the other groups. More patients need to be evaluated for statistical data analysis. In 5 patients with BNCT of cutaneous malignant melanoma, again no toxic or adverse effects were seen. The treated cancer nodules in the skin responded well, and, depending on size, were seen to fully disappear with no recurrence so far in one patient 2.5 years after BNCT. The normal skin showed lower radiation effects than are normally seen after conventional radiotherapy. The convenience of a single BNCT treatment, versus multiple treatments over about two months required by current conventional radiotherapy, was considered to improve the quality of life.

Based on these data, further clinical trials for the purpose of treatment optimization are justified. These trials are expected to involve optimization of the BPA dose and evaluation of retargeting techniques, i.e., extending from a single treatment session to repeated sessions—probably two, one day apart—so that targeting of boron-compound to tumor cells may be improved. No compound other than BPA is foreseen for clinical use in the near future in the USA. Yet, biodistribution studies with BSH may be justified as preliminary to eventual dual compound application with BPA for BNCT. Moreover, interesting new boron-10 labeled compounds as metabolic analogs and with new delivery systems are being developed for preclinical testing and perhaps for imaging purposes in humans. Neutron dosimetry needs adjustment for multiple beam projections in order to spare normal tissue.

While the primary focus at present is on BNCT protocols for brain tumors and

malignant melanoma, plans are being developed for clinical application of BNCT of affected joints in patients suffering from rheumatoid arthritis within the next 2–3 years at the Massachusetts Institute of Technology. Basic research is advancing well. Other malignant and non-malignant diseases were identified as potential later candidates for BNCT according to disease type, location, and responsiveness to other therapy modalities.

The following report also summarizes statements from the session leaders whose engagement and contributions are gratefully acknowledged.

BNCT Expectations and Challenges

After more than 3 decades of basic research, early clinical trials of BNCT resumed in the United States in 1994 for malignant melanoma and glioblastoma multiforme at the Tufts University Medical Center and Massachusetts Institute of Technology (MIT) in Boston, and for glioblastoma multiforme at the Brookhaven National Laboratory (BNL). These trials are intended to primarily demonstrate safety of the proposed therapies, and are designated as phase I clinical trials by the Food and Drug Administration. Although these trials have the potential to reveal some measure of efficacy, the database is not sufficient as yet to do so. Two such clinical trials with dose escalation have been completed at BNL with a total of 35 patients. They show that BNCT appears safe during the follow up period at the utilized levels of neutron dose and boron-phenylalanine (BPA). Also, the patients whose glioblastoma multiformes were treated with BNCT lived as long as the patients treated conventionally. Finally, BNCT treated patients appreciated the option of a single treatment vs. the multiple treatments required by conventional therapies. These initial results confirm the expectations raised two and a half years ago at the DOE workshop held in Williamsburg. While these results are encouraging, no statement regarding clinical efficacy can now be made.

The trials in the United States are expected to continue. The phase I clinical trial will be completed in one to two years. Phase II trials with BPA will continue during the next two to three years, and are likely to allow assessment of effectiveness at some level of tumor dose. Moreover, a phase I trial involving glioblastoma multiforme has recently begun in Europe, at the Petten reactor in Holland; this trial uses sulfhydryl duodecaborane (BSH) with retargeting in 4 fractions, one day apart. In Japan, the use of BNCT for skin melanoma and brain tumor will continue as discussed later in this report.

If a clear indication of efficacy evolves from phase II trials (compared to conventional control treatments), phase III trials are expected to begin in order to definitely ascertain the effectiveness of BNCT in peripheral melanoma, in brain metastases of melanoma and in glioblastoma multiforme, or in a subset of these malignancies. Other clinical phase I and phase II trials of BNCT may use advanced boron-10 labeled compounds.

It is hoped that the next few years will bring an answer to the applicability of BNCT in clinical practice not only with regard to treating glioblastoma multiforme and

melanoma but other malignant and non-malignant diseases as well. A number of questions were raised with regard to the conduct of future clinical trials:

- What lessons have been learned from the on-going BNCT trials?
- Should a trial of BNCT be permitted as a retreatment after a full course of chemotherapy and/or radiotherapy, and if so when? The present recommendation precludes BNCT as retreatment.
- To what degree and when does tumor surgery alter the blood brain barrier and local cerebral perfusion? This may affect the biodistribution of i.v. injected target compound.
- What target compound will likely succeed the presently used BPA and BSH? The differential uptake ratio of tumor/normal tissue appears sub-optimal for both compounds. Desirable new compounds should concentrate in tumors at more than 100 ppm giving a tumor to normal tissue concentration ratio of more than 10. Such new compounds should be retained in the tumor for several hours and be non-toxic.
- How can one assure homogeneous distribution of sufficient quantities of target compound in the tumor? The eventual success of BNCT depends on essentially 100% tumor cell kill. Does retargeting of tumor cells through fractionated injections of compound optimize the trial protocol?
- What is the optimal fractionation schedule of neutron irradiation in case of retargeting of tumor cells with compound? The spectrum of radiation qualities in the target body at the time of neutron irradiation of the tumor causes different acute or late effects.
- What is the best treatment plan for assuring effective depth dose distribution in the brain? Tumor recurrence was observed in regions with relatively low local dose. Does the dosimetry need to assure irradiation of larger volumes of the brain than the tumor volume, so that infiltrating tumors are properly exposed?
- Which software is optimal for effective therapy planning? Different planning procedures and software are in use in the BNL and Harvard-MIT programs; they need to be compared for data evaluation. Agreement on therapy planning will advance the on-going trials.
- What is the optimal unit of radiation dose for realistic use in BNCT? The presently used units are not uniformly accepted and do not comply with ICRU standards.
- Are BNCT protocols now ready for intercomparisons and inter-institutional data analysis? The continuation of BNCT trials will benefit from pooling experiences and data.
- Is a common referral base for BNCT patients in the USA or internationally now desirable? Other therapy trials operate with such referral bases.

- What other malignancies and non-malignant diseases are likely candidates for BNCT?
- Are ethical questions relating to BNCT trials fully explored and understood? Compassion for patients and realistic assessment of potential benefits of BNCT must be carefully balanced.

Many of the answers to the above question are essential contributions coming from this workshop. Most of the participants agreed with the need to complete phase I clinical trials with BPA in the USA within one or two years. Similarly, participants endorsed the desirability of phase II trials for BPA during the next 2–3 years. There was also no disagreement that BNCT effectiveness at some level would be demonstrated prior to the completion of the clinical trials. However, it remains to be seen if an adequate indication of effectiveness will emerge to justify the initiation of a phase III trial. A doubling of the minimum survival time for glioblastoma multiforme was suggested as decisive evidence of BNCT effectiveness and an adequate justification to proceed to a randomized phase III trial. Pre-clinical trials using BNCT are foreseen for non-malignant diseases.

The proper clinical follow-up of patients by their primary care physicians in close cooperation with the medical group that provides a trial was seen indispensable for long term and reliable evaluation of data. The costs of these follow-ups should be adequately incorporated into the accounting of the overall costs of the clinical research programs. Autopsies are particularly valuable and everyone involved should make all efforts to obtain at least partial autopsies when treated patients die of whatever cause.

For the purpose of optimally evaluating compounds that carry elements for capturing thermal neutrons, the concept of a 'clearing house' was discussed. This should also serve to coordinate the introduction of new compounds for neutron-capture-therapy. Presently, the evaluation even of one class of compounds is very demanding and the limited resources make this a daunting task.

The following research and development is foreseeable for the next few years:

- Microscopic imaging with high resolution track etch autoradiography and surface physics techniques combined with Monte Carlo evaluation of data will provide needed information on boron microdistribution and kinetics. This will lead to optimal treatment planning with neutron irradiation.
- Treatment planning systems in use by most groups will be sorted, cross calibrated and compared. This will allow an intercomparison between the different clinical programs. The time required for completion of treatment planning may be reduced to less than one hour and dose delivery may be possible with a spatial resolution of about 5 mm.
- A few promising new compounds labeled with boron-10 or another useful

element for neutron capture therapy will enter extensive preclinical testing.

- A few reactor based improved epithermal neutron sources and one or two accelerator sources of epithermal neutrons will be ready for preclinical and clinical trials.

Presentation of Clinical Data

a) The Harvard/MIT experience:

The presentation of data of the clinical BNCT trials presently conducted at the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center of Harvard University (MIT/H) began with an expression of appreciation to the Brookhaven National Laboratory (BNL) staff, which provided MIT/H with BPA-fructose (BPA-F) on several occasions and instructed MIT/H staff members to synthesize BPA-F. The review from MIT/H featured first the five patients who were treated for peripheral malignant melanoma on the skin of a leg or foot. The total target doses given in 4 daily fractions in four patients and in one patient in 1 exposure ranged from 10 to 12.5 RBE-Gy The single field neutron irradiation was started at 30–60 minutes after beginning of BPA-F infusion, 400 mg/kg body weight for the each of the four irradiation fractions and 250 mg/kg for the single irradiation. The boron-10 concentration ratio for tumor to blood ranged from about 2.5 to 3, with the skin having boron-10 concentrations similar to that of the peripheral blood in the various patients. Two patients showed partial response at 11 and 17 months after BNCT, two had complete response including the patient with a single irradiation schedule who was followed up to 34 months (as of the Workshop); one patient could not be completely followed. The complete remissions in two patients were confirmed by histological examination of biopsy tissue that was taken from the treated sites. The normal tissue was initially red with dry desquamation soon after BNCT, but at the time of biopsy was completely normal and elastic.

