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USE OF THE POWER BURST FACILITY FOR BORON NEUTRON CAPTURE THERAPY

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ABSTRACT

A program is under development at the Idaho National Engineering Laboratory (INEL) that involves using the Power Burst Facility (PBF) for research into Boron Neutron Capture Therapy (BNCT). BNCT utilizes the ionizing energy from boron-neutron capture to stop reproduction of or destroy cells in cancerous tissue in a two step process. The first step is to selectively concentrate a boron isotope within the tumor cell, that when activated by neutron capture emits highly ionizing, short range particles. The second step involves activation of the isotope only in the vicinity of the tumor with a narrow neutron beam. The (^{10}B[n,^{4}He]^{7}Li) reaction with thermal neutrons produces fission products with track lengths approximately equal to a cell diameter. The INEL program includes the modification of the PBF by the addition of a neutron filter and treatment area. The filter will down scatter high energy neutrons into the epithermal range and remove thermal neutrons and excessively damaging gamma components. The intense source of epithermal neutrons from PBF is considered necessary to achieve optimum therapy for deep-seated tumors with minimum damage to surface tissue. The neutron filter conceptualized for PBF utilizes aluminum and heavy water to down scatter neutrons into the proper energy range. Bismuth will be used for gamma shielding and cadmium will remove the thermal neutron contaminant from the beam. The INEL program leads to human clinical trials at PBF which is intended to prove that brain tumors can be successfully treated through noninvasive techniques. Further research into BNCT at PBF for other cancer types is also anticipated.

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BACKGROUND AND SIGNIFICANCE OF BORON NEUTRON CAPTURE THERAPY:

Despite rapid progress in cancer research and reasonably effective efforts at prevention, cancer will soon become the foremost killer in the United States. While developing immunological and chemical therapies offer promise for controlling the systemic disease, relapse in the brain remains a significant problem. Over 80% of patients with metastatic melanoma, and many patients with metastatic tumors of other origin, have brain lesions. Brain tumors are not as accessible to treatment with drugs or biologicals because those agents are excluded by a physiological barrier.[1] Approximately 4000 cases of the most aggressive brain tumor, Glioblastoma Multiforme, are diagnosed in the United States each year. Existing therapy offers little hope for survival with this disease. Median life expectancy is less than one year, and patients rarely survive therapy beyond two years.[2,3]

Boron Neutron Capture Therapy (BNCT) was first proposed as a possible treatment for cancer by Locher in 1936.[4] In concept, BNCT requires the uptake of an activatable nuclide within the tumor cell. The nuclide is then fissioned by neutrons resulting in a neutron-alpha reaction (i.e. $^{10}B + {}^{1}n \Rightarrow {}^{7}Li + {}^{4}He + 2.3$ MeV when a boron compound is used). This reaction produces, 94% of the time, ^{7}Li and ^{4}He (alpha) ions with 0.84 and 1.45 MeV of kinetic energy respectively, plus a 0.5 MeV gamma ray. Six percent (6%) of the time, no gamma ray is produced, with the ^{7}Li and ^{4}He ions sharing the 2.8 MeV kinetic energy. (Fig. 1.)

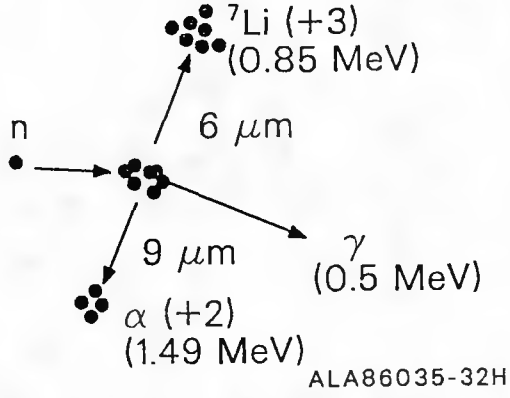

Fig. 1. Boron-10 Fission With A Thermal Neutron

The ionizing biologic effect of the fission fragments in the reaction has two particular advantages. First, the ionizing energy conveyed occurs within 10 micrometers with path length determined by the particular ion and its energy. Since the 10 micrometer path length is, generally speaking, equivalent to the diameter of the tumor cell, the ionizing damage is very cell selective. Second, the energy conveyed falls within the range of high linear energy transfer (LET) radiations, which have a greater biological effectiveness than more conventional radiation used in radiation therapy such as ^{60}Co rays and high energy x-rays.

