SMALL ACCELERATORS FOR STUDIES IN THE APPLICATION OF NEUTRONS IN BIOMEDICINE

S.R. Bull, R.H. Hoft, N. Slaten
Nuclear Engineering Program
University of Missouri-Columbia

and

J.M. Thomson
Radiotherapy Department
Ellis Fischel State Cancer Hospital
Columbia, MO 65201

Summary

A small accelerator which produces high energy (14.7 MeV) neutrons by the $H^3(H^2,n)He^4$ reaction has been utilized for two basic biomedical studies. First, fast neutron radiography has been explored as a technique for imaging biological objects. The primary objective was to test the sensitivity of the technique by measuring the differential attenuation coefficient necessary for object identification as a function of the sample thickness. Second, fast neutron radiotherapy experiments were undertaken. Animals with induced brain tumors were treated to observe the relationship between dose fractionation and cell repair. The results are encouraging and indicate the feasibility of further studies with a small accelerator.

Introduction

A small accelerator can serve as a useful tool in studying the application of neutrons in biomedicine. The two most obvious areas are the use of fast neutron radiography for imaging biological objects and fast neutron radiotherapy for treatment of cancer. It is generally recognized that existing small accelerators have insufficient neutron output for clinical applications, so work undertaken with such accelerators is by necessity either a feasibility study or work preliminary to clinical trials.

Neutron radiography has been explored recently as a technique for imaging biological objects with the eventual goal of achieving routine clinical diagnostic status.[1-9] It is a technique complementary to conventional x-ray methods[10] and may be useful for applications such as the imaging of air-filled cavities embedded in tissue, particularly in the vicinity of bones. Thermal neutron radiography methods[10] are well developed, but fast or resonance energy neutrons are necessary to penetrate practical biological specimens for imaging purposes. Previous work in our laboratory has been reported on measurement of the sensitivity and resolution of a fast neutron radiography facility[8] and on an improved collimator design.[9] The objective of the investigation reported here was to evaluate the differential attenuation coefficient necessary to achieve a minimum image contrast level.

Numerous investigators[11-14] have reported on the potential of fast neutrons for radiation therapy. The apparent favorable dependence on oxygenation for fast neutrons has been confirmed by several authors[12,15-18] as evidenced by oxygen enhancement ratios of ~3 for x-rays (low LET) and of ~1.8 for fast neutrons (high LET). Neutron source requirements to perform clinical fast neutron therapy have been described[13-14]; neutrons with 14 MeV energy have a suitable skin sparing effect and have depth dose characteristics similar to that of Co^{60} gamma rays. We believe the most desirable approach from an economic and utility standpoint for placement in a typical hospital is to utilize a compact accelerator which produces 14 MeV neutrons by the D-T reaction. Projected intensity requirements are a factor of 10 above existing D-T units. However, if current efforts[19-21] to increase the output of D-T units are successful, the opportunity for extensive clinical trials will be imminent. An investigation was undertaken in our laboratory to gain experience in fast neutron therapy work and to study the relationship between dose fractionation and cancer cell repair in mice.

Description of the Experiment

Neutron Source

The fast neutron source was a neutron generator (Picker Nuclear Accelerator) which accelerates deuterons to 150 kV to produce neutrons by the following reaction:

$$_1H^2 + _1H^3 \rightarrow _0n^1 + _2He^4 + 17.6\ \text{MeV}$$

This reaction, commonly designated as the D-T or T(d,n) reaction, yields a 14.7 MeV neutron in the forward direction. At a maximum beam current of 3.5 mA and with a 5 Ci tritium target, the unit is capable of producing 3.5×10^{11} neutrons/sec.

Fast Neutron Radiography

Collimator System. A useful neutron beam for producing radiographs was produced by positioning the neutron source in a reentrant tube in a large water tank. A beam of fast neutrons was extracted from the tank through a divergent collimator oriented at an angle of 65° with the accelerator axis (see Figure 1). This system provides a twelve-inch square radiography area approximately 26 inches from the source. The collimator was not oriented along the accelerator axis because x-rays are produced (up to 100 mR/hr) that stream along the axis.