These first results indicated that BNCT of malignant melanoma of skin was safe. Also, no significant chronic normal tissue reactions to radiation occurred in any of the patients followed. All patients showed partial tumor response with two having a complete remission up to nearly three years after BNCT, despite applied radiation doses which were well below the threshold for significant normal tissue reaction.

Because of many competing protocols for developing treatment for brain tumors in the Harvard hospitals, the number of patients referred there for BNCT of

glioblastoma multiforme is still relatively small. So far, nine patients with glioblastoma and one with melanoma metastasis to the brain have undergone BNCT at MIT/H. The study protocol escalates radiation dose to normal tissue and brain from 8.8 to 12.9 RBE-Gy. At the time of the workshop the 10.6 RBE-Gy level had been completed. The minimum tumor dose was about 2 RBE-Gy. Delayed radiation effects to normal brain tissue did not show upon repeat examinations with magnetic resonance imaging (MRI) or upon clinical examination. The patient with metastasis of melanoma in the occipital brain region had complete tumor regression 9 months after BNCT. In the other patients, tumor recurred after 3 to 13 months following BNCT, with a median survival time of close to 9 months. It should be noted that therapy after BNCT was not standardized.

For therapy planning and dosimetry, pharmacokinetic data were acquired by sampling venous blood during the time of irradiation. The samples were analyzed for boron-10 by conventional analytical techniques such as the prompt-gamma procedure. In consenting patients, stereotactic biopsies of tumor and adjacent brain tissues were obtained following a test dose of BPA-F. Intracellular boron-10 concentrations were measured by high-resolution quantitative autoradiography. Generally, 25 ppm average of boron-10 were measured in the peripheral blood at the end of the one hour infusion into the jugular vein with a rapid decline thereafter, whereas brain tumor tissues at the time of neutron irradiation had boron-10 concentration about 2–3 times that found in blood. On the basis of such data and the corresponding MRI's, dose-volume histograms were constructed for each of the 10 patients treated on the brain tumor BNCT protocol.

The ensuing discussion emphasized that about 30 RBE-Gy is considered the minimum necessary radiation dose to the brain tumor for effective BNCT. Yet, with as much as 110 RBE-Gy to the tumor about 75 % of the patients still had tumor recurrences. This may be due to the fact that the present BNCT protocol plans for four daily fractions. Depending on the dose reduction factor for fractionated exposure in BNCT of glioblastoma multiforme, a total dose of 110 RBE-Gy given in four daily fractions could be equivalent to a single dose of about 22 RBE-Gy. Another crucial factor in this evaluation is the boron distribution to tumor cells at the time of neutron irradiation. This was again referred to later in this workshop. For optimal efficacy, all tumor cells must have a boron uptake sufficient for cell killing upon the n-capture.

One 58 years old patient with a posterior-parietal brain tumor suffered a thalamic infarct after the first treatment was given. This infarct developed into a fatal event. No radiation induced injury to normal brain was evident on MRI, but massive edema around the irradiated, partially resected large tumor developed and is believed to be the cause of the patient's demise. This patient was admitted to BNCT with what was described a marginal condition, although each inclusion criterion had been met.

The minimum, average, and maximum radiation doses to tumor were estimated for each patient for different exposure modes. As an example, the resulting treatment plans for the patient with a melanoma metastasis to the brain compared the tumor dose obtained from the M-67 beam at the MIT-reactor with that from the fission converter beam (FCB) being under construction there. The latter is expected to increase the deliverable dose rate by a factor of two. As a consequence, with normal brain receiving the tolerance dose of 12.5 RBE-Gy, the minimum dose to tumor from the FCB will be about 40 RBE-Gy, which is well above the desired minimum of 30 RBE-Gy for inducing a remission of glioblastoma multiforme.

b) The Brookhaven experience:

At the time of the workshop, 35 patients had received BNCT at the Brookhaven Medical Research Reactor (BMRR); 34 of these patients can be evaluated. They are divided into four groups as shown in the table below.

Group	No. of Subjects	BPA-F Dose mg/kg	Reactor Power (MW)	Radiation Fields	Collimator Diameter (cm)	Median BNCT Dose (Gy-Eq)	
						Average Brain	Minimum Tumor
1	14	250	2	1	8	2.2	27
2	8	250	3	1	12	3.6	38
3	5	290	3	1 or 2	12	5.0	44
4	7	250	3	2	12	4.8	28

Groups 1, 2, and 3:

One of the 14 patients in group 1 was alive without any evidence of tumor recurrence at 21.5 months after diagnosis was made, and 20.6 months after BNCT. Five of eight patients in group 2 were alive and in one of these five patients the removal of the necrotic tissue from the tumor bed at 11 months after BNCT did not show any evidence of residual tumor. All five patients in group 3, the most recent group with the shortest follow-up, were alive and in good clinical status.

The median values for age, Karnovsky Performance Score (KPS), Curran Class, tumor volume and tumor depth in the 14 patients in group 1 were 57 years, 85, 5, 21 cm^3 and 5 cm respectively. The median survival time was 15.1 months after the diagnosis. The patients in groups 2 and 3 were clinically similar to patients in group 1; their median survival times could not yet be determined. The median post-BNCT follow-up

times for groups 2 and 3 at the time of the Workshop was 11.3 months and 4.5 months respectively.

Group 4:

The seven subjects in group 4 belonged to a two-field exposure study of BNCT. The aim was to determine the feasibility of offering BNCT to patients with larger and/or deeper tumors as compared to tumors in groups 1,2, and 3; also at test was reasonable safety with the potential for delivering a tumor control dose. The results suggest the two-field exposure may be as safe as the single-field exposure. However, the potential of the epithermal beam at the BMRR to deliver a tumor control dose to larger and/or deeper tumors was limited by the relatively inadequate flux of thermal neutrons at depth in brain. Further trials for tumors that are located deep in the brain and/or are large are being postponed until the proposed fission-plate convertor is installed at the BMRR.

The median age in this group was 48 years, the median KPS was 80, the respective Curran Class was 4, and the median tumor volume and tumor depth were 37 cm^3 and 6.8 cm respectively. The median survival of group 4 patients from diagnosis to the date of the Workshop was 11.5 months, and two of seven patients were alive at 11.5 and 11.8 months after the diagnosis.

Clinical and pathological findings:

Acute side-effects were observed in almost all patients following BNCT. They included alopecia, erythema, transient lymphocytopenia and transient granulocytosis. Moreover, when the irradiation field included an ear, temporomandibular joint (TMJ), parotid gland, conjunctiva or buccal mucosa, the observed grade 1 or grade 2 temporary side-effects included otitis externa, otitis media, parotitis, conjunctivitis, tenderness of TMJ and change in taste. All these side-effects were successfully treated by conventional medical management.

Seizures occurred in 7 patients after BNCT and were promptly controlled in all patients by conventional anti-seizure therapy. Only one of these 7 patients suffered the transient seizures as a direct consequence of BNCT.

Two patients with vasogenic edema around the residual tumor prior to BNCT also developed increased intracranial pressure at about 12 hours following BNCT. In both instances, an increase in the dose of dexamethasone was therapeutically effective.

No late side-effects were recorded after BNCT in any patient up to the time of the Workshop, but since tumor recurred in all at various time intervals, with associated clinical deterioration, late side effects of BNCT were hard to judge. Autopsies were

done in five patients who had been followed from 4.5 to 14.6 months after BNCT. Histopathological examinations of the brains of these five patients failed to show any BNCT induced damage to normal brain. Tumors recurred locally in one half of the BNCT patients, and locally plus regionally in the other half.

The Brookhaven data may be summarized as follows:

- The BPA-F infusions did not cause any acute toxic effects.
- Acute BNCT side-effects generally were transient and responsive to standard medical interventions
- Autopsy evaluation of normal brain in five patients found no histological damage to the normal brain after BNCT.
- The life expectancy of BNCT treated patients has been extended a few months beyond what would be expected following surgical debulking alone and is in the range of that seen in patients treated with conventional radio- and/or chemotherapy after surgery.
- Monitoring patients enrolled in groups 2 and 3 may yield some dose-effect relationships regarding tumor regression.
- The gross tumor BPA-F uptake correlated with tumor cellularity using morphometric techniques. This correlation justifies the use of a 3.5:1 tumor/blood boron concentration ratio for estimating tumor doses.
- Calculations indicate the possibility of treating large and deep brain tumors with BPA-F and the proposed improved beam (fission plate convertor).

The results of these safety-driven protocols led to the proposal to move on to optimization of future protocols. This will help to determine the potential of BNCT in eventually providing local tumor control. The proposed studies plan to deliver radiation doses close to the limits of tolerance of the normal brain; amendments are planned for the case of fractionated irradiation, likely to entail 2 fractions. In order to account for any sensitization effects induced by the first fraction, the total dose requires adjustment to a value about 10% below the brain tolerance dose. The protocol to be prepared in the very near future will include the following studies:

- Dose escalation to normal brain tolerance employing single-fraction irradiation with one or more fields is planned for such tumors which are located laterally in cerebral hemispheres but not in anterior-temporal and anterior-inferior frontal lobes.
- Two fractions of irradiation with two or more radiation fields will be chosen for tumors located in anterior-temporal and in anterior-inferior frontal lobes. Soft tissues such as the eye, ears, and salivary glands do presently not permit the delivery of an adequate dose in a single-fraction to tumors located in the given locations. This study will employ graded dose escalation, 3 patients per dose level.

