**INEL BNCT Research Program
March/April 1993**

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ABSTRACT

This report presents summaries for two months of current research of the Idaho National Engineering Laboratory Boron Neutron Capture Therapy Program. Information is presented on development and murine screening experiments of low-density lipoprotein, carboranyl alanine, and liposome boron containing compounds. Pituitary tumor cell culture studies are described. Drug stability, pharmacology and toxicity evaluation of borocaptate sodium and boronophenylalanine are described. Treatment protocol development via the large animal (canine) model studies and physiological response evaluation in rats are discussed. Supporting technology development and technical support activities for boron drug biochemistry and purity, analytical and measurement dosimetry, and noninvasive boron quantification activities are included for the current time period. Current publications for the two months are listed.

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ACRONYMS AND ABBREVIATIONS

BMRR	Brookhaven Medical Research Reactor
BNL	Brookhaven National Laboratory
BNCT	Boron Neutron Capture Therapy
BPA	Boronophenylalanine
BSH	Borocaptate Sodium ($\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$)
CT	Computed tomography
GHRH	Growth hormone releasing hormone
GIT	Georgia Institute of Technology
HRP	Horseradish peroxide
ICP-AES	Inductively coupled plasma-atomic emission spectroscopy
INEL	Idaho National Engineering Laboratory
ISU	Idaho State University
i.v.	Intravenous
LDL	Low density lipoproteins
MRI	Magnetic resonance imaging
NMJ	Neuromuscular junction
oCRH	Ovine corticotropin releasing hormone
TLD	Thermoluminescent dosimeter
WSU	Washington State University

INEL BNCT RESEARCH PROGRAM

MARCH/APRIL 1993

INTRODUCTION

This report contains an overview of progress for the Idaho National Engineering Laboratory (INEL) Boron Neutron Capture Therapy (BNCT) Research Program for March/April 1993, including information on the Research Programs, Technical Support Details, and Miscellaneous Project Information.

The following sections are the reports from the various investigators about their current research.

BORON DRUG DEVELOPMENT

Carboranyl Alanine and Low-Density Lipoprotein (LDL) Development and Evaluation

No report for this period.

Boronated Liposome Development and Evaluation

Compound Development: As part of the effort to produce lipophilic boron compounds for liposomal bilayer embedment, distearyl carborane, 9,12- $(C_{18}H_{37})_2C_2B_{10}H_{10}$, has been synthesized and isolated. Degradation of this carborane derivative with KOH/EtOH produced the dicarbollide anion $K[5,6-(C_{18}H_{37})_2C_2B_{10}H_{10}]$ in high yield. This species is of particular interest to the liposome project since this compound is, in essence, a lipid mimic. The two stearyl chains should pack efficiently within the distearylphosphatidylcholine:cholesterol bilayer employed in previous experiments. The anionic carborane head group imparts negative charge on the exterior of the vesicle which appears to increase the tumor specificity of the liposomes.

Starting materials have been synthesized for the investigation of the reactivity of $[B_{20}H_{18}]^{4-}$ with oxalyl chloride. Preliminary investigations

suggested that the expected product, $[B_{20}H_{17}CO]^{3-}$, could be formed. Problems due to isomerization were encountered earlier and hindered the complete investigation of the reaction at that time. The $[B_{20}H_{17}CO]^{3-}$ ion could prove to be as useful a synthon as $[B_{10}H_6CO]^-$, and additional effort has been directed at its production.

Liposome Encapsulation and Development: Three liposomal suspensions and one free compound have been sent to Vestar, Inc. for murine biodistribution experiments in the EMT6 tumor line. These are identified as follows:

1. Liposomes encapsulating $Na_3B_{20}H_{18}$ that also contain $K[C_2B_9H_{11}(CH_2)_{16}CH_3]$ in the lipid bilayer,
2. Liposomes encapsulating $Na_3B_{20}H_{17}NH_3$ that also contain $K[C_2B_9H_{11}(CH_2)_{16}CH_3]$ in the lipid bilayer,
3. Liposomes embedding the new double-tailed lipophilic compound, $K[CH_3(CH_2)_{17}]_2C_2B_9H_{10}$, and
4. A suspension of free $K[C_2B_9H_{11}(CH_2)_{16}CH_3]$.

