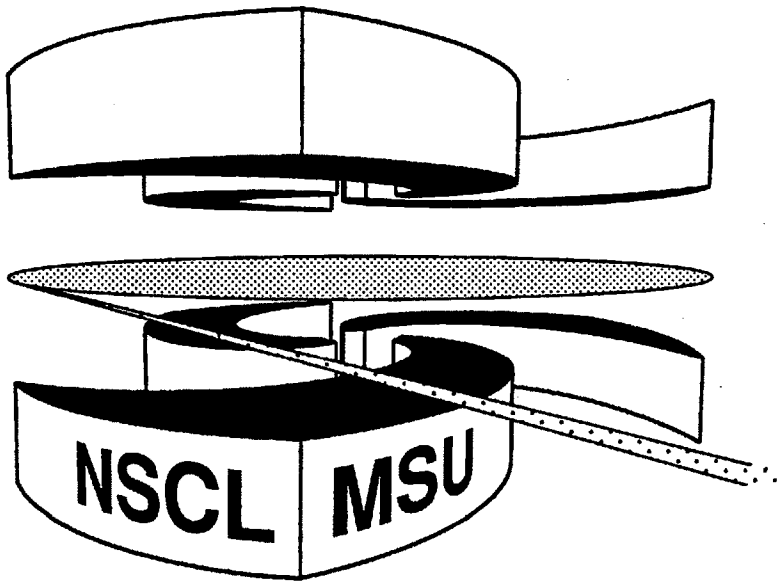
Michigan State University

National Superconducting Cyclotron Laboratory

FEASIBILITY STUDY OF BORON NEUTRON CAPTURE THERAPY USING THE K100 SUPERCONDUCTING CYCLOTRON AT HARPER HOSPITAL (DETROIT, MI)

WARREN D'SOUZA



MSUCP-75

AUGUST 1994

FEASIBILITY STUDY
OF
BORON NEUTRON CAPTURE THERAPY
USING THE
K100 SUPERCONDUCTING CYCLOTRON
AT
HARPER HOSPITAL (DETROIT, MI)

WARREN D'SOUZA

ADVISORS: DR. HENRY G. BLOSSER &
DR. RICHARD L. MAUGHAN

NSCL
MICHIGAN STATE UNIVERSITY
REU SUMMER 1994

Introduction:

All conventional cancer treatment methods such as surgery, chemotherapy and radiation therapy are faced with the challenge of selectively destroying the tumor region without harming healthy tissues. Boron Neutron Capture Therapy (BNCT) is one kind of radiation therapy that seems to be a good approach in this direction. It is based on the interaction of low energy neutrons generated in an external beam with boron (^{10}B) localized in malignant cells. The neutron beam at Harper Hospital, Detroit is of mean energy 20.4 MeV and is produced by the interaction of 48.5 MeV deuterons accelerated in a superconducting cyclotron and incident on a thick, internal berrylium target [4,5]. The goal of this project was to assess the feasibility of obtaining a neutron beam suitable for BNCT with the Harper Hospital "K100" superconducting cyclotron.

Boron Neutron Capture Therapy:

Boron Neutron Capture Therapy (BNCT) first proposed by G. Locker in 1936 includes two steps i) the incorporation of a high boron (^{10}B) concentration in the tumor cells and ii) the irradiation of tumor cells with low energy neutrons. ^{10}B has a large capture cross section (3838 barns) for neutrons in the thermal energy range (< 0.5 eV) [2]. When the neutron strikes boron the following reaction takes place:

$$^{10}B + n \rightarrow {}^{7}Li + {}^{4}He + \gamma\,(0.48\ MeV)\ [93.7\ \%]\ [2]$$

The average Q value of this reaction is +2.35 MeV [4]. (When γ ray is emmitted the Q value is 2.31 MeV, when it is not the Q value is 2.79MeV). The alpha particles and lithium recoil ions created carry a large amount of energy. Alpha and Li nuclei energies are 1.78 MeV and 1.01 MeV respectively when the γ ray is not emitted, and 1.47 MeV and 0.84 MeV respectively when the γ ray is emitted. The energy loss is 250 keV/μm for alphas and 350 keV/μm for Li recoils. The products of the above nuclear reaction also have short ranges of ~10 μm (alphas) and ~5 μm (Li recoils) [4] which is typically the dimension of cells. In this way a local tumor dose due to the high LET alpha particles and Li recoil ions is achieved. Radiation damage can thus be induced solely within tumor regions and healthy cells are spared.

Neutron Beam Characteristics for BNCT:

The major concern for carrying out BNCT is obtaining a suitable beam of neutrons in terms of intensity and energy spectrum. A sufficient number of neutrons must be available for the neutron capture reaction. The ideal beam must have a high neutron flux of about 5 E+09 neutrons/cm^2.sec so as to obtain a thermal fluence of 10^{12} - 10^{13} neutrons/cm^2 in the tumor [2]. In addition the dose to normal cells due to the presence of gamma rays and fast neutrons must be minimised.