- An exploratory study plans the inclusion of glioblastoma multiforme tumors which have not been debulked, have a volume of less than 20 cm^3, are located in accessible regions and are otherwise eligible for BNCT. The tumors must be proven by biopsy, and neurosurgeons shall clarify that gross debulking poses an unacceptable risk. These non-debulkable tumors will be treated with two fractions. The first dose will be less than that in the main dose escalation protocol for 2 fractions. At each dose level, three patients will be studied before proceeding to the next level with about 15% dose escalation at each step.

c) The Japanese experience

After the early BNCT trials in the USA were discontinued in the 1960s, BNCT as a form of treatment for malignant gliomas moved to Japan under the direction of Dr. Hatanaka in Tokyo. This program is now under the direction of Dr. Nakagawa, following the death of Dr. Hatanaka. This treatment program uses sulfhydryl-duodecaborane (BSH). A second program in Kobe applies BNCT with boron-phenylalanine (BPA) mainly for malignant melanoma of the skin, under the direction of Dr. Mishima.

The BNCT of malignant melanoma in Kobe is well documented in the literature and has resulted in some tumor regression sand total remissions.

Early reports on the results of BNCT of brain tumors showed surprisingly high survival rates. This helped stimulate resumption of clinical work in the USA. However, only recently has there been an attempt to critically analyze the Japanese experience. This is important in the light of cultural differences that lead to different standards for clinical reporting.

Consequently, the data for the 14 patients from the USA who received brain tumor BNCT in Japan entered a review conducted by Drs. A. Sperce (neurologist/neuro-pathologist) and Laramore (radiation oncologist). The analysis remained limited to this subset of patients because it was felt necessary to both review medical records for important prognostic factors and to obtain tumor pathological specimens for central review. One patient turned out to have a brain lymphoma and, thus, was excluded from the analysis. Of the 13 patients in the analysis, two had anaplastic astrocytomas and 10 had glioblastoma multiforme. Patients were classified according to the recursive-partitioning analysis of Curran, et al. On a pseudo matched pair analysis, the BNCT treated group had no therapeutic benefit. Median survival for the glioblastoma patients was 12 months. All have died prior to the time of the Workshop, and all had tumor recurrence and some also brain necrosis with concomitant cerebral failure. The only long-term survivors were the two patients with anaplastic astrocytomas, performance classes I and II, who would have had a high survival probability also with

conventional forms of treatment.

This work must be put in perspective relative to the BNCT trials in the USA. The treatments in Japan used thermal beams and BSH given intra-arterially; the tumor to blood concentration ratio remained between 0.5 and 1.0. Moreover, the thermal beam required an open craniotomy, and led to an irradiation time of 6–8 hours. The current programs in the USA circumvent most of the difficulties inherent in the Japanese setup. Currently, work in Japan has shifted to the use of epithermal treatment beams from two reactors and emphasizes the treatment of high grade gliomas and malignant melanomas.

Treatment Planning and Dosimetry

a) Primary and secondary radiation units in BNCT

- *Base and derived quantities and units in BNCT*:

The presently applied dosimetric units for BNCT are not easily transferable to the units common in conventional radiotherapy; they also do not comply with the recommendations of the International Commission on Radiation Units and Measurements (ICRU). Thus, the concept of absorbed dose was discussed first.

The quantity 'absorbed dose,' at a given point, is the relevant quantity in radiation therapy and commonly used for the different modalities of irradiation such as in external beam therapy with photons, electrons, neutrons, protons, etc. The absorbed dose, at a point, is defined as the 'mean energy imparted' per unit mass, in a volume surrounding that point. The averaging process implies that a large number of ionizing particles cross the defined volume of interest (ICRU Report 33). A strict relation exists between absorbed dose and cell lethality, and it varies with different types of radiation.

The situation is more complex in BNCT where different types of radiation contribute to the absorbed dose at a given point; thus, the following dose components arise:

- gamma rays from the reactor and from the hydrogen capturing neutrons;
- the 'nitrogen dose,' which is the absorbed dose from the capture of thermal neutron by nitrogen-14 atoms giving rise to accelerated protons and carbon-14 atoms;
- fast neutrons;
- the so called 'boron dose,' which is the absorbed dose from the capture of thermal neutrons by boron-10 atoms giving rise to accelerated alpha particles and recoiling lithium-7 atoms ranging together over about 13–15 μm, i.e., a cell diameter.

The concept of absorbed dose can be applied to the first three components as is done in the conventional therapeutic radiation modalities, since the energy depositions occurs stochastically within the neutron radiation field. However, the concept of absorbed dose has limitations in the case of the boron dose, since the incorporation of boron-10, thus the number of alpha particles and recoiling lithium-7 atoms, is not uniform in the tissues in the neutron radiation field. In fact, the boron concentration varies from one cancer cell to another one depending on the type of boron-10 labeled substrate, the tumor type, cell metabolism and local blood supply. Under such conditions, the 'averaging process' implied in the definition of the concept of absorbed dose is no longer meaningful.

- *Modifying factors:*

In clinical situations, it is only possible to average the boron concentration over a large population of cells and thus derive a kind of average dose. If tumor cells do not contain boron or contain less boron than normal tissue, any increase in neutron fluence will yield no therapeutic benefit but will disproportionately increase the toxicity in normal tissues. Therefore, so-called Compound Factors or modifying factors may only allow a therapeutic gain calculation, if the boron-10 distribution in the tumor regarding cells and extracellular space is known. In case of less boron in a given tumor cell than in the extracellular space, a negative therapeutic gain would result with respect to normal tissues even if the average boron concentration in the tumor over normal tissues may indicate a significant gain.

In normal tissues, the same difficulties apply to some degree. However, the boron concentration in blood of a given patient can be determined accurately and repeatedly during irradiation and the distribution of boron may follow a relatively predictable pattern. Known RBEs and Compound Factors from experiments may be used to establish a starting dose for phase I dose escalation studies. The ultimate tolerance has to be determined by careful dose escalation studies where particular attention must be paid to the possibility of unexpected boron uptake in a sensitive normal cell population in the exposed tissue.

- *Recommendations*:

According to the foregoing discussion, at least three aspects need to be considered in BNCT:

- fractionation of the irradiation (number of fractions, dose per fraction, overall time);
- number of administrations of boron-10 labeled compound;

- timing of drug administration(s) and irradiation(s).

BNCT consisting of a single fraction neutron irradiation following a single administration of boron-10 labeled compound can not be considered as optimal, even if the time interval has been optimized (ratio of blood vs tumor boron concentration). The experience accumulated in conventional radiation therapy over many decades has proven the benefit of fractionation: no tumor has been cured, or can be cured, by one or a few radiation fractions. Even in fast neutron therapy, e.g., high LET irradiation, the TAMVEC experience has shown that 2 fractions per week could be dangerous and that at least 3 fractions per week are needed. Also in chemotherapy, a large number of repeated drug administrations are required, and no example testifies to the efficacy of a single drug administration. Although the situation of BNCT as a binary form of therapy is different involving, for example, both active and passive transport of the boron compound in the tissue, it seems to be much safer to follow the general rules currently and successfully applied in radiation therapy, in chemotherapy and in combined radio- and chemotherapy.

The 'non-boron dose' components, see above dose components, significantly contribute to the dose to the cancer cells, as well as to the normal tissues and thus should be optimized.

Regarding dose escalation, three aspects need to be understood:

- escalation in exposure time;
- escalation in the amount of boron administered;
- escalation in both factors.

Escalation in exposure time will proportionally increase the contribution of the four radiation components (see above) contributing to the absorbed dose at the point(s) of interest. Also, the normal tissues at risk will receive higher doses and they will come closer to their tolerance limit.

As far as the boron dose in concerned, a therapeutic gain arises only when the boron concentration is principally higher in all the cancer cells than in the normal tissues at risk. In contrast, if the boron concentration in some cancer cells is lower than in the normal tissue cells at risk, increasing the exposure time will result in a negative therapeutic gain. This is true, of course, in any case with some cancer cells having not incorporated any boron at all.

The same arguments likely apply to any single administration of larger amounts of boron compound because of given alterations in local tumor blood supply, cell metabolism, effects of previous treatments. In contrast, an improved therapeutic gain could be expected with increasing the number of boron administrations properly spaced in time. This would result in a more homogeneous boron distribution in the tumor than is expected from one administration alone, since repeated administrations increase the probability of the boron compound to reach all the tumor cells.

Regarding the question of retreatment, the discussion led to generally advise

against it according to the extent that the normal tissue tolerance in BNCT is approached.

Uniform definitions of terms and concepts, as well as the same dosimetric protocols should be used by all clinical centers involved in BNCT. This is essential for relevant exchange of information, data analysis, and for evaluating the outcomes of the various trial phases.

In addition, it was stated to be important that the BNCT community adopts, each time it is possible, the general terms and concepts currently used by the radiation therapy community in general. This should crucially help to exchange information, to compare the results and simply improve credibility. In that respect, the ICRU definitions of volumes, and the ICRU recommendations for reporting the treatment, with regard to the specification points, should be followed and adapted and supplemented when necessary, to the specific situation of BNCT.

b) Computational dosimetry and treatment planning for BNCT

- *Status of the relevant technology*:

For approximately ten years the DOE has supported the development, maintenance, and deployment of two independent software systems for computational dosimetry and treatment planning of BNCT. One of these systems has been developed by the Idaho National Engineering & Environmental Laboratory (INEEL) with clinical collaboration from the Brookhaven National Laboratory (BNL). The other was initially developed at Tufts/New England Medical Center and is currently maintained in connection with the MIT/H clinical BNCT program. Both of these systems are successfully used to support human clinical BNCT trials under FDA-approved clinical protocols. This is a remarkable achievement considering the fact that BNCT needed a new expertise for performing the complex, mixed-field dosimetry calculation, with patient geometry constructed directly from the relevant medical images.

