Fermi National Accelerator Laboratory

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THE CANCER THERAPY FACILITY AT THE FERMI NATIONAL ACCELERATOR LABORATORY: A PRELIMINARY REPORT

Lionel Cohen, M. D.

Miguel Awschalom, Ph. D.

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1. INTRODUCTION

When a malignant tumor is treated by ionizing radiation with curative intent, the eventual outcome tends to be one of three almost equally likely contingencies. These contingencies include (a) apparent cure or long-term control, (b) failure of local control with persistent or recurrent cancer, and (c) distant metastases or uncontrolled widespread dissemination. Independently of these main contingencies there may or may not be significant complications of treatment.

There are, consequently, two equally important salients in the advancing front of cancer therapy. One is the continued improvement of methods for preventing, retarding, or controlling metastatic spread. The second is control of that group of relatively radioresistant locally recurrent tumors which do not have distant metastases. This latter group comprises about one-sixth of all cancer cases.

There is also a biologically significant subset of patients in whom locally recurrent and distant metastatic disease appear together, a

correlation which suggests some systemic defect, perhaps a failure of host-resistance or immuno-surveillance mechanisms. One would expect that a combination of measures directed towards boosting host-resistance mechanisms, systemic therapy of both overt and latent metastases, and techniques for improving local control, would yield a gain in cure-rate substantially greater than the sum of effects of the same procedures applied individually.

1.1 Failure of the Local Radiation Response

Irradiated tumors regress as their constituent cells are killed or sterilized, and are cured when all viable cells have been ablated. The risk of tumor recurrence due to some persisting viable cancer cells tends to follow a steep sigmoid (Poisson) dose-response function. A relatively minor reduction in cellular radiosensitivity could, therefore, result in a sharp diminution in the prospect of cure at a given radiation dose.

Because steep dose-response curves are characteristic of both normal tissues and tumors (Fig. 1) a reasonable prospect of uncomplicated cure is possible only within a narrow range of dosage The delivered dose must be large enough to ensure local tumor control yet well below that producing unacceptably severe normal tissue damage. Tumors are classified as "radiosensitive" if the difference between these two dose levels (median values) is large A difference equal to at least four times the standard deviation is necessary for reasonably

safe and effective treatment. With less well separated functions, cure can be effected only in a proportion of cases with critically defined dosage at at a considerable risk of failure from either recurrent cancer or high-dose complications. In slightly less favorable circumstances, that is with either less responsive tumors or more sensitive contiguous normal tissues or organs, uncomplicated cure is impossible and such tumors would be considered "radioresistant".

Cellular radiosensitivity depends on the size and complexity of critical intracellular "targets" (DNA), the distribution of high-energy ionizing or excitatory events within the DNA and surrounding medium, the integrity of enzyme systems concerned with replication and repair of induced damage in DNA, and certain biochemical factors (notably oxygen tension) affecting the number and mobility of activated secondary radicals.

Local failure to control the disease may be associated with tumor cells which are relatively resistant to radiation. While the intrinsic radiosensitivity of mammalian cells, both normal and malignant, is almost constant (survival curves all show similar slopes) some tissues and tumors appear relatively resistant to conventionally fractionated treatment because of a greater-than-average capacity to repair cumulative sublethal damage. This is characteristic of many structured tissues (notably in the alimentary tract) and the tumors arising from them. Another cause of persistant cancer cells is the relative

radioresistance of small oxygen-deprived yet viable cell populations within certain poorly vascularized tumors.

Several possible approaches to the problem of local radioresistance are being explored in radiobiological laboratories, and some are reaching the stage of clinical trial. These include hyperbaric oxygen-saturation techniques or administration of electron-affinic chemical radiosensitizers (radiobiologically analogous to oxygenation) to deal with radioresistant hypoxic tumor cell populations. Other possibilities are localized hyperthermia (converts sublethal reparable lesions in DNA to irreversible lethal damage), and the use of corpuscular radiations with high rates of linear energy transfer (LET) such as neutrons, heavy ions, and negative pions. The possible applications of hyperthermia and chemical hypoxic cell sensitizers have yet to be evaluated. The advantages of high-LET radiations are two-fold in that the repair capacity of relatively resistant cells and the protective effects of hypoxia are both markedly reduced. These two effects have been thoroughly studied and quantified both in the laboratory and the clinic. The theoretical advantages of high-LET radiations are already well understood and active clinical trial of fast neutron beams are now under way in a number of centers.