The murine experiments have been completed. Results are pending.

Liposomes described by items 2 and 3 above have also been sent to Washington State University (WSU) for murine biodistribution experiments in the Lewis Lung tumor-line. These murine experiments have been completed. Results are pending.

Liposomes described by item 2 above have also been sent to WSU for initial experiments in rats bearing intracranial implanted brain tumors.

Pituitary Tumor Evaluation

Experiments designed to demonstrate corticotropin receptor dependent AtT-20 cell demise via BNCT have been carried out at Oregon

Health Sciences University. AtT-20 cells were incubated with either ovine corticotropin releasing hormone (oCRH), oCRH conjugated to enriched carborane cage ($^{10}\text{B}_{10}$ -CRH), or $^{10}\text{B}_{10}$ -CRH plus excess oCRH. This paradigm represents a classic competition experiment designed to block the $^{10}\text{B}_{10}$ -CRH AtT-20/BNCT cell effect. Cells were incubated at 37 C for 10 minutes under the three conditions above, washed with phosphate buffered saline, and subjected to the thermal column neutron beam for three minutes at full power (1 MW). Cells were then removed from the thermal column, washed, and cultured in 6-well plates for colony counting 14 days later. AtT-20 cell colonies from cells incubated with $^{10}\text{B}_{10}$ -CRH were significantly lower in number than from cells incubated with oCRH alone. However, when cells were incubated with $^{10}\text{B}_{10}$ -CRH plus excess CRH, this decrease was eliminated, such that the number of colonies of this group were similar to the cells incubated with CRH alone. These data suggest that the BNCT effect observed in our studies with the releasing factor CRH as the boron carrier in AtT-20 cells is CRH receptor mediated, and not due to a nonspecific effect. These experiments will be repeated to validate the results.

Experiments using growth hormone releasing hormone (GHRH) as the boron carrier and CH₃ pituitary somatotroph tumor cells are currently on-going. Specificity of CRH for its receptor and/or GHRH for its receptor and the ability of these releasing hormones to modulate BNCT cell death are also on-going.

Human cancer cells, representing malignant melanoma, breast cancer, prostate cancer, pancreas cancer, and meningioma neoplasias, are currently available in our lab. New hormonal boron carriers are being synthesized to test the efficacy of BNCT on a variety of endocrine mediated and hormone responsive malignancies.

BORON LOCALIZATION SCREENING

Boronophenylalanine (BPA) Evaluation Studies

BPA efflux studies have been completed. Cellular and supernatant concentrations of BPA have been evaluated over a time course to determine BPA efflux. Cell pellets and supernatant samples have been sent to INEL for boron analysis. Results are pending and, upon receipt, will be incorporated into a manuscript which is currently in preparation.

LDL Studies

In Vivo Screening: LW-I-55 & LW-I-67: Evaluation of these boronated LDLs has been completed using BDF mice bearing B16-BL6 melanoma. Tissue and blood samples have been sent to INEL for analysis. Results are pending.

In Vitro Screening: LW-I-83: Murine B16-BL6 melanoma, murine Lewis Lung carcinoma, rat RG2 glioma, U87MG human glioma, and one normal control cell line (murine mammary fibroblasts) were used. Cell pellets and supernatant samples have been sent to INEL for boron analysis. Results are pending.

LW-I-51: Three different cell lines were used: murine Lewis Lung carcinoma, B16-BL6 melanoma and normal murine fibroblasts (Figure 1). Data analysis indicated that boron levels were highest at 24 hours in the Lewis Lung carcinoma, averaging 22 $\mu\text{g/gm}$ pellet.

LW-I-55: B16-BL6 melanoma and murine Lewis Lung carcinoma cells were used for this comparison (Figure 2). Data indicate that Lewis Lung carcinoma showed more uptake than melanoma. Maximum boron levels found in the melanoma were determined to be 5.0 $\mu\text{g/gm}$ cell pellet at 12 hours, whereas, the maximum amount found in the carcinoma was determined to be 8.0 $\mu\text{g/gm}$ cell pellet at 24 hours.