It is to be emphasized that even though the two software systems are presently used at both BNCT clinical trial sites in the USA, the work of the two different development groups is by no means redundant. For instance, the INEEL/BNL system has been designed from the beginning with much broader applications, beyond the use of an epithermal neutron beam. Indeed, the DOE may expect to be in the position of having supported the development of a computational tool that will prove useful in all fields of neutron radiotherapy as well as possibly for some non-neutron applications.

Even if the two separate DOE-sponsored dosimetry software systems were totally redundant, the dual system strategy of the DOE for developing these tools was successful and should be continued. The cost is relatively modest in the overall BNCT

effort; moreover, several significant innovations emerged, both as a result of occasional 'friendly competition' between the two development groups as well as from synergistic cross-fertilization of good ideas. For example, the INEEL/BNL system of radiation dose computation has often featured significantly faster execution speeds than the MIT/H system. This is a result of the the former system concentrating on such algorithms that were specifically written for medical neutron transport applications, while the the latter system, for quite valid reasons, preferred a standard, but slower, general-purpose Monte Carlo Program (MCNP) for the dose computations. More recently, however, the MIT/H group created a special version of the MCNP with an improved execution speed by adopting the INEEL/BNL experience with certain improvements and advancements in geometric representation and particle-tracking algorithms. Conversely, because of the decision to build the INEEL/BNL geometric reconstruction algorithm to be independent of image-modality, the MIT/H system now has a greater degree of computer-automated reconstruction of patient geometry when used with CT. Developers of the INEEL system have had the opportunity to learn from the MIT/H team.

In summary, in terms of the requirements and expectations established at the Workshop, the tools for computational dosimetry and treatment planning of BNCT are becoming well-established. One system or the other, and in many cases both, now can meet most of the current expectations; significant improvements are expected in execution speed, clinical user-friendliness, and breadth of application, e.g., regarding fast-neutron therapy with adjuvant BNCT. The participants considered BNCT to be in a successful stage of development with definite advancements in therapy planning.

- *Issues related to specific applications of computational dosimetry in BNCT*

The participants supported the cross-correction of results between the INEEL/BNL and the MIT/H computation systems. An excellent opportunity to do this comes from the developing research at the MIT on BNCT for synovectomy that will probably lead the INEEL/BNL system to be licensed to MIT in 1999. Also, the MIT/H group now validly normalizes the dosimetry calculations to in-phantom measurements. The INEEL/BNL group, on the other hand, successfully prefers a stage by stage validation of the complex computational sequences involved; the objective is to achieve *a-priori* consistency of theory and measurement in the final results. Both approaches are clinically valid.

The participants also addressed the issue as how to define the tumor and target volumes when performing dosimetry calculations. Much of this is a matter of personal preference and experience. Within a fairly broad range of what is considered by the radiation oncologists to be acceptable, different treating physicians will likely

maintain different views on how to define these regions for prescribing an optimal therapy.

c) *Single dose tolerance of normal brain*

The tolerance of the normal brain tissues exposed to BNCT is obviously the main limiting factor to the tumor doses. The BNL group has utilized a rat spinal cord model and the thermal beam at the BMRR to define the relative biological effectiveness (RBE) of the primary and secondary beam components and the neutron capture fission reaction. The model uses paralysis as an endpoint. The Seattle group used the epithermal beam at the BMRR for testing the response of the normal dog brain as to the RBEs for the various beam components; the two endpoints were brain lesions visible by magnetic resonance imaging (MRI) in otherwise healthy animals, and severe neurological dysfunction from brain necrosis appearing about 5 months after treatment and leading, in fact, to a rapid death. On MRI, tissue lesions appeared after 9 Gy, whereas neurological symptoms became obvious after about 12 Gy. The results obtained have been used to set the doses for additional studies regarding both multifraction exposure and retreatment.

The discussions of these data attempted to define tolerance in the normal human brain. The human brain is much larger, and the treatment field is larger. The use of a 1 cm^3 volume brain for setting the maximum dose was considered overly conservative since the dog tolerance was derived from the response of about 20% of the brain volume, i.e., at least 30 cm^3. The results observed in normal brain tissue of the animals are now used in the treatment planning for human patients.

The estimated RBEs and the so-called Compound Factors expressing the biological effectiveness of the boron-compound used, are relatively uncertain; but the sum of all the factors appear to be reasonable.

The following factors appear justified:

- RBE
  Fast neutrons = 3.3
  Nitrogen capture protons = 3.3
  Incident and capture gamma radiation = 1.0
- Compound Factor
  BPA = 1.3
  BSH = 0.33

d) Multifraction irradiation studies

In their work with the epithermal beam at the BMRR, the Seattle group again used the

dog brain model and split the total dose into 2 and 4 equal fractions given at 24 hour intervals. Tissue repair following the low LET components did not appear in these studies and the results were identical to single dose response. There was an increased skin reaction following the fourth fraction compared to single dose exposure. The BNL group using the rat spinal cord model also compared the single fraction to 2 and 4 fractions given at 48 hour intervals. While a slight amount of repair could here be measured, this was much less than observed in a gamma irradiated control group. The presently inevitably low dose rate in BNCT may negate the repair that is now included in computational fractionation.

The discussion resulted in a general consensus that the human trials should start fractionation by dividing the total single dose into equal fractions and not assume any repair initially. Also, because the soft tissue response may be worse after fractioned irradiation, the proposed fractionation schedule should not involve all fields equally, but the irradiated fields should change to optimally spare normal tissues. The main purpose of the fractionation scheme in BNCT remains the optimal compound distribution within the tumor in terms of retargeting to potentially reach all tumor cells.

e) Reirradiation tolerance

The Seattle group presented results from seven dogs that received BNCT twice. First treatment involved the administration of 250 mg BPA/kg followed by epithermal neutron irradiation at the BMRR. The estimated dose to about 20% of the brain volume, i.e., to about 30 cm^3, was 11.5 Gy in three dogs and 12.5 Gy in four dogs. These doses were expected to result in no lethal outcome and close to 50% MRI changes based on previously published single-fraction work. After six months, the dogs were treated again with the same dose to the same region. All seven dogs developed lethal lesions. The time interval between the second irradiation and the onset of pathological symptoms was unexpectedly short; in three dogs neurological findings appeared at approximately two months. It was concluded from these studies that the damage from the first irradiation was not repaired with the consequence of a shorter than usual time interval until onset of lethal lesions after the second irradiation.

In rat experiments, the BNL group gave three different doses of 6 meV photons to a 2 cm long segment of cervical spinal cord. After six months, BPA was administered intravenously and the same region of the spinal cord received various BNCT doses to determine the dose effective at 50 % level, the ED_{50}, at the time of retreatment. For the groups that had initially received 22, 40, or 80 % of tissue tolerance, the retreatment ED_{50} were 77, 80, and 50% of tolerance, respectively. This set of data from rat studies, thus again, showed a sparing effect with indication of repair.

An additional group of rats received initially BNCT and showed at six months a

remaining 55% of tolerance. These BNCT retreatment results were graphed with other published data on rat spinal cord using photons or mixtures of fast neutrons and photons. The BNCT data and the published data from fast neutron/photon experiments fit the generalization that the retreatment tolerance depends on the magnitude of the initial dose. If the initial dose was about 50% of tolerance, the retreatment tolerance of the normal brain is reduced to about 80%. If the initial treatment dose was 80% of tolerance, at retreatment the remaining tolerance is only about 50% of the ED_{50}.

The ensuing discussion emphasized the uncertainties on how to relate the animal data to the human situation. For example, the rat spinal cord model provides no information on volume effects. The volume of the dog brain is about 150 cm^3, thus much larger volumes received higher doses than one schedules in patient treatments. It was also pointed out that the tolerance of the normal human brain to BNCT is unclear. How to fold volume effects into the tolerance data available from published data on clinical photon irradiation, experimental BNCT, and the current clinical BNCT trials is an area needing further investigation. The discussion also addressed the magnitude of the tumor dose that could be delivered in BNCT as retreatment. Since normal brain tolerance obviously limits the dose for retreatment, and if this consideration reduces the total tumor dose to below the value of a single dose, serious ethical questions arise. The general opinion of the participants tended to assemble more preclinical and single fraction clinical BNCT data before the recommending BNCT as a retreatment option after failed photon therapy.

f) Clinically implemented dosimetry

A review gave the design and operation of the INEEL treatment planning system for clinical studies at BNL. It emphasized how the shapes of the computed isodose curves depend not only on the neutron beam spectrum but also on the specific dose components and their mix present at a given position in the target tissue. Thus to be considered are the dose components discussed above, namely from the boron neutron capture process, the gamma-dose from beam contamination and neutron capture reaction predominantly with hydrogen ($^1H(n;\gamma)^2H$, the dose from the neutron capture reaction with nitrogen ($^{14}N(n;p)^{14}C$), and the dose from fast neutrons reacting mainly with hydrogen nuclei. The calculations considered the following factors of boron concentration in relation to the circulating blood: in brain 1, in the scalp 1.5, in mucosae 2.0, in the tumor 3.5. The respective Compound Factors, as discussed above, were taken to be 1.3 for the brain, 2.5 for the scalp and mucosae, and 3.8 for the tumor. The RBE for other high LET dose components attained the value of

3.2. Dose-volume histograms were shown to be good computational tools for examining the biological impact of various treatment plans. The INEEL treatment planning program could be interfaced to a 3-D anatomy and isodose display module developed at BNL.