The type of neutron spectrum selected depends on the type of tumor to be treated:

- thermal neutrons (0.025 eV) are chosen for superficial tumors, down to a depth of 3 cm
- for deeper tumors (down to 7-8 cm), epithermal neutrons (0.5 eV - 10 keV, ideally 2 keV) are

preferred [2]. These neutrons would be moderated in tissue before being captured by ^{10}B.

Nuclear reactors are probably the most suitable sources for the needed beam requirements. However it is unreasonable to have a nuclear reactor located in a hospital environment. Hence the idea of using an accelerator based source was looked into. The accelerator whose use in BNCT was looked into was the cyclotron machine at the Gershenson Radiation Oncology Center at Harper Hospital, Detroit. This "K100" superconducting cyclotron was the first superconducting cyclotron built in the world for medical applications and is now used extensively for neutron therapy.

K100 Cyclotron and Clinical Components:

The basic component of the neutron therapy facility at Harper Hospital is an isochronous superconducting cyclotron that accelerates deuterons to an energy of 48.5 MeV. The deuteron beam strikes an internal Be target at a glancing angle of 20.3° [5]. This is done to reduce the very high power density in the internal beam (~ 11 kw.cm^{-2}) at the maximum beam current of 15 μA [5]. The target assembly is comprised of the Be target brazed to a channeled copper backing plate which is water cooled.

The magnet design is of the "pillbox" type in which the magnet is completely contained within the steel of the yoke. The magnet yoke serves as part of the shielding system protecting the patient from the primary radiation beam outside the defined radiation beam. The magnet coil is contained in a specially designed cryostat which allows the magnet to be rotated through 360°. When operating the machine at full beam current the helium consumption is immense (7-8 l/hr). The magnet pole pieces are 30 cm in radius and have three spiral sectors [5]. The field strength at the center of the magnet is 4.6 T at the operating current of 203 A [5].

Some of the specific features of the cyclotron follow from the choice of rf frequency, i.e. 105 MHz [5]. This allows a radio station transmitter to be used as the source of power for the rf system. The neutron yield is higher with the $^{9}Be(d,n)$ reaction as compared with the corresponding proton reaction. This allows for a lower beam current for a particular neutron dose rate. The neutron yield is also forward peaked and hence shielding requirements for patient protection are reduced at the non-forward angles [5].

The neutron beam exits the cyclotron vacuum chamber through a stainless steel window. The forward peaked neutron beam is asymmetrical in one plane [5]. A flattening filter is used to produce a beam with a clinically acceptable dose distribution. The 'flattened' beam passes through three parallel plate monitor ionization chambers which monitor the dose delivered and beam stability. The light localizer is used for patient positioning and is located after the dose monitor chambers. All these components are mounted within the magnet yoke.

The multi-rod collimator is located outside the magnet yoke. It consists of two opposed arrays of tungsten rods which can be pushed into position by two templates made from high density polystyrene foam to form a shape that defines the radiation field. The maximum field size is 26.5 cm x 30 cm [5]. The collimator can be rotated through 180° and the distance between the collimator and the isocenter is 40 cm [5].

Harper "K100" Cyclotron Beam for BNCT:

The neutron therapy beam at Harper Hospital is of mean energy 20.4 MeV and is produced by 48.5 MeV deuterons striking a thick internal Be target [4,5]. The ^{9}Be(d,n) reaction is usually employed with cyclotrons in preference to the ^{3}H(d,n)4He reaction since the neutron yield is higher and the problem of the lifetime of the tritium target is avoided [1]. Figure 1 [1] shows the angular distribution of neutrons from the ^{9}Be(d,n) reaction at deuteron energies of 16, 33 and 50 MeV. It can be seen from figure 2 [1] that the angular distribution of these neutrons is forward peaked i.e. the maximum flux occurs at 0°. The flux of neutrons at 0° is 5.8 E+11 neutrons/μC.sr at the deuteron energy of 50 MeV [1].

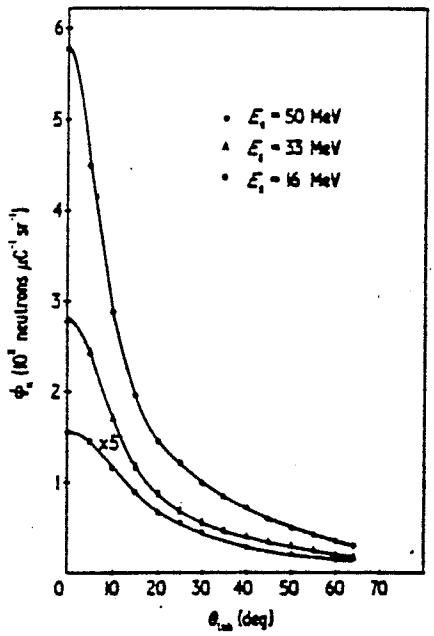


Figure 1. Angular distribution of the neutrons from the ^{9}Be(d,n) reaction at E_d = 16, 33 and 50 MeV, ref. Meulders *et al.*