Boron Neutron Capture Therapy (BNCT) of malignant brain lesions was evaluated in the United States in the late 1950's and early 1960's. The early trials failed because of technological immaturity. The causes of failure were identified at the time of the trials as:

1. Excessive radiation damage to the vasculature system leading to hemorrhage
2. Treatment-related edema and intracranial pressure
3. Use of low energy (thermal) neutrons that caused surface (scalp) damage but failed to penetrate to the depth of the tumor.

INEL PROGRAM

A comprehensive program for BNCT using an epithermal neutron beam from the Power Burst Facility (PBF) has been prepared at the Idaho National Engineering Laboratory (INEL). The PBF must be modified to provide the epithermal neutron beam by the addition of a neutron filter which will down scatter fast neutrons into the epithermal range and remove the damaging thermal neutrons and gamma radiation. The reactor building must be modified with the addition of a patient treatment room, patient monitoring room and shielded shutter doors to reduce radiation levels during patient setup. (Fig. 2)

The use of epithermal neutrons should offer significant advantages over the early trials. It should be possible to deliver destructive doses to the internal tumor without surgery and without great damage to the healthy tissue. Optimum treatment conditions for brain tumors require boron activation by epithermal neutrons which have sufficient energy to penetrate the scalp and skull to the depth of the tumor but inadequate to damage tissue that does not contain boron. The epithermal neutrons then slow down (thermalize) forming a capture peak a few centimeters into the brain at the tumor site. Feasibility studies have indicated that capabilities and facilities presently available can be adapted or modified to generate all data required for scientific assessment of the BNCT process. Those same technological capabilities will also provide the ability to assure safety of human treatment and to limit human treatment to those individual cases for which there is a reasonable probability of efficacy.

United States research into BNCT, since the 1960 trials, has focussed on development of improved boron delivery agents that offer better tumor retention and blood clearance, thereby reducing vasculature damage. Borocaptate Sodium ($Na_2B_{12}H_{11}SH$) or BSH and the related dimer BSS ($Na_4B_{24}H_{22}S_2$) and BSSO the oxidized dimer ($Na_4B_{24}H_{22}S_2O$) appear to offer the necessary characteristics. Brookhaven National Laboratory (BNL) researchers have recently reported the first experimental proof of in-vivo efficacy using the BSS dimer and a malignant intracranial neoplasm implanted in a rat model.[5] Dr. H. Hatanaka's clinical experience using BSH and a low-energy neutron source (summarized in Fig. 3),[6] is very