Liposome Evaluation Studies

In Vivo Screening: $\text{K}^+[\text{C}_2\text{B}_9\text{H}_{10}((\text{CH}_2)_{17}\text{CH}_3)_2]^-$ (embedded in the lipid bilayer), $\text{K}^+[\text{C}_2\text{B}_9\text{H}_{10}((\text{CH}_2)_{17}\text{CH}_3)_2]^-$ (embedded in the lipid bilayer) and $\text{Na}_3\text{B}_{10}\text{H}_{12}\text{NH}_3$ (liposome encapsulated) were screened *in vivo* for boron uptake using C57 mice bearing Lewis Lung carcinoma. Tissue and blood samples have been sent to INEL for boron uptake analysis. Results are pending for both of these compounds.

$\text{Na}_2\text{B}_{20}\text{H}_{18}$: Balb/C mice bearing P1798 lymphosarcoma were used for this evaluation study.

Figure 1. Comparison of carcinoma, melanoma and normal fibroblasts ability for boron uptake *in vitro*.

Figure 2. *In vitro* comparison between B16-BL6 melanoma and Lewis Lung carcinoma for preferential incorporation of boronated LDL.

Tumor-to-blood ratios were found to be highest at 72 hours (7.6:1). Boron levels in the liver peaked at 6 hours averaging 107.2 $\mu\text{g/gm}$ tissue. The maximum average concentration found in the tumor occurred at 18 hours (23.4 $\mu\text{g/gm}$ tissue).

$\text{Na}_2\text{B}_{10}\text{H}_6\text{NCO}$: CD_2F_1 mice bearing P1798 lymphosarcoma were used to evaluate this liposome encapsulated compound. Boron levels were maximum in the tumor at 6 hours with an average concentration of 11.5 $\mu\text{g/gm}$ tissue. The highest level of boron in the blood occurred at 6 hours, averaging 18.8 $\mu\text{g/gm}$.

$\text{K}^+[\text{C}_2\text{B}_9\text{H}_{11}(\text{CH}_2)_{18}\text{CH}_3]^-$: CD_2F_1 mice bearing Lewis Lung carcinoma were used to evaluate this compound which has been embedded into the liposome bilayer. Before screening this compound was determined *in vitro* to be noncytotoxic. *In vivo* evaluation showed that with multiple injections, a maximum tumor-to-blood ratio of 3.6:1 at the 72 hour time point could be reached. Blood boron levels peaked at 26.9 $\mu\text{g/gm}$ 6 hours after liposome injection. Maximum tumor boron levels occurred at 12 hours with an average value of 23.3 $\mu\text{g/gm}$ tissue.

$\text{K}^+[\text{C}_2\text{B}_9\text{H}_{11}(\text{CH}_2)_{18}\text{CH}_3]^-$ (embedded in lipid bilayer) and $\text{Na}_2\text{B}_{10}\text{H}_6$ (liposome encapsulated): C57 mice bearing Lewis Lung carcinoma were used in the *in vivo* evaluation of this compound. Average maximum boron levels in the liver were calculated to be 245.97 $\mu\text{g/gm}$ tissue at the 72 hour time point for the multiple injection group. Tumor-to-blood ratio was at its highest at 72 hours (1.3:1).

In Vitro Screening: $\text{K}^+[\text{C}_2\text{B}_9\text{H}_{11}(\text{CH}_2)_{18}\text{CH}_3]^-$ were evaluated using B16-BL6 melanoma, Lewis Lung carcinoma and normal fibroblast cell lines. Results showed that B16-BL6 melanoma incorporate $\text{K}^+[\text{C}_2\text{B}_9\text{H}_{11}(\text{CH}_2)_{18}\text{CH}_3]^-$ more readily than the carcinoma. Normal fibroblasts boron concentrations were found to be negligible. For B16-BL6 melanoma the maximum concentration of boron was 24 $\mu\text{g/gm}$ pellet at 24 hours postinoculum.