Image Production. A direct exposure method was used with a scintillator screen and film combination placed directly behind the object to be radiographed. Kodak Type AA Industrial X-ray Film was used throughout the work and standard developing procedures were

followed. Two different converter screen materials were used:

1) Calcium tungstate ($CaWO_4$) x-ray fluorescent screens mounted in an aluminum cassette.
2) A ZnS (Ag) scintillator material dispersed in a hydrogeneous medium and contained in an aluminum cassette.

A comparison of these screens has shown that the ZnS (Ag) screen is approximately 1.5 times faster than the $CaWO_4$ screen.

Test Object. A test container which ranged in thickness from .875 inches to 4.875 inches was constructed and filled with tissue equivalent solution (56.9% water, 28.4% glycerol, 7.6% urea, and 7.1% sucrose). Vinyl tubes of .5, .375,.1875, and .056 inches ID were placed at various locations in the test container (see Figure 2). The differential attenuation coefficient was then correlated with the radiograph image contrast by filling the tubes with air, isopropyl alcohol, acetone, methyl alcohol, or water.

Fast Neutron Radiotherapy

Collimator System. The collimator system consisted of a 48 x 48 x 18 inch tank with a housing mounted in the center for the target end of the neutron generator. This tank, filled with water, is set on the front edge of a 48 x 48 inch steel table mounted on 8 inch castors (see Figure 3). The housing for the tritium target and drift tube of the neutron generator consists of a 14.5 x 14.5 x 18.0 inch parallelpiped section in the center of the tank. The section contains two removable 1-inch thick semicircular plates. They are 5 inches ID, 18 inches long and supported by a 6 inch ID steel pipe of the same length. Final collimation is achieved by a steel plug with a divergent opening that ranges from 1.75 inches ID to 4.0 inches ID. This produced a circular beam of 14.7 MeV neutrons 5.5 inches diameter at a source to skin distance of 3.25 inches (8.3 cm). The low output of the neutron generator prohibited the use of significantly larger source to skin distances.

Procedure. The animals used in the experiment were C57 Bl 6J mice that were 6-8 weeks old and were housed in the Experimental Animal Facility at the university. The ependymoblastoma tumor was obtained from the National Institute of Health and was carried in live animals. Solutions were made up of sterile solution and tumor cells and the animals were innoculated by injection of 0.025 ml of the solution into the brain.

The animals were innoculated on day 0 and neutron treatments were started on day 3. The dose was delivered to the head by positioning the animals with their heads in the edge of the 5.5-inch diameter neutron beam. They were placed on a circular disk which was rotated to insure a uniform neutron intensity at all positions.

Total doses of 250, 400, and 500 rads of fast neutrons were administered by each of the following fractionation schedules:

1) One dose: day 3.
2) Three doses: days 3, 4, and 5.
3) Five doses: days 3,4,5,6, and 7.

The single dose of 400 rads was inadvertently omitted from the study. Also, two control groups were maintained. One group received the innoculation but no treatment and one group received no innoculation and no treatment. A total of 176 animals were included in this study, each group typically consisted of 15-20 animals.

A related study was conducted to observe the effect of various combinations of neutrons and chemotherapy on the brain tumors. The drugs used in the study were BCNU and Ara-C. For this portion of the study 250 rads of fast neutrons were administered in a single dose on day 2.

Dosimetry

The fast neutron fluence (and dose) at the neutron radiograph object position or at the skin of the animals was measured with a small Cu foil. The 11.5 MeV threshold $Cu^{63}(n,2n)Cu^{62}$ reaction was utilized and detection of the annihilation gammas gave the administered fast neutron dose. A neutron flux monitor was also employed for continuous monitoring of the neutron output.

