In recent years there has been a growing interest in the use of fast neutrons in human cancer therapy. In 1966 a group at the Medical Research Council Cyclotron Unit in London initiated a clinical trial of fast neutrons in the control of large tumors. This is the first effort of its type since the earlier trials of Stone and Larkin in the late 1930's. The Hammersmith trials have benefited from a better understanding of the biological effects of neutrons. Although it is too early to conclude on a clinical basis, the fast neutrons have caused no unexpected or overly severe effects on normal tissues. It appears that fast neutrons may well become a particle in great demand for clinical applications of the future. Accelerator engineers and scientists can contribute to this effort by making an improvement in fast neutron energy, dose rate and variability of incident deuterium energy (for the reaction Be(d,n)B10 4.36 MeV) to regulate neutron depth of penetration. Most of the advantages of the cyclotron approach correspond disadvantages for the D-T generator and vice versa. At any rate, the ability to be made in a compromise and numerous other factors must also be considered. To be useful for therapy applications, either device must be relatively close by and accessible to the radiotherapist. This is much more easily accomplished in the case of the D-T generator because of its compactness and mobility. It does, however, have the problem of very poor dose output and depth of penetration which limits its use to moderately deep-seated lesions. The only disadvantages of a large cyclotron are those of size and expense. If such a device could be made available to radiotherapists, a significant therapy program could be established and areas heretofore unexplored could be investigated.

Although at first thought one would preclude the idea of a hospital building and operating a large isochronous cyclotron, one could envision, however, a metropolitan medical complex of several hospitals jointly sharing the use of such a device. It is considered realistic that such a facility could be operational on a round-the-clock basis by virtue of its versatility in numerous areas of medicine. Patient therapy using not only fast neutrons but possibly light and heavy ions of many different types, could be undertaken during clinical hours with biomedical and radiobiological research programs being implemented in the evening following by the production of many types of short and long lived medical isotopes at night. These isotopes could be ready for patient use at the beginning of the next day. Therapy could be conducted on an out-patient basis with hospitals in the vicinity transporting patients to and from the therapy center. Such an approach could justify not only the expense of the cyclotron, the facility, and the operations staff, but also could lead to productive in-house research teams collaborating with various programs underway at the individual medical research centers in the area.

The rationale for neutron therapy is based almost entirely on radiobiological evidence. Hypoxic cells (those lacking an adequate supply of oxygen) are more resistant to X and gamma (cobalt therapy) radiation than normal oxygenated cells. While most cells in normal tissues are well oxygenated, most solid tumors have hypoxic regions. With conventional radiotherapy (X-ray or cobalt), the maximum tumor dose is determined by the tolerance of the adjacent normal cells, and a situation may exist where the adjacent normal tissue is severely damaged by radiation and yet hypoxic tumor cells remain viable. Fast neutrons by virtue of their interaction in tissue, appear to be much more efficient in the destruction of hypoxic cells. Thus the probability of tumor regrowth may be significantly reduced.

The completion of a program by the University of Pennsylvania at TAMVEC, studying the effects of P-388 leukemia cells in cultures and in mice, led to an interest by the M. D. Anderson Hospital & Tumor Institute of Houston for possible treatment of humans. A joint M. D. Anderson - TAMU proposal to undertake this project is before the National Institute of Health at the present time.

Undertaking human cancer therapy in a facility designed for research into the basic sciences is not a casual matter. The program requirements are stringent and a sincere commitment to the project by all concerned is essential. Since in our case the medical unit conducting the therapy is to be somewhat remote from the accelerator facility, provisions are being made (Fig. 1) to house the patients for a few hours during the treatment cycle. This would be a requirement even if the hospital were only one or two blocks away.

Although fast neutrons are the most promising among the NIB devices for neutron therapy, a heavy ion therapy facility could also be justified. Such a facility would be useful as a complement to the cyclotron, and perhaps as a stepping stone to the high energy heavy ion facility. The Massachusetts Institute of Technology Cyclotron is probably the only such facility in the world. It is utilized for research purposes only and has had only limited clinical applications. It is not practical to transport such a heavy ion accelerator into a medical hospital.