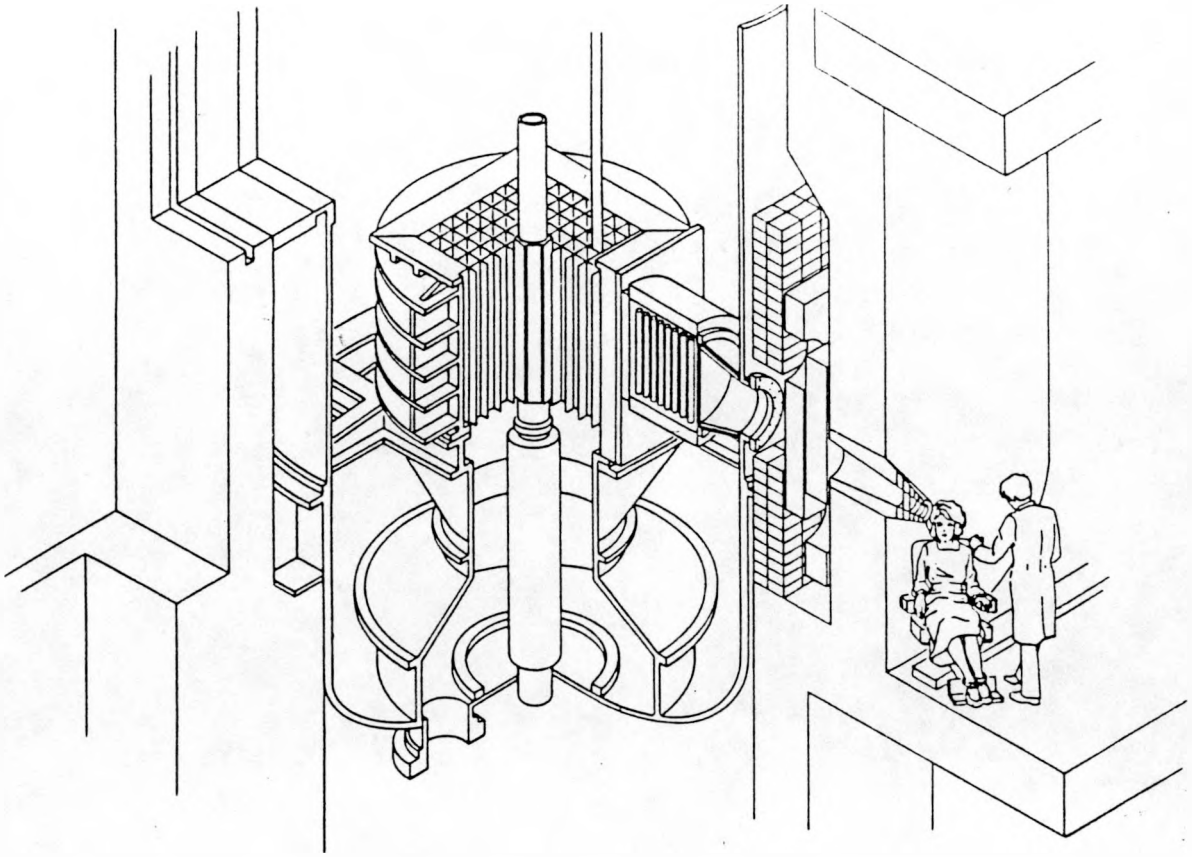

Figure 2. BNCT Therapy In PBF-Artists Concept

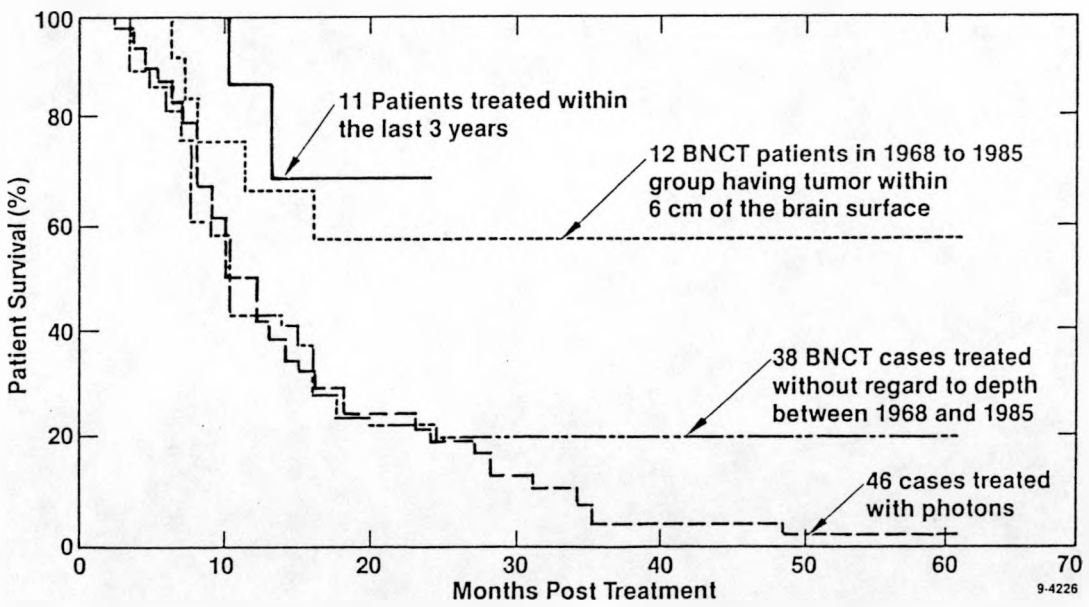

Fig. 3. Grade III/IV Astrocytoma Survival Data of Dr. Hatanaka

encouraging and has stimulated world wide effort to further develop the technology. (Grade III/IV Astrocytoma is a function classification of brain tumor patients. The referenced grades are advanced and in the symptomatic area typical of Glioblastoma Multiforme.)

Dr. Hatanaka's results have been criticized for lacking research vigor, but careful scrutiny by several physicians leaves little doubt that Dr. Hatanaka has survival rates unequalled by any other clinician.

The INEL program is a collaborative endeavor of leading U.S. technologists in each speciality field required for successful completion of overall program objectives. These objectives are: (1) to provide data required for a decision to proceed to human clinical trials of BNCT, using $Na_2B_{12}H_{11}SH$ (BSH), as a nonsurgical treatment for Glioblastoma Multiforme and (2) to provide facilities, technology, data, and institutional approvals required for initiation of human clinical trials.