Discussion of Results

Fast Neutron Radiography

The neutron to gamma ray ratio at the radiograph position was 4.05×10^5 n/cm^2-mR. The fast neutron flux was measured by Cu activation as described above and the gamma ray flux was measured with thermoluminescent dosimeters. A fluence of about 5×10^8 n/cm^2 produced the best image of the test container.

Radiographs of the test container with the various combinations of tube sizes and contrast media were scanned with a densitometer. Figure 4 illustrates typical results for the contrast as a function of the equivalent tissue thickness. While some contrast does exist in all cases, it can be visibly detected only for the air filled tube. This is not an unexpected result since the difference in the attenuation coefficient between the fill material and tissue is small except for air. The calculated attenuation coefficients and corresponding differential attenuation coefficients (using $\mu_{tissue} = .09$ cm^{-1}) are as follows:

$\mu_{Air} = 0.0$ cm^{-1} ($\Delta\mu = .09$ cm^{-1})

$\mu_{Isopropyl\ Alcohol} = .074$ cm^{-1} ($\Delta\mu = .016$ cm^{-1})

$\mu_{Acetone} = .078$ cm^{-1} ($\Delta\mu = .012$ cm^{-1})

$\mu_{Methyl\ Alcohol} = .082$ cm^{-1} ($\Delta\mu = .008$ cm^{-1})

$\mu_{Water} = .095$ cm^{-1} ($\Delta\mu = .005$ cm^{-1})

The capability of imaging materials other than air in tissue successfully with fast neu-

trons will require improved detection, collimation and image enhancement methods.

Fast Neutron Radiotherapy

A dose profile was taken radially along the body of the animals to determine the body dose. Up to 25% of the given dose to the head was received by the body. This was a consequence of inefficient collimation because it was necessary to maintain a short source to skin distance as noted above.

Figure 5 is the survival curve to 45 days after innoculation as a function of the total neutron dose administered. A schedule of 3 fractions was consistently best, 5 fractions was next, and 1 fraction was least effective. The highest survival rate (62.0%) was achieved with 500 rads. No doses above 500 rads were administered, but it appears that the optimum dose is above 500 rads.

Figure 6 shows the daily survival curves for the 500 rads dose group for the different fractionation schedules along with the control group that was innoculated but received no treatment. As illustrated previously, the schedule of 3 fractions was most effective. No animals survived past the 21st day for the group receiving no treatment. One animal of the control group that was not innoculated and received no radiation died on the 29th day.

The results suggest that there is an intermediate optimum number of dose fractions and presumably there is also an optimum total dose. Further experiments are planned to clarify this point.

Preliminary studies utilizing a combination of fast neutrons, BCNU, and Ara-C imply increased survival is obtained. The results of this study will be described in another report.

Although the experiment had the disadvantage of low neutron output, valuable experience was gained in fast neutron radiotherapy techniques.

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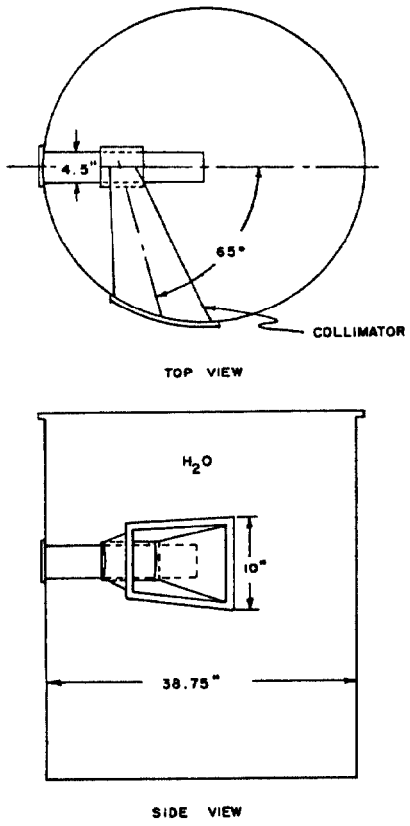

Fig. 1. View of divergent collimator.