In summary, the following general issues need consideration in programming of treatment planning:

- 3-D dose distribution in all body parts, with sufficient resolution, perhaps of 5 mm, and with separate dose components regarding the RBEs to be validated by experiments,
- accuracy of dose estimates optimally 5 % but not less than 20 %, using proper transport media relating to different body structures, shapes and sizes,
- modeling based on x-ray computed tomography (CT), MRI, and functional imaging with nuclear medicine techniques, preferentially in a fused mode,
- normalization of data to those obtained by use of phantom experiments,
- arbitrary plane isodose display that is superimposed on the corresponding anatomy,
- dose-volume-histograms, giving volumes, and the maximum, minimum and average doses,
- interface to calculate the prescription of exposure regarding the MW power of the reactor and time of irradiation.
- adequately fast computational facilities, in a stochastic, deterministic or hybrid mode to be decided.

For the processing of treatment planning, the following general issues appear summarily essential:

- informed consent of patient, and all legally required forms and signatures,
- treatment room availability for pre-therapy acclimitization of patients to the particular setting,
- availability of all necessary images for prescribing the individual treatment, with written directives containing tumor and target region contouring, beam placement, computed dose, evaluated plan, beam choice and vector to patient, and on-line assays of boron-10 concentration in peripheral blood,
- availability of baseline clinical tests,
- assurance of sterility and absence of pyrogen in the boron compound solution to be injected.

The absorbed doses delivered at BNCT at BNL were established by using the treatment planning software package developed at INEEL. High spatial resolution of this system allows the creation of detailed models of body support devices, as well as patient's

heads including anatomical structures, e.g., tumor and target volumes, as well as various regions of the brain such as cerebral hemispheres, cerebellum, brain stem, basal ganglia, and optic chiasm. These models are then used in Monte Carlo (MC) calculations, which combine the patient geometry with neutron beam characteristics and body elemental cross-sections, locally absorbed energy distribution, RBE and Compound Factors to produce three-dimensional dose distribution. Results of the MC calculations can then be displayed as isodose contours of total dose or any major BNCT dose component over an arbitrary plane of the MRI. Also, dose-volume histograms for structures defined in the model and any dose component can be drawn, and minimum, maximum and average doses can be obtained. It takes approximately 1.5 hrs of computer time to calculate one case by the current version of the software. This will be upgraded early next year reducing computer time to less than 30 min. The results obtained from the INEEL system were verified by measurements as well as independent calculations using the MCNP-MC code. Continuous close collaboration between BNL and INEEL leads to further improvement of the system and adjustment to clinical needs.

Accordingly, the doses deliverable in BNCT at BNL may be summarized as follows:

- The dose to the contralateral hemisphere can be minimized through careful treatment planning even when two-field irradiation is applied. A third field could be applied from the contralateral side to further increase the dose to deep parts of the tumor,
- the gradients of various dose components are different and their relative contribution to the total dose varies with depth. This may have radiobiological consequences to be incorporated in the treatment plans for the fractionated mode of irradiation,
- the dose-volume histograms, average doses and their components for various brain structures are different in two-field irradiation; for example, more than 50% of the dose delivered to the contralateral hemisphere derives from gamma radiation. This dose distribution can be exploited for the fractionated mode of irradiation,
- increasing the normal brain peak dose in dose escalation studies seems to be safe because only a small fraction of the normal brain will receive doses higher than those that were proved to be clinically safe. Moreover, the fraction of the normal brain, which will receive the highest dose is located within the target volume, a region which comprises the tumor and a 2 cm tissue shell around it. These high-dose volumes will be comparable to the volumes receiving doses as high as 15 Gy in patients treated by conventional stereotactic radiosurgery.

The analysis of doses to the normal brain tissues in BNCT patients treated so far supports the proposed dose escalation and fractionation for the next protocols.

g) BNCT: an adjuvant to fast neutron radiotherapy

Fast neutron radiotherapy alone or as adjuvant to treatments has shown its efficacy in more than 30,000 patients with cancer. Numerous, randomized clinical trials have been conducted and neutron radiotherapy gave better local control than conventional radiotherapy for advanced salivary gland tumors, prostate cancer, and sarcomas. For other tumors such as squamous cell tumors of the head and neck and non-small cell lung cancer, the results are equivocal, and for tumors such as glioblastoma multiforme there is no evidence of therapeutic efficacy. Because of the limited tolerance of tissues, the tumor doses can not be significantly increased beyond their current values. A neutron capture therapy boost can selectively increase the tumor dose and has the potential of dramatically improving tumor control.

As fast, i.e., high energy, neutrons pass through tissue they spontaneously produces an attendant cloud of 'slow,' i.e., low energy or thermal, neutrons that are effective in neutron capture reactions. This thermalized component of the fast neutron radiotherapy beam has been analyzed at the University of Washington Medical Center (UWMC). Model calculations predict a ten to one hundred fold increase of local effectiveness in killing of cells with a boron-10 concentration in the range of 30 μg/g. This prediction has been verified with *in vitro* measurements on the U79 cell line, and *in vivo* in the 36B10 rat glioma model; the concept showed its validity also in a human melanoma patient using BPA as the boron-10-carrier.

Non-small cell lung cancer has been selected for the next phase of study. A prior randomized trial showed an apparent therapeutic benefit for the subset of patients with squamous cell lung carcinoma; also, the analysis of the pattern of failure indicated the spinal cord to be the dose limiting organ in many cases. According to plan at UWMC, the borane $^{10}B_{10}H_{10}$ will be used which is not a metabolite nor tumor specific but which is excluded from the cerebral spinal fluid. However, an appreciably high blood/tumor ratio needs consideration in determining the allowable augmented dose to the spinal cord. Animal studies confirm an extremely low pharmacological toxicity and indicate a potentially high tumor boron concentration (~100 ppm).

Present work at the UWMC tests the efficacy of a BNCT boost in the fast neutron therapy of spontaneous lung tumors in dogs. The next steps aim at validating the toxicity and kinetics of the borane concentration in the blood in normal human volunteers. Then, tumor uptake of the compound will be investigated in patients with non-small cell lung cancers and glioblastoma multiforme, at the time of surgical resection. Institutional Review Board (IRB) approval has been obtained and forwarded to the Food and Drug Administration (FDA) for final endorsement to the holder of license of an Investigational New Drug (IND). Eventually, Phase I/II trials

will use functional and structural changes in PET images for assessing treatment efficacy, as a surrogate endpoint for survival.

Compounds for Clinical BNCT

The design of the overall BNCT program must include continuing studies in chemistry for preparing optimal compounds for biological, preclinical, and clinical work such as that now in progress in the USA and abroad. Specific concerns address the design of boron compounds and their *in vivo* delivery to target cells; the latter issue is often overlooked. If research funding were abolished or even decreased in these areas, improvement of BNCT would be restricted to neutron sources and biology, manipulation and modifications of clinical use of the two compounds of the 'first generation', boron-phenylalanine (BPA) and sulfhydryl-duodecaborane (BSH). Furthermore, there is no physical or medical reason that BNCT must be limited to glioblastoma multiforme and melanoma nor confined to modifications of the present protocols with epithermal neutrons. The $^{10}B(n,\alpha)^{7}$ Li reaction is a unique binary source of localized high LET particles and its potential applications in medicine are limited by available resources rather than ideas.

New therapeutic applications arise from the synergistic matching of the neutron source with the best available boron compound for a given disease under attack. This demands the definition, emphasis and support of certain critical areas of research. Three areas of investigation relevant to the chemistry of compounds for BNCT are: compound design, synthesis and evaluation.

a) Compound design

Compound design is based upon the differential performance of tumor cells and normal cells including the vasculature which supplies these cells. The type and metabolic characteristics of the tumor to be treated and the selected neutron source can be dominant parameters.

In order to achieve an optimal targeting and retargeting, the synthesis and biochemical/biological evaluation presently focusses on low molecular weight boron compounds. Whatever the compounds, they should adequately concentrate boron-10 in ideally all cells of the target tissue to a value of about 10^9 boron-10 atoms per cell, or approximately 30-35 μg boron-10 per g tissue average. At the same time, the ratio of boron-10 concentrations in target tissue and normal tissue such as in the tumor to

normal brain, and the corresponding ratio of concentrations in tumor and blood must ensure high radiation doses to the tumor while the maximal tolerated doses to normal brain and the vascular endothelium are not exceeded. In addition to targeting the main tumor mass that has not been excised, it is essential that the compounds have the capacity for crossing the normal blood-brain barrier (BBB). This is essential for targeting those tumor foci that have infiltrated normal brain. These tumor islands must also be destroyed since they could be the basis for tumor recurrences and thus account for therapeutic failures.