For the Harper cyclotron the solid angle subtended by the full aperture collimator is 1/50 sr and the machine is run at a beam current of ~ 10 μA. The number of neutrons coming out of the collimator can thus be calculated:

$$5.8\,E{+}11\frac{neutrons}{\mu C\,.\,sr}\,.\,\frac{1}{50}\,sr\,.\,10\,\mu A$$

which gives 1.16 E+11 neutrons/sec. The mean energy of these neutrons is 20.4 MeV. Their energy must be reduced to the order of a few keV (epithermal neutrons ~ 2 keV) so that they can be used for BNCT. Hence the need arises for a moderator. A moderator is a material that slows down neutrons by successive collisions thereby, decreasing their energy.

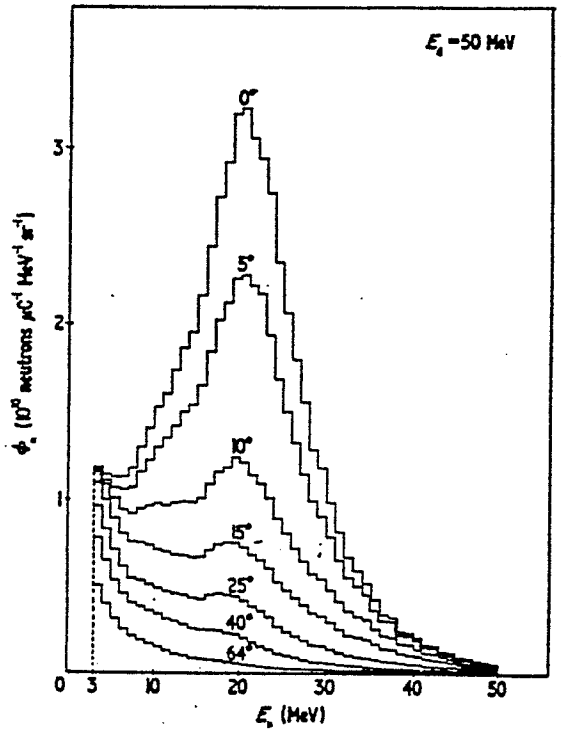


Figure 2. Energy spectra of the neutrons emitted at different angles, θ from the ^{9}Be(d,n) reaction at E_d = 50 MeV. Values of are given for each spectrum, ref. Meulders *et al.*

In some recent calculations done at the Paul Scherrer Institute (PSI) suitable moderators were being tested for neutron capture therapy (NCT). These calculations were done using the Monte Carlo N-Particle Transport (MCNP) code. Spectra giving neutron fluence from two simple layouts were published i.e. neutron sources at the center of Al and Fe spheres of radius of 0.6m. The quantities of main interest in NCT are average energy and fluence. Several materials were tested and it was found that the average energy was reduced most effectively with Al/Fe in a 1:1 ratio by atom. To reduce the average energy further without affecting the neutron fluence by much, 10 - 20 cm of carbon and heavy water (D_2O) were tested. A considerably higher neutron fluence was obtained with heavy water [3]. A 25 mm layer of lead was also added to reduce the number of γ's produced since γ dose is undesirable in neutron capture therapy. Since no experimental measurements had been made it was decided to conduct an experiment to study such calculations.

Experiments (Paraffin and Aluminum as moderators):

Heavy water is by far the most effective moderators for neutrons. Heavy water is not easily available in the United States and it is also very expensive (pure grade D_2O costs about $400 per kilogram). Heavy water must be obtained from Canada where it is used in nuclear reactors. The fact that it takes 4-6 weeks to process an export licese for the shipment of heavy water as well as its cost compelled us to hold off making measurements with it until we had some concrete calculations. This left us with paraffin which is a good moderator of neutrons. It is easily obtainable and cheap. Paraffin is a family of alkanes and has the general chemical formula CH3 (CH_2)4n CH_3 where n = 1,2,3...

The method of measuring neutron fluence selected was activation foils. Activation foils are one of the most widely used types of neutron detectors. Some of the advantages of using activation foils are i) they can be used over a wide range of flux levels ii) they take up very little room and do not require the use of electronic equipment during the time of irradiation iii) the foils may be activated and measurements of the activity can be made at one's convenience after the experiments and iv) the presence of gamma rays or other types of radiation does not affect the activation of such foils [7].