$\text{K}^+[\text{C}_2\text{B}_9\text{H}_{11}(\text{CH}_2)_{18}\text{CH}_3]^-$ (embedded in the lipid bilayer) and $\text{Na}_2\text{B}_{10}\text{H}_6$ (liposome encapsulated): were evaluated using B16-BL6 melanoma, Lewis Lung carcinoma, rat RG2 glioma and normal fibroblast cell lines and analyzed by INEL for boron uptake. Boron levels were

highest at 24 hours in the Lewis Lung carcinoma having an average value of 15.1 $\mu\text{g/gm}$ pellet. Normal fibroblasts did not readily take up this boronated compound (Figure 3).

$\text{Na}_2\text{B}_{10}\text{H}_6$: Analysis of this liposome encapsulated compound using B16-BL6 melanoma, rat RG2 glioma, Lewis Lung carcinoma and normal murine fibroblast cell lines has been completed. Levels of boron peaked at 6 hours in the rat glioma with an average concentration of 1.2 $\mu\text{g/gm}$ pellet. In comparison, normal fibroblasts concentrations were highest at 12 hours having an average concentration of 1.3 $\mu\text{g/gm}$ pellet.

DRUG STABILITY, PHARMACOLOGY AND TOXICITY

Toxicological Evaluation of Borocaptate Sodium (BSH)

For several months, Idaho State University (ISU) researchers have been reporting that intravenous (i.v.) infusion of BSH is particularly lethal when administered to rats instrumented for measurement of cardiovascular function. The most recent studies indicate that for instrumented rats, i.v. administration of BSH doses as low as 150 mg/kg can cause death. Such doses are not lethal in noninstrumented rats, and instrumented rats infused with saline instead of BSH remain robust for the duration of the six hour experiment. Last month, it was hypothesized that this BSH-instrumentation interaction may indicate a toxic synergism between BSH actions on the heart and an instrumentation-induced activation of the sympathetic autonomic nervous system. This interaction was postulated to potentiate BSH-induced arrhythmogenesis, which in turn caused cardiovascular collapse and death. To test this hypothesis, we pretreated instrumented animals with β -adrenergic (propranolol) and α -adrenergic (phenoxybenzamine) antagonists prior to administration of BSH. If sympathetic activation was sensitizing the heart to the effects of BSH, then blocking the receptors mediating this activation should prevent the low dose BSH lethality observed in instrumented rats. However, suppression of sympathetic

Figure 3. The preference of the liposome is Lewis Lung carcinoma. Normal fibroblasts do not appear to readily take up this liposome encapsulated compound.

function failed to antagonize the lethal effect of low-dose BSH injected into the instrumented rats. The failure of the hypothesis to predict this results invalidates the hypothesis and rules out a role for sympathetic activation. The one caveat to this conclusion is that if BSH binds and inactivates the β -antagonist, this test of the hypothesis would be invalid. Studies on BSH-neuromuscular junction blocker interactions (below) suggest that this may be occurring. ISU researchers are currently determining how best to evaluate this possibility.

ISU researchers have also reported that i.v. injection of BSH rapidly and effectively reverses respiratory paralysis induced by the neuromuscular junction (NMJ) blocking drug, gallamine. Recent experimentation indicates that BSH also reverses the effects of a second NMJ blocking drug, pancuronium. Gallamine triethiodide (15 mg/kg) or pancuronium bromide (2 mg/kg) administered by i.v. to Long Evans rats caused prolonged skeletal muscle paralysis and respira-