At present, BPA and BSH are two old and fairly well understood agents in clinical trial; they belong to the 'first generation' of compounds and are not optimal for several reasons. One is the lack of tumor selectivity of both compounds, with BSH being concentrated in brain tumors for their lack of blood brain barrier, whereas BPA is actively transported across the blood brain barrier and concentrates in the tumor because of an increased rate of protein synthesis in the tumor cells; it is, however, not incorporated into protein. New and more selective compounds for given target tissues need to be developed and carefully evaluated for clinical application. Several compounds have been synthesized and are known to cross the BBB as does BPA. They need further evaluation for optimal targeting of tumor cells.

Of the 'second generation' boron compounds, porphyrin carriers currently undergo animal testing and show a promising high ratio of boron concentrations in tumor and normal brain; yet, the toxicity of porphyrin is still a problem. 'Third generation' compounds include boron labeled analogues of natural small molecular precursors of cell metabolism, lipoprotein, liposomes, various DNA binders, ligands for specific cell receptors, as well as radiation sensitizers and various pharmaceuticals.

Compounds chosen for biological evaluation need, of course, to be tested for toxicity. This must be sufficiently low for further evaluation in brain tumor-bearing animals. It is essential that those compounds demonstrating promise as tumor-targeting agents must ultimately be screened in animals with intracranial lesions that simulate clinically-observed glioblastoma multiforme. All new compounds must be compared biologically against the two agents that are now used in clinical trials of BNCT, namely BSH and BPA. Any new compound must be at least as good as BSH and BPA in terms of tumor boron concentration in order to be considered for further evaluation. Such evaluation would include more extensive toxicological studies in larger animals together with radiobiological studies.

For many treatment targets, cellular characteristics are fairly well understood. However, in order to design the optimal compound with a corresponding structure/function relationship items such as hydrophilicity *versus* hydrophobicity, stereochemical consequences of introducing large substituents, disruption of hydrogen-bonding opportunities, alteration of electrical charge and dipole moments need

consideration. One often sees tailored molecules equipped with elegant specificity linked to hydrophobic carborane cages or hydrophilic polyhedral borane cages without success in biological application. This failure may derive from finely tuned cell metabolism being incompatible with compounds carrying large structural units such as the carboranes. This speaks against small compounds as boron carriers unless one has Quantitative Structure Activity Relationship (QSAR) data available and the ancillary data required to use them appropriately.

On the other hand, macromolecular compounds carrying large numbers of boron atoms can be precisely assembled and attached to ligands targeted for receptor sites that are specific for, or over-expressed by tumor cells. Certain of these macromolecular carriers can be designed to function as compounds in their own right or used as reagents for conjugation to primary structures such bioligands. Thus, small liposomes with diameters of 50–100 μm and constructed of lecithin-phosphatidylcholine appear to be exceedingly effective as carriers of hydrophilic boron compounds to be delivered *in vivo* where access to the tumor cells is open, i.e., where the blood brain barrier is inactive or destroyed. The carrier liposomes may have external targeting devices although these systems have been examined with only a small number of tumor models. Also, lipophilic carboranes may be incorporated into the liposome wall. Ideally, an i.v. injection of properly tailored liposomes may deliver a boron compound to cell receptors followed by internalization of the hydrophilic boron compound into the cytoplasm of the targeted cell followed by rapid migration and binding of the compound to the cell nucleus and its DNA. Such systems are under investigation.

b) Compound synthesis

Crucial, yet often overlooked, for new compound development is the identification of a source of suitable ^{10}B-enriched precursors for compound synthesis and the development of high-yield synthesis reactions which reduce costs.

Examples of potentially wide applicability are the linking of carboranes to peptides by way of SH-or NH_2 bonding or the labeling of a variety of organic molecules especially nucleosides by using particular side chains on carboranes such as through phosphate diesters. Nucleoside linked carborane phosphate diester has been found in the cell nucleus at concentrations of 1–6 x 10^6 boron atoms per cell.

c) Interinstitutional compound evaluation

A first step in compound evaluation is the identification of representative tumors to be targeted, including glioblastoma multiforme. The kinetics of compound uptake and distribution in the tumor and its cells needs to be appropriately demonstrated *in*

vivo. Also, the toxicity of the compound should be known. Animal models will provide for testing of many needed parameters to prepare a compound for clinical use even if the study of compound distribution and toxicity in humans is essential. Little of this work is under way in a logical manner with newly developed compounds.

The basic and indispensable data on compound behavior *in vivo* should be provided through an interinstitutional project. The corresponding program would be not prohibitively expensive with defined procedures. A special group of experts should draw a program and, if a consensus is reached, additional funding should be sought for the purpose. Funding for compound evaluation without continuing support for new compound development would defeat the purpose. Obviously, the development of improved compounds for BNCT of glioblastoma multiforme or other targeted tumors should be of highest priority; trials with suboptimal compounds are in progress. It should also be recognized that boron agents are not pharmaceuticals and offer no efficacy of their own. Thus, different rules and administrative regulations apply which make compound development for BNCT less expensive and consequently easier to change due to reduced investment.

d) Optimization of compound targeting

An alternate way of boron compound delivery to brain tumors uses intracarotid (i.c.) injection. Thus, BSH or BPA so administered gave a double tumor boron concentration compared to values obtained following intravenous injection. This result was further improved fourfold following the disruption of the blood brain barrier (BBB) by hyperosmotic mannitol injection. In contrast, boron concentrations in normal brain and blood at 2.5 hours following i.c. injection with or without disruption of the BBB had fallen to levels equivalent to those observed after i.v. injection. These relative increases in tumor boron uptake were associated with corresponding increases in mean survival times (MST) of F98 glioma bearing rats following BNCT. The MSTs of rats given i.c. BSH or BPA were 52 and 95 days respectively when the BBB was disrupted, versus 40 and 52 days without BBB disruption. The control rats received the compounds by i.v. injection and had MSTs of only 33 and 37 days. These results demonstrate an improvement of compound delivery resulting in a significant enhancement in therapeutic efficacy in a rat brain tumor model that until recently has been incurable by any therapeutic modality. Moreover, when BSH and BPA were given together by i.c. injection into rats with a disrupted BBB, as many as 25% of the animals were cured. This strategy to optimize delivery of BSH and BPA may be applicable clinically and relatively soon be incorporated into the protocols of ongoing clinical trials. In preparing for this as a first step, boron-10 distribution in tumor cells after intra-arterial administration of BSH and BPA should be evaluated in glioblastoma

multiforme patients at the time of surgical resection of the tumor. If enhanced tumor uptake of boron and the ratio of boron concentrations in tumor and blood on the one hand and in tumor and normal brain on the other are improved over the corresponding values from presently used schedules, a BNCT study should be initiated comparing i.v. versus i.c. administration of the boron compound. The disruption of the BBB by hyperosmotic mannitol is clinically used to enhance the delivery of cytotoxic chemotherapeutic agents at various institutions, including the Ohio State University. Concomitantly, studies in canines may help in assessing the safety of the procedure.

Besides hyperosmotic mannitol, the pharmaceutical RMP-7, a synthetic nanopeptide and bradykinin analogue, is used to disrupt the BBB and has been shown to enhance the delivery of BPA to a similar degree as with mannitol. Current studies with RMP-7 aim at optimizing the delivery of BPA.

Taking advantage of specific tumor cell receptors, high molecular weight ligands such as boron-10 labeled epidermal growth factor (B-EGF) will require strategies that are different from those for low molecular weight compounds such as BSH and BPA, in order to optimize boron delivery to tumor cells. Using the C6 rat glioma model, intratumoral (i.t.) injection of B-EGF resulted in a 1,000 fold increase in EGF uptake by receptor-positive C6 glioma cells compared to values obtained following i.v. injection. Intratumoral injection is being used clinically at Duke University Medical Center to deliver ^{123}I-labeled anti-EGF receptor monoclonal antibodies (MoAbs) to residual tumor cells after surgery in patients with glioblastoma multiforme. This technique or one of its variants may be applicable to deliver B-EGF or boron-10 labeled MoAbs for BNCT after primary tumor resection. Obviously, different delivery strategies appear to be needed for low and high molecular weight boron containing compounds and the development of these strategies should proceed in parallel with compound synthesis.

Besides primary targeting, potential retargeting of malignant brain tumors by boron compounds is presently an important issue in designing new protocols for optimization of BNCT. The purpose of retargeting is to assure that all cells in the target tissue take up sufficiently large amounts of boron for the capture reaction to be effective. The efficacy of retargeting depends on the degree of local tissue perfusion at the time of compound administration. Various strategies may achieve the goal of retargeting. Canine studies are planned to test for optimal fractionation of compound injections followed by repeated neutron irradiation, as discussed above.

e) In-vivo imaging of compound biodistribution

Various modes of imaging allow the *in vivo* assessment of boron compound distribu-

tion. Particularly discussed were magnetic resonance imaging (MRI) and positron emission tomography (PET) as potent tools to quantitatively observe *in vivo* the biokinetics of a given boron carrying agent.

Boron MRI has not yet reached clinical efficacy suitable for BNCT treatment planning. Current protocols can generate boron-11 images. Yet, they have a relatively poor spatial resolution and, moreover, require special equipment regarding the instrument transmitter and receiver hardware; also the software needs adjustments. It is currently impossible to image boron-10 due to its poor nuclear magnetic characteristics; the atoms quadrapole leads to extremely short relaxation times (T2) making standard MRI protocols inappropriate.

Future work may allow for somewhat improved boron-11 imaging by using high field clinical research magnets, over 7 tesla; this is likely not suitable for boron-10. The latter may eventually be better imaged with conventional MRI equipment allowing the generation of new pulse sequences geared to the spin-transfer polarization between hydrogen and boron. Also, heteronuclei such as fluorine-19 may serve for compound imaging by MRI. For example, MRI using ^{19}F-BPA is a logical step; yet, the relatively large quantity of labeled compound to be administered for MRI would require toxicity testing.