For BNCT the quantity of main interest is the flux of neutrons in three energy ranges, thermal energy neutrons (< 0.5 eV), epithermal or intermediate energy neutrons (0.5 eV - 10 keV) and high energy neutrons. For deep seated brain tumors the goal is to maximize the flux due to epithermal neutrons (~ 2 keV) while minimizing the flux due to the thermal and high energy component of the neutron beam. The foil materials selected for use in the experiment were natural gold (Au), scandium (Sc) and titanium (isotopes ^{46}Ti and ^{47}Ti). Table 1 summarizes the neutron energy detected by the foils along with their cross section values for neutrons in the particular energy ranges.

Table 1. Activation foils with the neutron energies detected, cross sections and half lives

Neutron Energy	Element of Interest	Nuclear Reaction	Half life of Product Nucleus	Elemental Cross Section
0.025 eV	Au	$Au^{197}(n,\gamma)Au^{198}$	2.69 d	100 barns
5 keV	Sc	$Sc^{45}(n,\gamma)Sc^{46}$	83.83 d	11.3 barns
2.2 MeV	Ti	$Ti^{47}(n,p)Sc^{47}$	3.34 d	21.4 millibarns
3.9 MeV	Ti	$Ti^{46}(n,p)Sc^{46}$	83.83 d	10 millibarns

These isotopes when irradiated by neutrons are transformed into other elements that have unstable nuclei and so emit β^- particles along with γ particles. By measuring the γ activity of the radioactive nuclides, the neutron fluence can be determined. The equation used to determine the neutron fluence was:

$$N_0 = \phi \sigma N$$

where
N_0 is the number of radioactive nuclei produced in the foil,
ϕ is the neutron fluence,
σ is the total cross section of the radioactive nuclides (obtained from Reactor Experiments Inc.),
N is the number of target atoms in the foil.
There is some ambiguity as to how the cross section values were arrived at. Shown in Figure 3. is the cross section for gold as a function of energy. It is not clear what area under the curve was integrated to obtain the values listed by Reactor Experiments Inc.

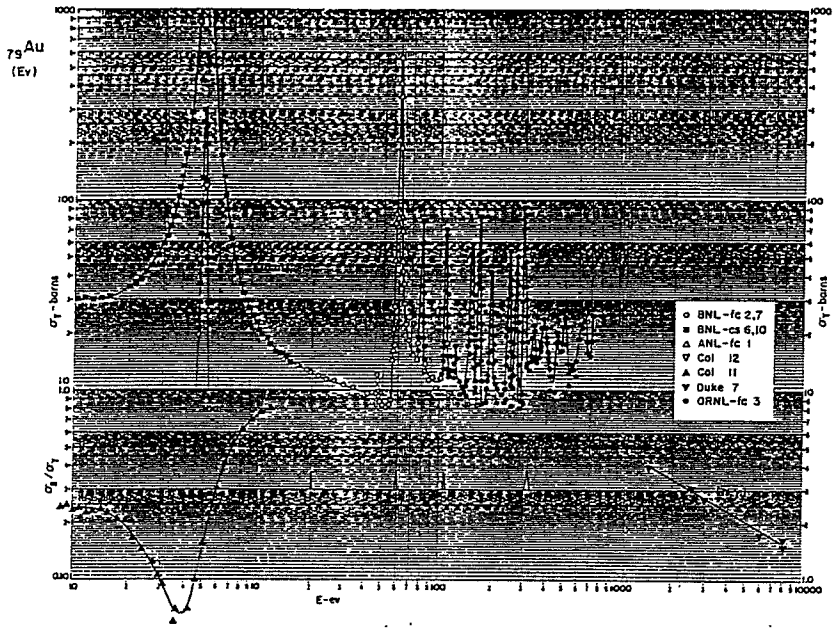


Figure 3. Cross section for Au (1eV - 10keV), ref. J. Hughes *et al.*

The γ rays were detected using a counting system that consisted of a germanium detector, preamplifier, amplifier, multi-channel analyzer, analog to digital converter and the computer software 'Canberra'. The radioactive nuclides created during the irradiation process have characteristic γ spectrums that consist mainly of a photopeak and the compton edge. The area under the photopeak gives the measured activity of the radioactive sample. Other factors such as detector efficiency at different energies and branching ratios have to be taken into consideration when making calculations. In order to determine the number of radioactive nuclei the following relationship was used: $A_0 = \lambda N_0$

where A_0 is the initial activity and λ is the decay constant.

The neutron flux Φ can be obtained by dividing the neutron fluence by the irradiation time.

In the first run a set of foils were placed along the beam central axis at a distance of ~ 34" from the front face of the collimator with no paraffin to slow down the neutrons. The cyclotron was run at an almost steady beam current of ~ 10 μA and the foils were irradiated for approximately 12 minutes. For the second run the multi-rod collimator was filled with paraffin. The collimator is a 8.9" x 8.9" square and 13.975" deep. In addition ~ 75 cm of paraffin was stacked up in front of the collimator. A set of foils (i.e. Au, Sc and Ti) were placed along the beam central axis 185 cm from the beam target. Another set of foils were placed 15" off the beam central axis 175 cm from the beam target. The cyclotron was again run at a beam current of ~ 10 μA and the foils irradiated for 20 mins. Table 2 shows the neutron flux values obtained for the two setups at 3 different energies.