Power Burst Facility

The PBF is an open pool, light water cooled reactor capable of operating either in a steady state or transient mode. A closed loop coolant system provides forced cooling of the core. The reactor system is capable of continuous operation at power levels to 28 MW. The PBF core is contained within a 1.3 meter-diameter, 0.9 meter-high cylindrical envelope. The fuel rods are composed of ternary (20.6% urania, 61,8% zirconia, and 7.6 % calcia) ceramic fuel pellets contained in a ceramic (zirconia, calcia) thermal insulator and a stainless steel cladding tube.

The core loading will be changed for BNCT by the addition of fuel to the core quadrant near the patient treatment location to enhance the neutron beam. The additional fuel will replace partially fueled canisters located at the edge of the core. The spacing of fuel rods in the core provides an intentionally under moderated core, which, combined with the relatively low ^{235}U atom density, results in a high fast neutron flux. The PBF reactor is the most powerful U.S. source of an intense current ($\sim 10^{10}$ n/cm^2-s) of epithermal neutrons with contaminants (gamma photons and neutrons above 10 keV) reduced to the extent they are clinically insignificant. This intense, high-purity, epithermal neutron beam is required in order to evaluate the optimum therapeutic dose rate and the potential for BNCT to make the transition from the research laboratory to the medical community and become a practical, therapeutic tool available to the large number of patients needing the treatment.

PBF Neutron Filter Design and Installation

The design objective for the PBF reactor modification is to obtain the most desirable balance between the competing parameters of maximized epithermal neutron component and minimized fast neutron, thermal neutron, and gamma components.

Functional and operational requirements for the BNCT neutron beam and related hardware at the PBF reactor are:

1. The epithermal neutron flux, averaged across the beam, will be $\geq 7 \times 10^9$ n/cm^2-s at the patient location for neutron energies in the range 1 eV < E_n < 10 eV for a 20-MW(t) reactor power level.

2. The fast neutron contaminate (E_n > 10 keV) in the beam path shall result in a tissue dose < 2.6×10^{-11} cGy/(n/cm^2) of the epithermal flux at the patient location.

3. The incident gamma radiation in the beam shall result in a tissue dose rate $\leq 2.0 \times 10^{-11}$ cGy/(n/cm^2) of the epithermal flux at the patient location.

4. The reactor will operate at a constant power level not to exceed 20 MW during neutron therapy and < 1 MW during setup and patient positioning.

5. The center line of the treatment position will be approximately 3.4 meters from the vertical center line of the PBF reactor core.

6. The radiation shielding shutter doors will operate remotely and provide a reduction factor of $\geq 4.0 \times 10^4$ for incoming and induced radiation (neutron and gamma) in the neutron beam when the door is closed and the reactor is operating at $\leq$ 1 MW.

The neutron filter as designed is a 120-cm diameter, 100-cm long, 304 stainless steel tank, filled with closely spaced aluminum plates, (Fig. 4). Space between the aluminum plates is filled with heavy water (D_2O). Spacing is adjusted to achieve a 90%/10% aluminum/D_2O volume ratio for neutron spectra adjustment. The D_2O will be circulated for cooling the 78, 0.99-cm aluminum plates. The aluminum plates and D_2O coolant simulate a homogenous mixture in the filter region.

Design calculations for the PBF aluminum/D_2O filter are performed with two independent computer models. Both models rely on core/reflector interface neutron currents calculated by the two-dimensional DOT core model.[7,8] These currents are input to the RAFFLE Monte Carlo filter model and to the DOT filter model.[9] The RAFFLE representation of geometry and physics data is more rigorous than the DOT results. The DOT model is required to provide the detailed angular fluxes at the beam exit for patient dose calculations. The calculational models used for the aluminum/D_2O filter design for PBF were also used to design the aluminum oxide neutron filter for the Brookhaven Medical Research Reactor (BMRR). Measurements of the filtered neutron beam flux and spectrum were made at BMRR to verify the predictions made by the design codes.

Bismuth and cadmium for gamma shielding and thermal neutron removal is provided in a transition section on the patient end of the main neutron filter. The transition piece is connected to a 1.25-meter O.D. nozzle