PET has been used to clinically investigate uptake of fluorine-18 labeled BPA in brain tumors. So far, only three patients have undergone this examination in the USA and show distinct uptake of the labeled compound in the tumor with the tumor size appearing somewhat larger that in the MRI scans. The results confirm the reports from a greater number of patients in Japan. To date, the data look promising in that answers to important clinical questions may be obtained. Still, before treatment planning is modified on the basis of PET data, more patients must be scanned. For further development of functional imaging with PET also carbon-11 labeled BPA was prepared and the results compared to the fluorine-18 labeled BPA, at the University of Tennessee.

It is currently assumed that ^{18}F-BPA mimics BPA *in vivo* based on a limited number of animal experiments; here, nude mice were implanted with human glioblastoma tumor cells and i.v. injected with the appropriately labeled compounds for kinetic studies of tracer uptakes into the developed tumor. Although the assumption of biokinetic compatibility of ^{18}F-BPA and BPA is reasonable, further validation is needed. The presently available ^{18}F-BPA data suggest the following:

- BPA uptake can be followed from the time of injection to the *in-vivo* biodistribution, using the ^{18}F decay statistics. Interestingly, the data obtained from the three patients with glioblastoma multiforme in the USA closely resemble the data that were obtained at the BNL; here, boron concentrations were measured as a function of time during and after BPA injection, in the peripheral

blood, in the tumor, and normal brain tissue, yielding uptake, and washout rates in each patient.

- ^{18}F-BPA imaging after surgery confirms that normal brain does not unusually accumulate BPA. This is also true for edema areas of the brain. However, this preliminary data was obtained after a bolus injection of the compound and does not necessarily apply when BPA is infused slowly. The images also reveal that residual tumor tissue after surgical resection takes up ^{18}F-BPA more effectively than normal tissue; the ratio of tracer concentrations in tumor and blood exceeds the corresponding ratio for normal brain and blood by a factor of more than three. The images also showed a tracer distribution that superimposed rather well with the contours of absorbed doses generated at BNL using tissue samples obtained during debulking surgery. The concurrent findings from a single brain autopsy lead to the preliminary conclusion that the post-surgery PET data may improve the BNCT planning protocol.
- PET with ^{18}F-BPA after BNCT revealed that the tracer accumulated in tissue near the original tumor boundaries. It remained uncertain whether the uptake delineated necrotic tissue or tumor regrowth. Superposition of this PET data on a gadolinium-enhanced MRI of the same patient showed the tracer to be within the gadolinium enriched region which suggests necrotic tissue to be responsible for the tracer uptake.
- PET could be used to monitor biodistribution of any potential BNCT compound as long as it could be labeled with a positron emitting isotope. The non-invasive procedure would be widely applicable and, moreover, bypass the need of tissue biopsy or animal sacrifice.
- Control experiments using agents such as radioactive thallium or, possibly, a perfusion agent should demonstrate input functions and validate the proposed kinetic model.

The usefulness of PET is likely to improve due to the current development of research instruments giving a resolution of 2 mm. High resolution PET would also allow a more effective evaluation of potential BNCT compounds in animals, would, therefore, improve modeling, and would help in calculating local dose for therapy planing.

The presentations also outlined the use of PET to monitor copper-64 labeled boron-10 labeled porphyrins (BOPP) that has been proposed for use in BNCT. It is as yet uncertain which of the various boron-10 labeled porphyrin analogues may eventually find acceptance for clinical trials since animal studies have indicated toxicity of some porphyrins and apparently also their accumulation in the arterial membrane.

The participants emphasized the great potential of dynamic PET for BNCT in delivering *in vivo* biokinetic data including sequential, time-dependent ratios of boron

concentrations in various body sites such as in tumor, normal brain, and circulating blood. Much remains to be done in acquiring sufficient data to validate the technique.

Additional Targets for BNCT

a) Malignant tumors

The issue of using BNCT to treat malignancies other than glioblastoma multiforme and malignant melanoma was discussed at length. The participants agreed that many tumor types in a variety of locations are good candidates for treatment with BNCT. These tumors fail to respond to conventional therapies, are universally fatal and until late in their evolution are generally well localized. They are likely treatable with localized high LET irradiation, especially that in BNCT. Also, BNCT of these tumors may be easier and more successful that of glioblastoma multiforme. Unfortunately, the current resources for evaluating BNCT for tumors other than those presently in clinical trials are limited. In addition, available resources should be concentrated on completing the current clinical trials in order to reach statistically significant data on safety and , if possible, efficacy. The likelihood of completing current clinical trials would suffer from a serious expansion of clinical and laboratory BNCT protocols. Nonetheless, laboratory research and biodistribution studies using appropriate tumor models should be encouraged with the prospect of a potential expansion into clinical application.

On the other hand, the evaluation of BNCT as a boost in fast neutron therapy of selected tumors should continue and evolve into multicenter trials supported by the National Cancer Institute of the National Institutes of Health. Fast neutron therapy has shown significant efficacy in selected tumor classes, and data on dosimetry and toxicity are available. Therefore, addition of BNCT as boost, as discussed above, should result in easily interpretable results and be acceptable to the radiation therapy community. Furthermore, such a clinical trial would provide important information helping research in BNCT. As experience with BNCT accumulates, as neutron beam quality improves and as better and more selective compounds for neutron capture reactions become available, it is likely that tumors other than glioblastoma multiforme and malignant melanoma will be identified for neutron capture therapy.

b) Non-malignant diseases

Two non-malignant diseases have been suggested as potential candidates for treatment by BNCT. Coronary artery restenosis following balloon angioplasty may

benefit from BNCT. Secondly, chronic joint diseases such as rheumatoid arthritis or degenerative arthritis have been successfully treated with intraarticular injections of radionuclides such as yttrium-90, a beta emitter; BNCT for synovectomy poses a lower risk than radionuclide-synovectomy. Moreover, because of the high LET irradiation BNCT may be more effective.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by recurrent swollen, inflamed and painful joints. It afflicts 1–2 % of the US population. Since the cause of RA is unknown, patients are treated symptomatically. Anti-inflammatory drugs are effective in approximately 90% of all patients. In the remaining 10% patients, the inflammation in one or more joints will not respond to drugs and a more severe approach is taken. In the USA, the only option is surgical synovectomy, a costly and painful procedure followed by extensive physical therapy and rehabilitation. Symptomatic relief lasts roughly 2–5 years since the cause of RA has not been addressed.

Radionuclide synovectomy using beta-particle emitters injected directly into the joint is routinely used in Europe and elsewhere and gives about the same symptomatic relief, for the same fraction of patients, for the same length of time, as surgery. Radionuclide-synovectomy is less costly, less painful and requires no rehabilitation time relative to surgery. It is, however, not approved for routine clinical use in the USA due to concerns regarding healthy tissue irradiation caused by leakage of the beta-emitter away from the joint.

Boron Neutron Capture Synovectomy (BNCS) is proposed as a way to carry out radiation synovectomy without the concern regarding leakage of a radioactive substance. A boron-10 labeled compound injected into the joint space would be followed by local irradiation with a beam of low-energy neutrons.

To-date, extensive investigation of BNCS has been carried out. This work involves both the testing of boron-10 labeled compounds also *in vivo* and the design and construction of accelerator-based neutron beams specifically for this purpose. The two compounds checked so far are expected to affect specifically different synovial regions. This approach arose out of the uncertainty as to which cells, if not all, need to be ablated. The energy deposition from the boron neutron capture reaction ranges only over about 15 μm, whereas surgical and radionuclide synovectomy using β-emitters seek to destroy the entire synovium consisting of the subsynovium and the cells lining the joint cavity. It may, however, be necessary to destroy only the phagocytic and enzyme-releasing cavity lining cells. The compounds investigated are potassium-duodecaborane, $K_2B_{12}H_{12}$, expected to pass through the entire synovial membrane, and boron metal particulate, taken up by the phagocytic lining cells only.

Compounds are evaluated, first, using samples of human arthritic synovium taken from the surgical operating room. Co-incubation with the boron compound for a

given period of time precedes boron-10 assessment by prompt gamma neutron activation analysis at the MIT reactor. If a compound appears promising following uptake and washout studies in the tissue biopsies, it is then evaluated *in vivo*. For this, the antigen-induced arthritis model in the rabbit is used. Following intra-articular injection of the compound, the animal is sacrificed at a given time for examination of tissues such as synovium, cartilage, ligaments, bone, various organs and fluids for boron-10 uptake analysis.

Results to date are encouraging. In the rabbit model, boron-10 uptake in the synovium at about 20 min after intra-articular injection of $K_2B_{12}H_{12}$ ranges from 265 to 950 ppm. This concentration level has fallen to 30–50 ppm boron-10 at one hour later. While this level is more than sufficient to evaluate the efficacy of BNCS in the animal model, the rapid wash out of the synovium may limit the ultimate use in clinical medicine unless injection and neutron irradiation can be timed closely. Better compounds should be developed and evaluated for eventual clinical trials.