Table 2. Flux of neutrons in the high energy, epithermal energy and thermal energy ranges.

Energy	Flux #/cm^2.sec
2.2 MeV	1.7 E+08
5 keV	4.8 E+06
0.025 eV	6.7 E+06

a) No moderator - foils along beam central axis, 185 cm from Be target

Energy	Flux #/cm^{2}sec
2.2 MeV	< 2.0 E+06
5 keV	6.5 E+06
0.025 eV	6.9 E+06

b) Paraffin - foils along beam central and 185 cm from Be target

Energy	Flux #/cm^2.sec
2.2 MeV	< 2.0 E+06
5 keV	8.8 E+06
0.025 eV	7.7 E+06

c) Paraffin - foils perpendicularly displaced 15" from beam central axis at point 175 cm from Be target

5.8 E+11 neutrons/μC.sr are produced in the forward direction from a 50 MeV deuteron beam incident on a Be target [1]. This is comparable with the K100 cyclotron deuteron beam energy. The distance of the foils from the beam target was 185 cm. Hence the flux of neutrons (without a moderator) at this distance can be calculated (irradiation time was ~ 12 min. and the beam current was 10 μA).

$$(5.8E{+}11\ \frac{neutrons}{\mu C.sr})\left(\left(\frac{1}{185}\right)^2 \frac{sr}{cm^2}\right)(10\mu A)$$

Thus the flux of neutrons is 1.7 E+08 /cm^2. This is in close agreement with our experimental measurement (see table. 2). The results from this experiment led us to conclude that the ratio of the flux of neutrons in the epithermal range to the flux of neutrons in high and thermal energy ranges off the beam central axis was higher than along the beam axis.

Along with the foil activation technique, a microdosimetric study of dose enhancement in the moderated beam due to boron neutron capture was also made by Chandrasekhar Kota of which only a brief mention will be made in this paper. The measurements were made using two Rossi-type spherical proportional counters each with an inner diameter of 12.7 mm and 8 mm thick walls made of A150 tissue equivalent plastic (TEP) which were identical in all respects but

one. One of the counters had its wall uniformly loaded with 50 ppm of ^{10}B to simulate a uniform distribution of 50 ppm of ^{10}B in the tumor volume. The two counters were filled to a pressure of 8.8 kPa with a propane-based gas to simulate a 2 μm diameter sphere of tumor.

Figure 4 is a graph of dose deposited versus lineal energy. The solid line represents the complete spectrum. The increase in the alpha and lithium ion peak in the ^{10}B counter can be seen in the plot. The spectrum was recorded using three amplifiers whose dead times were matched to obtain the complete spectrum.

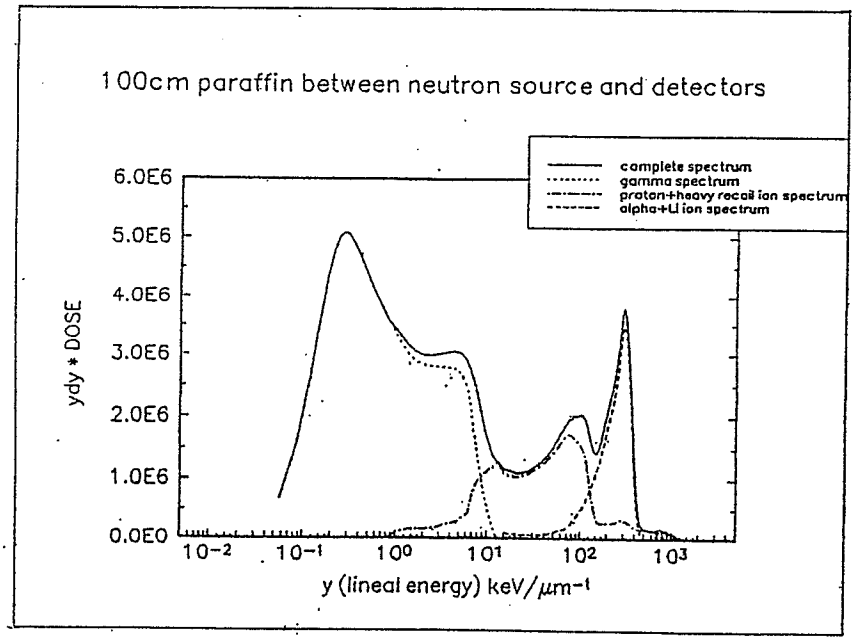


Figure 4. Spectrum obtained from proportional counters.