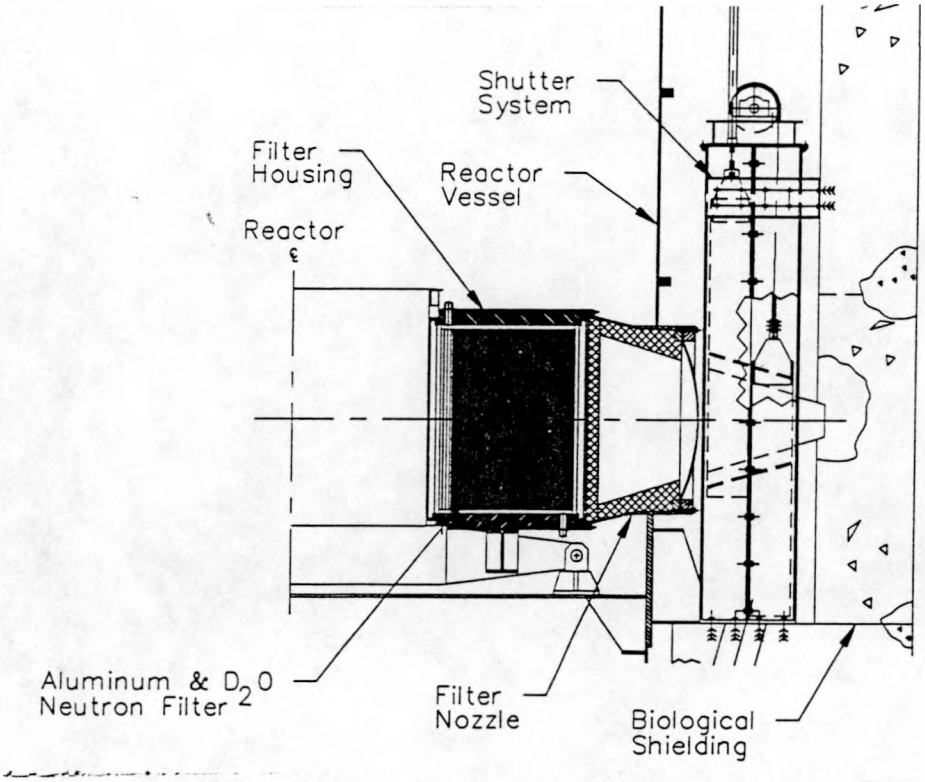

Fig. 4. Filter, Shutter, and Nozzle - Elevation View

section, which extends through the reactor vessel wall. The inside diameters of the nozzle section and transition piece are lined with bismuth to shield the beam from gamma radiation produced by ^{16}N decay in the reactor coolant water.

The neutron shutter, which will be opened and closed to commence and terminate treatment, will be placed outside the reactor vessel near the patient. The shutter is a two-piece, lead and polyethylene shield, 60-cm thick, with the two parts connected by a chain over sprocket. Hydraulic cylinders move the shielding to open or close the shutter. Conical openings in the shielding align when the shutter is opened to allow the neutron beam to reach the patient to commence treatment. Treatment is terminated by a timed sequencer, which will reverse the action of the hydraulic cylinders, closing the beam path with the shielded shutters. Reactor power will be lowered to < 1 MW after the shutter is closed.

The entire sequence will be monitored by a physician and a reactor operator from the patient monitoring room near the patient treatment room. The monitoring room is equipped with instrumentation to measure beam strength and quality before, during, and after treatment and is

shielded from the therapy room by a shielding labyrinth. Remote video observations of the patient and two-way voice communication will be provided between the patient and physician.

BNCT Research and Analysis Laboratory

The use of the PBF in BNCT represents a new mission at the INEL. Research into medical therapy, using an INEL reactor, has not been performed previously to the extent projected for BNCT. This research will require diagnostic tools not used in existing programs and not available at INEL. A laboratory facility near PBF has been proposed to provide an international center close to the source of the epithermal neutrons for research related to development of BNCT for treating a variety of human tumors. The laboratory will provide state-of-the-art medical and physics research facilities and diagnostic tools; laboratories and kenneling to support animal research; and offices, limited overnight human housing and various auxiliary facilities. The laboratory will host both domestic and international research and must provide the proper tools to support biological, medical, and physics research. Hospital facilities for human research will be provided by the Eastern Idaho Regional Medical Center (EIRMC) in Idaho Falls.

CONCLUSION

BNCT will first be applied to the aggressive brain tumor Glioblastoma Multiforme because of the insidious nature of the disease and because the orphan disease status facilitates United States Food and Drug Administration (FDA) approvals. Researchers expect, however, that BNCT will also be effective for other types of cancer in various parts of the body. Advanced research directed toward treatment of other cancer types is not part of the presently proposed three-year program plan, however, PBF is envisioned as becoming a baseload-funded international research tool, as well as a brain tumor treatment center.

It is anticipated that human clinical trials will prove that BNCT can be provided on an outpatient basis and provide an order of magnitude improvement over present treatment methods for Glioblastoma Multiforme, and subsequently for other tumor types for which present treatments are ineffective. Success in this endeavor will be a tremendous benefit to mankind and will be a powerful demonstration of the beneficial uses of nuclear reactors.

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