A neutron beam for BNCS has been prepared and installed at MIT's Laboratory for Accelerator Beam Applications (LABA). The corresponding D_2O/graphite assembly will allow rabbit knee treatments in 4-13 minutes for a 1 mAmp proton beam, based on the uptake levels of $K_2B_{12}H_{12}$ already observed in this animal model. BNCS of the relatively large human knee, however, will demand more time and an increase in the proton current, which is feasible. In view of having prepared the radiation facility further efforts are focussed on developing and testing of suitable boron compounds for human use.

It is hoped that approval may be obtained from the FDA to study biodistribution and begin clinical trials in three years. The substantial animal work and beam design already accomplished should aid compound development for human use.

Follow-up and Patient Selection

Reporting of clinical trials depends on the study design as determined by its objectives. A detailed description of the requirements of phase I through phase III clinical protocol design is beyond the scope of this report. The current phase I clinical trials of BNCT at the Brookhaven National Laboratory and the Massachusetts Institute of Technology with the Harvard University Medical School lead the way. These trials have been reported at this Workshop and provide excellent examples of how preliminary data are collected to answer the basic question regarding BNCT:

—Can this therapy be delivered safely?

Conventional study design for BNCT is complicated by the binary system involved; a pharmaceutical grade boron-containing chemical compound is used together with a beam of epithermal-thermal neutrons to induce the boron neutron capture reaction in the selected target tissue. In consequence, some ambiguity exists as to what constitutes a phase I and phase II trial. To establish toxicities in a phase I trial and tumor response in a phase II trial, requires an escalation both of the amount of injected boron compound and an escalation of the neutron radiation dose. Obviously, this essential binary requirement for the therapy trial reflects the problems in using conventional methods to describe BNCT in the trial phases.

Initial testing of BNCT for glioblastma multiforme and malignant melanoma primarily aims at confirming safety, as determined mainly by avoidance of therapy induced CNS complications. Follow-up examinations with neurodiagnostic imaging such as MRI and CT allow the recognition of structural changes associated with functional neurological complications. These may be related to cerebral edema, and also tissue degeneration in the form of necrosis. So far, autopsy data is essential to differentiate tumor progression from radiation necrosis even if functional imaging, for example with PET, may give the same diagnosis *in vivo*, i.e., non-invasively, either prophylactically as part of the follow-up after BNCT or specifically at the time of appearance of symptoms. The most obvious endpoint for these studies is survival, which can be compared to historical or case matched controls.

The clinical trials with suboptimal local radiation doses to the tumor, as they were presented at this Workshop, justify the statement that BNCT according to the current protocols appears to be no more harmful than conventional radiation therapy, although its present efficacy is in the same range as that of conventional therapy. Also, the convenience of a single treatment with BNCT helps justify the recommendation to continue the running trials and prepare for optimization of local dose delivery to the tumor. When BNCT trials demonstrate efficacy beyond that of conventional aggressive therapy, controlled phase III trials will be necessary to prove its benefit and should be an interinstitutional effort funded by the National Institutes of Health.

The participants acknowledged 12.5 Gy to be the limit of tolerance of the normal brain exposed to BNCT. This makes escalation of compound administration more crucial than that of radiation dose in order to optimize doses to the tumors. Thus, more than 350 mg of BPA per kg body weight may eventually be given per treatment session. The foreseen installation of fission plates at the MIT reactor and the BMMR will enhance the neutron fluence, shorten the irradiation times and eases the expected fractionation modality of exposure. In order to avoid problems in evaluation of patient data, BNCT for glioblastoma multiforme should be restricted to histologically

defined tumors of given size ranging from 60 to 70 cm^3 (including surrounding edema) and not causing midline shift.

The patients should be fully informed of the results of the current clinical trials, with emphasis on the uncertain outcome of the trials and the questionable benefits of BNCT over other aggressive conventional therapies.

Clinical follow-up of all treated patients in close association with the primary physicians is paramount and should be formalized for better data evaluation. The initiation of regular consultations between the Brookhaven and the Boston groups should allow for easy adjustment of protocols and evaluation of data with the hope of better patient referral. Interinstitutional cooperation at the experimental, preclinical and clinical levels should help the assessment and completion of the present trials. Clinical trials at other centers in the USA can be encouraged when the on-going trials indicate efficacy beyond the present level. Studies aimed at various novel approaches to compound delivery such as the combined administration of different boron-10 labeled compounds in conjunction with disruption of the BBB , as discussed at this Workshop, should be continued to maturity for eventual clinical application. A program to obtain clinical pharmacokinetic, biodistribution, and toxicity data to justify seeking FDA approval of intracarotid injection of BSH is underway.

Summarizing Statements

- BNCT in the present protocols is safe and well tolerated.
- The benefit of BNCT is still uncertain.
- The trial results justify BNCT optimization.
- New compounds providing for neutron capture should be tested interinstitutionally.
- BNCT is promising as adjuvant to fast neutron therapy.
- BNCT may be effective for intractable rheumatoid joint disease in peripheral locations.
- The on-going and future clinical trials need to be a coordinated effort.
- Completion of current clinical phase I trials is urgently needed.

Expected Outcome

- Guidance to DOE in managing the BNCT program.
- Immense benefit to all from the open and critical discussions.

Appendix A: Workshop Agenda

Sunday, November 2:

7:00 PM: Informal discussion of agenda *R.F. Hirsch, L.E. Feinendegen and meeting participants*

9:00 PM Adjournment

Monday, November 3:

8:30 AM Welcome and Introduction *R.F. Hirsch, L.E. Feinendegen*

9:00 AM I. BNCT Expectations and Challenges *O.K. Harling*

10:00 AM II. Presentation of Clinical Data,

- Experience at Harvard Medical School and Massachusetts Institute of Technology *P.M. Busse, R.G. Zamenhof*
- Experience at Brookhaven National Laboratory *A. Chanana, J.A. Coderre, A.Z. Diaz*
- The Japanese experience *G.E. Laramore*

1:30 PM III. Treatment Planning and Dosimetry

- Primary and secondary radiation units in BNCT *R.A. Gahbauer*
- Neutron dose, compound concentration, cell and tissue dose *D.M. Nigg, F.J. Wheeler*
- Normal tissue tolerance *J.A. Coderre, P.R. Gavin*
- Clinically implemented dosimetry *J. Capala, R.G. Zamenhof*
- BNCT as adjuvant to fast neutron therapy *G.L. Laramore*

Tuesday, November 4:

8:30 AM IV. Compounds for BNCT

- Compounds for clinical BNCT *M.F. Hawthorne*
- In-vivo assessment of compound biodistribution *T.F. Budinger, G.W. Kabalka*
- Retargeting of compounds to tumor cells *A. Soloway*
- Optimal delivery of compound *R.F. Barth*

1:30 PM V. Additional Targets for BNCT

- Malignant tumors *J. Boggan*
- Non-malignant diseases *J.C. Yanch*

VI. Patient Selection and Follow-up

- Optimal criteria for selection of patients *P. Gutin*
- Follow-up protocol, reporting *M. Predos, J.H. Goodman*

Wednesday, November 5:

8:30 AM VII. Identification of Issues for Breakout Sessions *L.E. Feinendegen*
9:00 AM VIII. Breakout Sessions
11:30 PM IX. General Discussion and Recommendations *D. Joel, T.L. Phillips*
12:45 PM Closing Statements *R.F. Hirsch, L.E. Feinendegen.*
1:00 PM Workshop Conclusion

Appendix B: Attendees

Dr. Susan A. Autry, *Sacramento, California*
Dr. Rolf F. Barth, *Columbus, Ohio*
Dr. James Boggan, *Sacramento, California*
Dr. Thomas F. Budinger, Berkeley, California
Dr. Paul Busse, *Boston, Massachusetts*
Dr. Jacek Capala, *Upton, New York*
Dr. Arjun Chanana, *Upton, New York*
Dr. Jeffrey A. Coderre, *Upton, New York*
Dr. A. Z. Diaz, *Upton, New York*
Dr. Ludwig E. Feinendegen, *Germantown, Maryland*
Dr. Reinhard A. Gahbauer, *Columbus, Ohio*
Dr. Patrick R. Gavin, *Pullman, Washington*
Dr. Joseph H. Goodman, *Columbus, Ohio*
Dr. Philip Gutin, *New York, New York*
Dr. Otto K. Harling, *Cambridge, Massachusetts*
Dr. M. Frederick Hawthorne, *Los Angeles, California*
Dr. Roland F. Hirsch, *Germantown, Maryland*
Dr. Darrel Joel, *Upton, New York*
Dr. George W. Kabalka, *Knoxville, Tennessee*
Dr. George L. Laramore, *Seattle, Washington*
Dr. Hungyuan Liu, *McClellan AFB, California*
Dr. Ruimei Ma, *Upton, New York*
Dr. Michael E. Miner, *Columbus, Ohio*
Dr. Trent Nichols, *Knoxville, Tennessee*
Dr. David W. Nigg, *Idaho Falls, Idaho*
Dr. Theodore L. Phillips, *San Francisco, California*
Dr. Richard C. Reba, *Chicago, Illinois*
Dr. Guido Solares, *Boston, Massachusetts*
Dr. Albert Soloway, *Columbus, Ohio*
Dr. Prem C. Srivastava, *Germantown, Maryland*
Dr. Thomas A. Strike, *Bethesda, Maryland*
Dr. Scott E. Taylor, *Berkeley, California*
Mr. Floyd J. Wheeler, *Idaho Falls, Idaho*
Dr. Richard Wiersema, *San Diego, California*
Dr. Jacqueline C. Yanch, *Cambridge, Massachusetts*
Dr. Robert G. Zamenhof, *Boston, Massachusetts*