The flux values obtained in the first two runs sparked off interest in the off-axis location of foils. For the third run it was decided to repeat the first two runs, except, this time the foils were placed along a straight line (~ 75 cm from the front face of the collimator) along the beam central axis and 9" and 18" off the central axis. The irradiation time was increased to an hour. At the same time it was planned to check the calculations done at PSI (mentioned earlier) with an experiment. However Fe could not be used due to the fact that it would be magnetised by the cyclotron magnet. Heavy water was not available at the time and so Al by itself was chosen as a moderator. This would also provide a comparison between Al and paraffin as moderators. Table 3 shows the results from the experiment.

Table 3. Flux of neutrons in the high energy epithermal energy and thermal energy ranges.

Energy	Flux #/cm^2.sec
2.2 MeV	1.5 E+08
5 keV	8.1 E+06
0.025 eV	8.1 E+06

a) Paraffin - foils along beam central axis, 185 cm from Be target

Energy	Flux #/cm^2.sec
2.2 MeV	6.1 E+05
5 keV	7.4 E+06
0.025 eV	6.7 E+06

b) Paraffin - foils perpendicularly displaced 9" from beam central axis at a point 185 cm from Be target

Energy	Flux #/cm^2.sec
2.2 MeV	< 5.6 E+08
5 keV	6.8 E+06
0.025 eV	7.5 E+06

c) Paraffin - foils perpendicularly displaced 18" from beam central axis at a point 185 cm from Be target

Energy	Flux #/cm^2.sec
2.2 MeV	< 5.6 E+08
5 keV	7.6 E+06
0.025 eV	1.0 E+07

d) Aluminum - foils along beam central axis, 137 cm from Be target

The following conclusions were made from the results of the third and fourth runs: i) paraffin is a better moderator than Al and ii) in the off-axis arrangement the fast neutron component of the beam is significantly reduced while the epithermal component is increased.

Monte Carlo N-Particle Transport Code (MCNP):

Monte Carlo methods do not solve explicit equations but rather obtain answers by simulating individual particles and recording some aspects of their average behavior. The average behavior of particles in the physical system is then inferred from the average behavior of the simulated particles. Monte Carlo techniques can be used to duplicate theoretically a statistical process (such as interaction of nuclear particles with materials) and are particularly used for complex problems that cannot be modeled by computer codes that use deterministic methods [7]. The individual probabilistic events that comprise a process are simulated sequentially. The probability distribution governing these events are statistically sampled to describe the total phenomenon. The statistical sampling process is based on the selection of random numbers and is analogous to throwing dice in gambling - hence the name Monte

Carlo [7].

MCNP 4A is a continuous energy, generalized-geometry transport code that can simulate electron, neutron and photon transport. The MCNP code had to be installed on a NSCL computer. The next task was to learn how to use the code. It uses a user supplied file and several cross section and data files as input to produce a desired output (tallies). To familiarize ourselves with the code we first ran a few sample problems. Feeling confident to move on, we decided to reproduce the results obtained at PSI. Neutron sources were started at the center of Al, Fe and Al/Fe (1:1 ratio by atom) spheres of radius 60 cm. The energy spectrum used was an evaporation spectrum ($p(E) = C\ E \exp(-E/a)$, $a = 1.2895$). In addition 10 and 20 cm of heavy water and carbon were added outside the Al/Fe sphere to compare their effectiveness in moderating neutrons. The neutron fluence spectra obtained have been included in this paper. (See figure 5 a-g). The neutron fluences have been normalized to be per initial particle.

Conclusion:

The flux of neutrons needed for BNCT so that the dose may be delivered in two - three hours [3] is 5 E+09 /cm^2.sec [2]. The flux values obtained in the epithermal energy range with paraffin acting as the moderator were about three orders of magnitude smaller. This indicates an incredibly long treatment time which is not feasible. However the effectiveness of heavy water or a combination of materials was not tested. MCNP could play an important role in this. The setup at Harper Hospital can be simulated using the code to determine the flux distribution of neutrons. Preliminary calculations were tried with no success.

Acknowledgements:

I would like to thank my advisors Dr. Henry G. Blosser and Dr. Richard L. Maughan for their continued advice and guidance during this project. I would also like to thank Aaron Galonsky, Reg Ronningen, Ron Fox, Richard Au, Jeff Schubert, Lung-Sheng Lee, Chandrasekhar Kota and Nancy Davis for their help during the course of this project. Finally, I would like to thank NSF for providing funds to make this research possible and MSU for giving me the opportunity to do undergraduate research.

REFERENCES

[1] J. P. Meulders, P. Leleux, P. C. Macq and C. Pirart, Fast Neutron Yields and Spectra from Targets of Varying Atomic Number Bombarded with Deuterons from 16 to 50 MeV, *Phys. Med. Biol.* 20:235-243, (1975).