Fig. 1 - Patient Handling and Treatment Facilities

The treatment room itself should be aesthetically pleasing and non-mechanical looking as possible. In designing such a facility, one must always bear in mind that patients undergoing therapy have little appreciation for the "beauty" of all the electrical and mechanical devices in an accelerator facility, and they should be exposed to as little of this "culture" as possible.
Preliminary investigations developing the fundamental information necessary to undertake human fast neutron cancer therapy have been underway at the TAMVEC for well over a year. Incident beam energies of 16, 30, 50 and 60 MeV deuterons yielding 7, 14, 22, and 26 MeV neutrons respectively have been investigated for use in human therapy. The 16 MeV deuterons were chosen as a base line for comparison with the maximum energy of the Hammersmith Hospital cyclotron. The choice of 30 MeV deuterons was made to compare with the neutron output of the D-T generator. The 50 and 60 MeV deuterons were selected for good dose depth and dose delivery.

Investigations have proceeded in three main areas of interest: physics, cellular and small animal radiobiology, and animal tumor therapy. The work in physics has been primarily related to general dosimetry, radiation quality and the determination of shielding and collimation parameters needed to produce isodose profiles of adequate definition for human therapy. General collimation requirements are presented in Table I.

### Table I

**Fast Neutron Collimation Specifications**

<table>
<thead>
<tr>
<th>Neutron Energy</th>
<th>20 - 30 MeV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction Used</td>
<td>Be(^{(d,n)})B(^{10}) + 4.36 MeV</td>
</tr>
<tr>
<td>Gross Attenuation</td>
<td>1/2%</td>
</tr>
<tr>
<td>Beam Flatness</td>
<td>1% (SSD - up to 200 cm.)</td>
</tr>
<tr>
<td>Collimation Quality</td>
<td>1% (2 cm. from edge at patient)</td>
</tr>
<tr>
<td>Field Defining Inserts</td>
<td>5 x 5 cm. to 30 x 30 cm.</td>
</tr>
<tr>
<td>Target Thickness</td>
<td>Variable</td>
</tr>
</tbody>
</table>

These specifications are in addition to the more obvious requirements of low activation, realistic size and cost. Figure II depicts the results of some of the narrow beam shielding measurements recently concluded. Broad beam measurements are scheduled in the near future.

Figure II shows the general plan of the treatment room and a preliminary collimator layout.

**Fig. II - Cross Attenuation of Neutrons Produced by 50 MeV Deuterons Incident on Beryllium**

**Fig. III - Patient Treatment Room and Medical Control Area**

Cellular and small animal radiobiological studies have been centered on survival characteristics of asynchronous cultures in vitro and single dose survival sensitivity of intestinal mucosa in mice. A randomized trial has been initiated to compare the effects of fast neutrons and conventional radiotherapy on the local control of spontaneous animal tumors (Fig. IV). This study is seeking to evaluate normal tissue response and the effects of varying treatment methods, tumor dose and fractionation schedules. To date about 30 animals with a variety of lesions have been treated and although the local control rate was low, tumor regression has been noted and there have been no unexpected complications.

**Fig. IV - Great Dane Undergoing Treatment with Fast Neutrons**

These pre-proposal investigations are supported jointly by Texas A&M University and M. D. Anderson Hospital & Tumor Institute and will proceed through 1 July 1971 - the anticipated date of funding. Should the project be continued, it is anticipated that a pilot clinical trial would begin in January 1972 concentrating on head, neck and breast tumors. The interim time would be used to renovate the treatment room and build a patient handling facility. If the program proceeds successfully, a supplement would be requested in January 1973 for the addition of a larger treatment room and improved patient accommodations, Fig. V.

**Fig. V - Expanded Patient Therapy Facilities**

This five year project has an overall goal to demonstrate whether human fast neutron cancer therapy can improve the local tumor control rate, or with uncharged control rates, decrease the incidence of radiation complications and bothersome skin damage.

### Bibliography

4. To be published.