tory failure. In the absence of artificial respiration, these doses of NMJ blockers were fatal. If artificially respiration, however, rats recovered within 45 to 60 minutes. BSH (75-200 mg/kg, i.v., rate: 28 mg/kg/min) was infused 5-15 minutes after full NMJ blockade was established. Rats regained their ability to spontaneously breathe almost immediately after the start of BSH infusion, indicating a BSH-induced reversal of the skeletal muscle paralysis induced by the NMJ blockers. BSH infusion re-established a normal respiratory pattern, and stable cardiovascular function was maintained throughout the time period that control rats (NMJ antagonist without BSH) remained paralyzed. The rapid, effective and sustained reversal of respiratory paralysis by BSH suggests that this drug might be a useful antidote for treating overdose of NMJ blockers. It also raises the specter that BSH may be altering the function of nicotinic cholinergic receptors. If so, this could be of toxicological significance, since this receptor type mediates nu-

merous physiologically important functions in both the peripheral and central nervous systems. An alternative explanation for the BSH antagonism is that BSH may be acting as a "chemical sponge", binding the quaternary NMJ blocking drugs, and preventing them from interacting with the receptor sites. If such chemical binding is indeed occurring, it emphasizes the need to better evaluate and understand potential BSH-drug interactions. Experiments to improve our understanding of these NMJ blocker-BSH interactions are underway.

TREATMENT PROTOCOL DEVELOPMENT

Large Animal Model Studies

Pharmacokinetics: No additional dogs have been infused.

Normal Tissue Tolerance (Neutron Irradiation): Brookhaven National Laboratory (BNL) was assisted with irradiation of their BPA-fructose dogs. Four dogs were irradiated the first part of March, with a two hour wait post infusion and then a 75 minute irradiation. Three dogs in a second group were irradiated the latter part of March, with a 90 minute wait post infusion and then a 70-75 minute irradiation.

Three dogs, at 25 ppm and 19 Gy, had their 12 month post irradiation checkups. The computed tomography (CT) and magnetic resonance imaging (MRI) scans revealed no changes. Afterwards the dogs were euthanized and necropsied.

Two dogs, at 25 ppm and 27 Gy, had their 18 month post irradiation checkups. The CT and MRI scans revealed no changes.

Eight dogs were irradiated during March. Two dogs were irradiated with blood boron concentrations of 70-100 ppm to a neutron dose 36-42 Gy. One dog was irradiated with blood boron concentration of 40-60 ppm to a neutron dose of 30-40 Gy. One dog, split dose done over two consecutive days, was irradiated with blood boron concentration of 25 ppm to a neutron dose of 13.5 Gy both days for a total neutron dose of 27 Gy. Four dogs underwent

skin reflection surgery and were irradiated to a dose of 15 Gy with no BSH.

At this time there are no clinical abnormalities attributable to irradiation treatment.

Spontaneously-Occurring Brain Tumor Dogs: Three potential candidates were seen at WSU during March and April. On further evaluation all three of these dogs were ruled out as possible brain tumor treatment candidates. (Two dogs did not have tumors; one dog died before diagnostic workup could be instituted.)

"Crystal" Ard (#35447-164), a five year old spayed female Malamute cross, had surgery to remove a large meningioma from the right frontal lobe on February 24. Three and a half weeks later, "Crystal" underwent irradiation treatment at BNL. She was treated with 101 ppm blood boron concentration to a dose of 31.2 Gy. "Crystal" is clinically very much improved following treatment with only some minor proprioception deficits remaining. She returned home two weeks post treatment and then returned for a three week post treatment MRI. The three week post MRI scan revealed an area of enhancement which is believed surgery related.

"Dudley" Fiset (#35447-151), an eight year old castrated Golden Retriever, is doing great.

"Brandy" Hoff (#35447-94), an eight year old spayed female Golden Retriever, is doing great. "Brandy" will be returning to WSU in June for her three and a half year post treatment check-up.

Physiological Response Evaluation and Interdiction

The remarkable result of BNCT's selective brain tumor ablation is reported in the paper titled "Truly Selective Brain Tumor Ablation by Boron Neutron Capture Therapy in Rat 9L Gliosarcoma." This represents the joint work with Jeff Coderre in which single BNCT schedules were utilized. The paper will be submitted to the *International Journal of Radiation Oncology, Biology, Physics* for publication in a special BNCT issue, probably in late 1993 or early 1994. A copy of the complete manuscript as submitted will be sent with the next progress report (May-June).