[2] N. Daymard, J. C. Abbe, J. P. Pignol, I. Kodeli, C. M. Diop, J. C. Nimal, Investigation of the Neutron Beam Characteristics for Boron Neutron Capture Therapy with 3D and 2D Transport Calculations, France.

[3] J. F. Crawford, H. Reist, H. Conde, K. Elmgren, T. Ronnqvist, E. Grussell, B. Nilsson, O. Pettersson and P. Stromberg, Neutrons for Capture Therapy Produced by 72 MeV Protons, New York (1992).

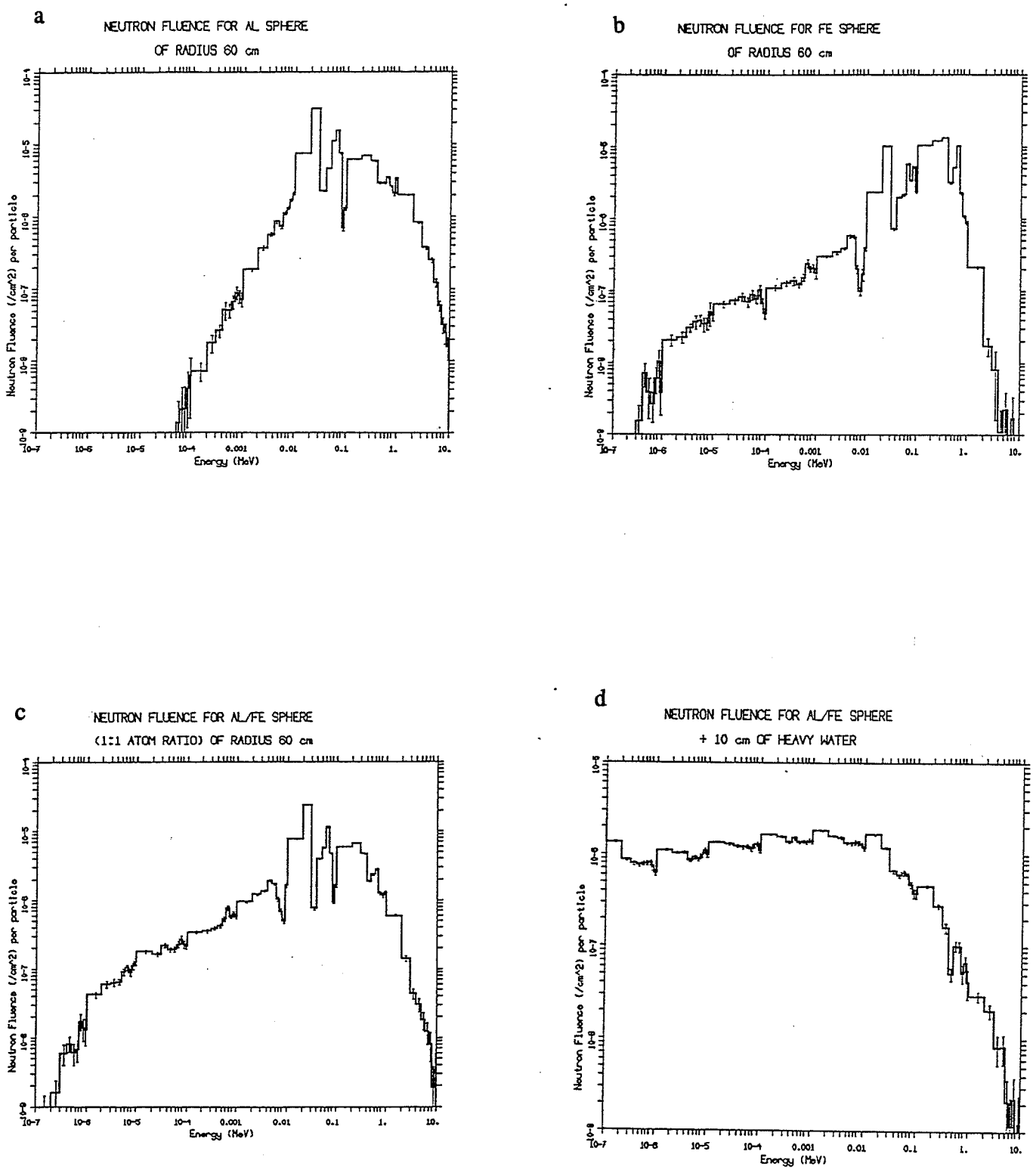
[4] R. L. Maughan, C. Kota, M. Yudelev, A Microdosimetric Study of the Dose Enhancement in a Fast Neutron Beam due to Boron Neutron Capture, *Phys. Med. Biol.* 37:1957-1961, United Kingdom (1992).