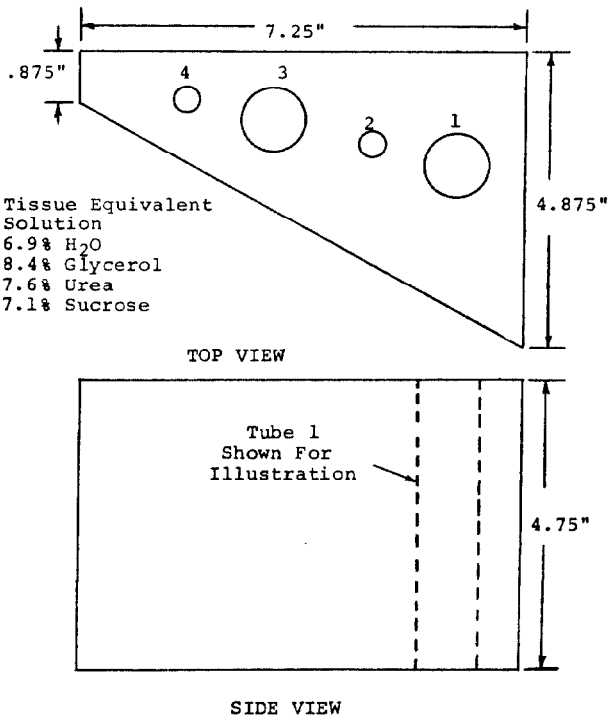

Fig. 2. System to study contrast as a function of the differential attenuation coefficient.

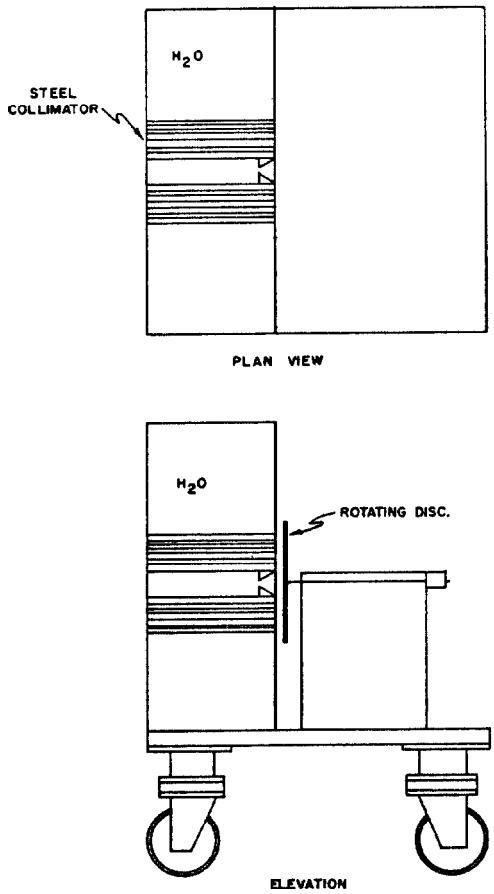

Fig. 3. Collimation tank and animal irradiation facility.