BNCT Fractionation Study - Part I: Eight rat brains have been received from BNL and processed for horseradish peroxidase (HRP) histochemistry. All of the brains have been sectioned. Approximately 75% of the data has been collected and the data analysis is 50% complete.

BNCT Fractionation Study - Part II: Twelve rat brains have been received and 30% of the processing for HRP histochemistry has been completed at this time. The work is proceeding on the remaining brains and the data acquisition will be starting when the processing is complete.

Canine BNCT Study - Part I: Seven dog brains were received. To date, all of this tissue has been sectioned; approximately 50% has undergone data acquisition. This is progressing slowly due to the lack of funding.

Canine BNCT Study - Part II: Two containers of tissue have been received. They appear to contain eight brains. The tissue is waiting for processing. This is progressing slowly due to the lack of funding.

SUPPORTING TECHNOLOGY DEVELOPMENT

Task 1: Biochemistry of BSH and Its Oxidation Products

No progress to report for this period.

Task 2: Noninvasive Boron Quantification

To aid in the analysis of brain tumor transport in a canine gliosarcoma model via gadolinium enhanced proton magnetic resonance imaging, University of Utah researchers have been evaluating methods for measuring spin-lattice relaxation (T1) using serially doped gadolinium phantoms in the clinical GE Signa scanner. In mid May actual tracking of gadolinium penetration into an implanted and growing tumor will provide information on the rate of blood-brain-barrier breakdown which relates to penetrability of BNCT agents.

Task 3: Real-Time Measurement Dosimetry Research

No progress to report for this period.

Task 4: Analytical Dosimetry

Treatment Planning Software: The rtt_MC Monte Carlo radiation transport module was modified to incorporate an improved interpolation scheme in the edit routines. rtt_MC automatically provides region edits and 3-dimensional voxel edits during a run. Point, line, surface, and volume edits can then be obtained for regions of interest by interpolation within the voxel space. The voxel edits are exact, providing flux and dose, integrated over each voxel. A plot, for example a line plot, of the voxel data provides a histogram shape. To obtain better reproduction of the true shape, intra-voxel interpolation must be performed. For the initial version of the edit routines, simple linear interpolation was performed with weighing functions for neighboring voxels. This scheme was found to be poor at the edges of the edit space and did not always reproduce the true volume integral. The new scheme uses a quadratic interpolation and the constraint that integration over any volume exactly reproduces the true volume integral. This preserves flux and dose gradients at the edges of the edit space. This scheme was implemented and found to be a significant improvement over the old method.

TECHNICAL SUPPORT CORE ACTIVITIES

Task 1: Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) Analyses of Boron in Biological Samples

The Fisons/ARL Model 3520 ICP-AES was out of service due to some problems in the monochromator which now have been fixed.

Freezer space is currently at a premium and all samples previously received, and researchers that have submitted samples for analysis must decide if they wish to retain samples for which

they already have results. The decision should also be made whether there is any need to do any analysis on samples that they do not have results for.

Samples Received	=	911
Samples Prepared for Analysis	=	~ 919
Samples Analyzed	=	~ 1157
Backlog:		
Awaiting Preparation	=	~ 4131
Blood, Liver, Spleen, & Tumor	=	~ 628
Other - Brain, Skin, Muscle, Kidney, etc.	=	~ 2698
Prepared, Awaiting Analysis	=	~ 97

Task 2: Boron Compound Purity Determinations

No new boron compounds were received during this period.

Task 3: Intra- and Intercellular Boron Analyses

No progress to report for this period.

Task 4: Neutron Beam Measurement Dosimetry

During March 8-12, four Labrador cross dogs were irradiated at the Brookhaven Medical Research Reactor (BMRR) filtered beam port for dose tolerance purposes. These dogs were infused with BSH at levels 25 to 80 ppm. The 25 ppm dog was irradiated to 2700 cGy in two fractions of 1350 cGy each with BSH, separated by 24 hours.

Also INEL WSU personnel provided dosimetry and veterinary services during this period for four Beagle irradiations for BNL.