[5] R. L. Maughan, H. G. Blosser, W. E. Powers A Superconducting Cyclotron for Neutron Radiation Therapy, *Medical Physics 21:779-785, (1984).*

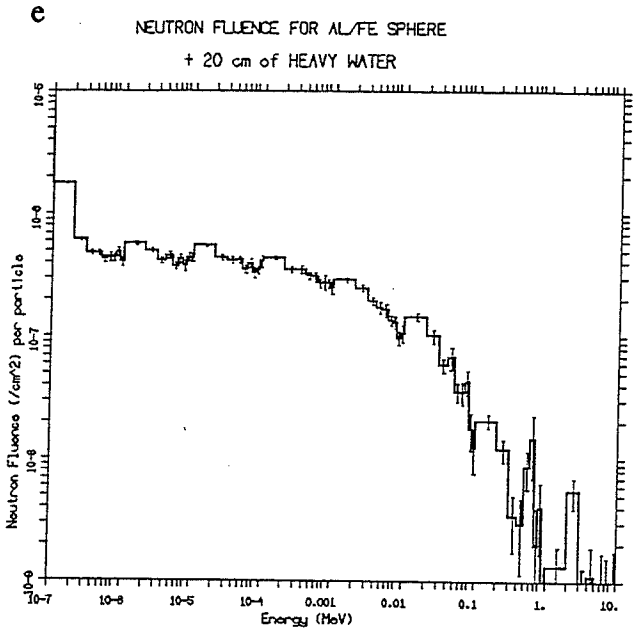
[6] Monte Carlo N-Particle Transport Code System (MCNP 4A), Los Alamos (1994).

[7] Reactor Experiments, Inc., Activation Foil Manual, California (1965).

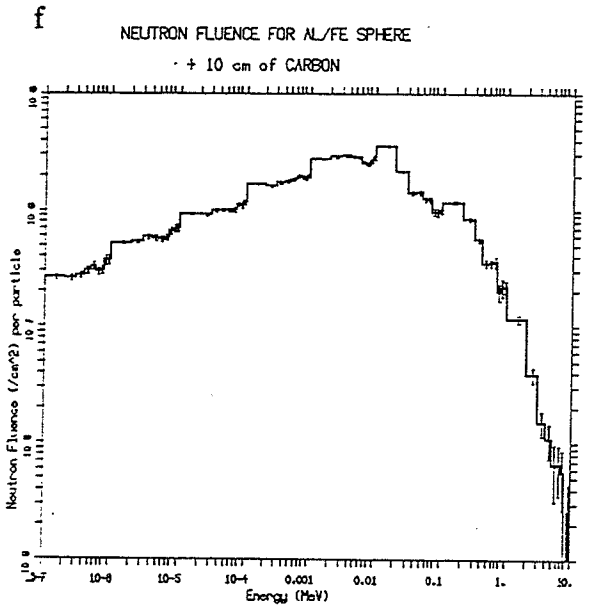
Figure 5. Neutron Fluence Spectra



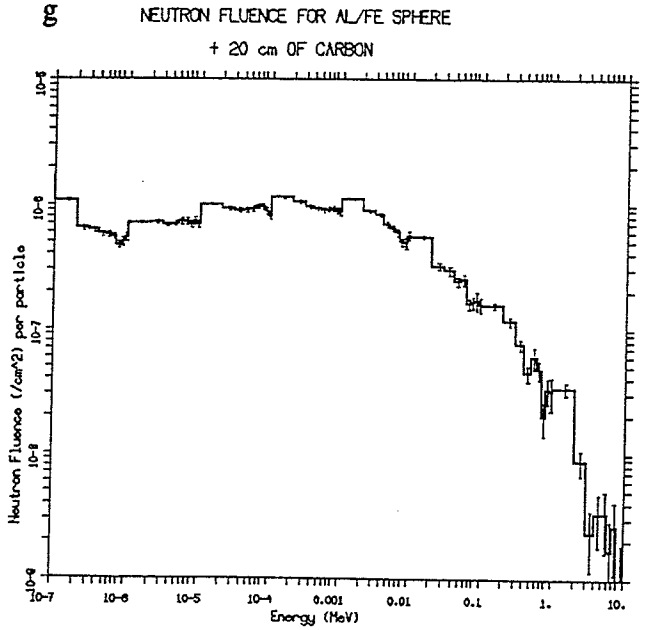
e


NEUTRON FLUENCE FOR AL/FE SPHERE
+ 20 cm of HEAVY WATER
Neutron Fluence (/cm^2) per particle
Energy (MeV)

f


NEUTRON FLUENCE FOR AL/FE SPHERE
+ 10 cm of CARBON
Neutron Fluence (/cm^2) per particle
Energy (MeV)

g


NEUTRON FLUENCE FOR AL/FE SPHERE
+ 20 cm OF CARBON
Neutron Fluence (/cm^2) per particle
Energy (MeV)