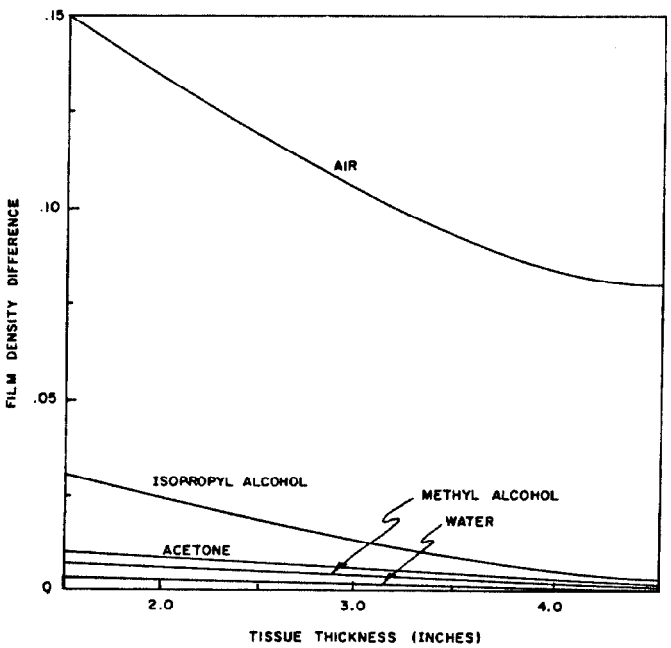

Fig. 4. Difference in density vs tissue thickness for 0.5 inch I.D. tube.

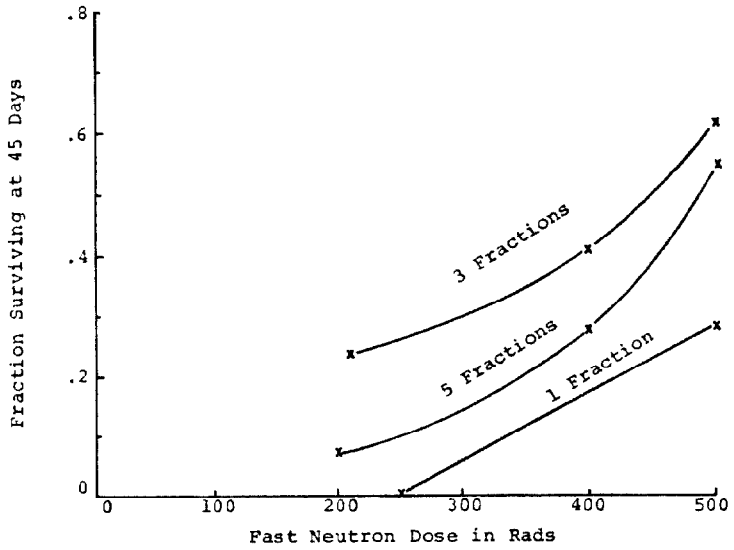

Fig. 5. Effect of fast neutron dose and fractionation on fraction of mice surviving at 45 days.

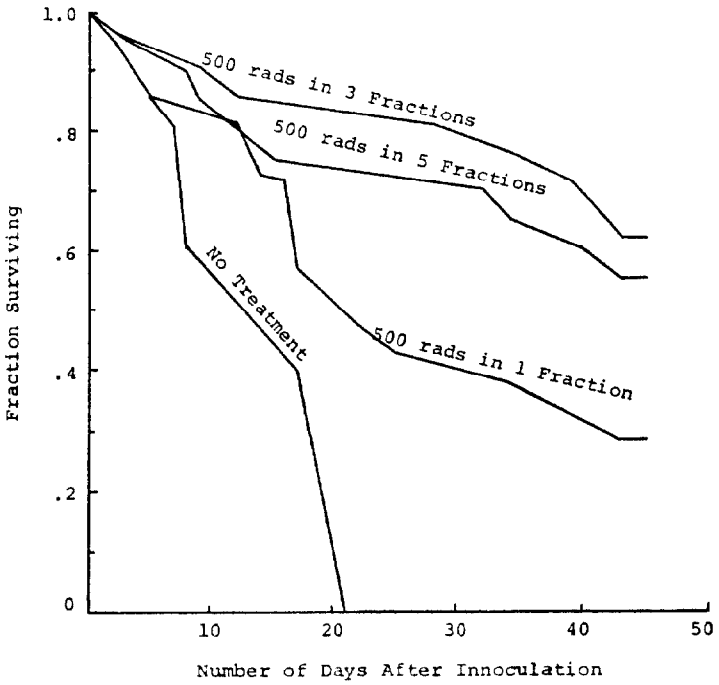

Fig. 6. Daily history of fraction of mice surviving after innoculation and fast neutron treatment.