During March 22-26, four reflected scalp dogs and one client dog were irradiated. Again, dosimetry and veterinary support was provided for three beagles irradiated for BNL.

Two INEL personnel traveled to the High Flux Reactor at Petten, The Netherlands, the week of April 19-23, to make neutron spectrum and dosimetry measurements in the plastic beagle and cylinder phantoms. The liquid Argon filter at Petten has been modified to improve the epithermal beam characteristics. The purpose of the trip was to repeat the measurements

made in 1991 to determine the extent of beam improvement.

A summary of the Petten irradiation follows. Neutron flux values will be reported later.

1. Indium inside boron sphere (2hr) - Fast Neutron Flux ($E > 1\text{MeV}$).
2. Beagle Head Phantom (15hr) - Thermal and epithermal neutron flux distribution.
3. Beagle Head Phantom (1hr) - Gamma dose distribution.
4. Spectrum Wheel (3hr) - Epithermal Neutron Flux ($0.5\text{eV} < E < 10\text{keV}$).
5. Cylindrical Phantom (15hr) - Thermal and epithermal flux distributions.
6. Cylindrical Phantom (1hr) - Gamma dose distributions. Compare thermoluminescent dosimeter (TLD) 400 response with TLD 700 response.
7. Cylindrical Phantom (1hr) - Compare dark and light irradiations of TLD 400's.
8. Uranium-235 inside boron sphere (15hr) - Fast Neutron Flux ($E > 1\text{keV}$).
9. Indium inside boron sphere (15hr) - Fast Neutron Flux ($E > 1\text{MeV}$).

Total irradiation hours: 70.

Total number of wires and foils irradiated and analyzed: 90.

Task 5: Canine Dosimetry Calculations

BMRR Support: Calculations were performed with the rtt_MC Monte Carlo software to compare with INEL measurements for the BNL ellipsoid phantom (Figure 4). The phantom was irradiated in the BNL epithermal beam with no delimiter in place. The comparison for neutron flux is shown in Figure 4. BNL has also performed measurements and calculations for this phantom. The BNL and INEL methods were completely independent and results were in quite good agreement.

Calculation and measurement errors: The statistical error in the Monte Carlo calculation varies from approximately 1% (standard deviation) at the peak values to about 10% at the 10 cm depth. The uncertainties in the measured values are estimated to be 10% or less.

Figure 4. BMRR ellipsoid phantom irradiation, measured and calculated results.

Dose rates were calculated for one client dog with a debulked tumor, and for the reflected scalp surgery dogs. It was desired to calculate these dose rates using the b-spline geometry capabilities of rtt_MC. However, unforeseen complications in producing an appropriate model from either MRI or CT images required using combinatorial geometry primitives to build the model for the client dog and scaling the b-spline model of a smaller Labrador imaged at the University of Utah for the surgery dogs. Calculations to determine dose rates for both the client dog and the surgery dogs were performed using the newest rtt_MC software.

The capability to read CT images generated on the GE 7800 (upgraded to 8800) on the WSU campus would be beneficial to the program due to both time and cost considerations. David Reddy of Radiologic, Inc. is currently working on this problem. The lack of available docu-

mentation on the 7800 format has slowed progress.

Calculations have been performed in support of rat irradiations at BNL in the thermal port of the BMRR. Thermal flux and dose have been calculated for various irradiation configurations. Preliminary calculated results, coupled with the physiological response reported in the January/February 1993 issue of the INEL BNCT Research Program report, indicate that an relative biological effectiveness dose of 60 Gy to the hippocampus may not be possible without inducing a fatal nasopharyngeal radiation response.

Task 6: BNCT Database Management System

Database development and data entry continue at WSU.

**Task 7: Georgia Tech Research Reactor
Physics Support**

Calculations continue to be performed to validate the design of the Georgia Institute of Technology (GIT) filter design. The MCNP model has been obtained from GIT and is being run on EG&G's computer system. Comparison of the two calculations will be discussed with GIT researchers.

**Task 8: Research Reactor/Accelerator
Physics Support**

No progress to report for this period.

**DATE
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