1.2 Medical Evaluation of Neutron Beams

It has been variously estimated that 15 to 25% of all cancer patients fail to respond to radiation therapy because of an intrinsic radioresistance

of the tumor possibly associated with lack of oxygen (hypoxia). It is generally recognized that radiation with neutrons or other heavily ionizing particles will almost certainly result in an improved response if not complete local control in many of these patients.

Preliminary trials using available cyclotrons as neutron generators notably at Hammersmith Hospital, London, England,[2] Naval Research Laboratory, Washington, D. C., M. D. Anderson Hospital in Houston, Texas, and the University of Washington, Seattle, as well as a few pilot studies in Europe, tend to confirm both biological and physical expectations. The efficacy and safety of neutrons has been demonstrated and it has been shown that favorable responses with "radioresistant" cancer types can in fact be attained. Further clinical trials of neutron therapy are required in order to determine if neutrons are indeed more effective than conventional therapeutic methods in specific areas.

While the physical and radiobiological problems associated with neutron therapy are reasonably well understood, a major drawback inherent in all proposed clinical trials of this nature is our lack of information on neutron dosage tolerance limits and tumor curative levels for different sites. It is probable that different dosage schedules will be required for particular tumors growing in particular organs. The material available for clinical trial must necessarily be subdivided into discrete anatomical and pathological groups, each of which will have to be examined for optimal dosage schedules separately.

All cancer therapy, including conventional radiotherapy, necessarily produces concomitant adverse reactions in normal tissue, and optimization of the treatment schedule implies the selection of technical factors which will minimize the risk of damage to normal tissues while maximizing the probability of tumor control. Neutron dosage and treatment time could be optimized for every combination of tumor and normal tissue by studying statistically significant numbers of cases in each group. Since the relative biological effectiveness of neutron beams (compared with photons) differs with different tumors and normal tissues, experimental animal data are not directly applicable to man, and final adjustment of dosage will be based on observed reactions in patients.

The national clinical neutron program will be well under way by the time this facility is operative. The Fermilab facility will then be committed to the national program but because of the high output, variable energy, and large patient population, a wider range of pilot and/or definitive studies may be undertaken.

Three kinds of clinical research operation have been proposed. These are (a) National cooperative clinical trials, common to the four neutron therapy facilities in the U. S., (b) Specific randomized studies at the Fermilab facility, and (c) Selected non-randomized pilot studies. Four sites have been selected for a tightly controlled, rigorously standardized, national coorperative trial to compare neutron and photon

irradiation. These include moderately advanced cancers of the head and neck (epidermoid carcinoma of oral cavity, oropharynx, hypopharynx and supraglottic larynx), primary malignant brain tumors (high grade astrocytoma or glioblastoma multiforme), advanced carcinoma of the cervix (Stages III and IVa), and locally advanced bladder cancer (Stages T3 and T4).

Randomized clinical trials at the Fermilab facility will include primary lung cancer, locally advanced accessible cancers of breast and skin (including melanoma), osteogenic sarcomas (where surgery is not feasible or is refused) and non-osteogenic connective tissue sarcomas. Many of the foregoing studies will include adjuvant chemotherapy. Pilot studies are proposed for deep-seated inoperable tumors of the gastrointestinal system for which the penetrating Fermilab neutron beam may be uniquely advantageous. These tumors would include adeno-carcinoma of the pancreas, stomach and colon and carcinoma of the esophagus.

With the volume of patients available it is proposed to establish at an early stage of research:

(a) normal tissue tolerance parameters for key organ systems affected by the tumors listed;

(b) dose response functions for most of the common "radioresistant" tumor types;

(c) magnitude of therapeutic gain factors, namely, relative biological effectiveness of neutrons for a tumor compared with that for the associated normal tissue, for specific tumors and various sites.

1.3 Clinical Trials and Protocols

Detailed provisional treatment protocols are being designed by concensus of opinion of all participating radiotherapists. In general, patients accepted for treatment will be allocated to various treatment groups as follows:

(a) randomization of suitable cases among three treatments, all potentially curative, comprising: photons in full dosage, photons followed by neutron boost, or neutrons in full dosage;

(b) when the response to photons alone is expected to be poor, randomization between two arms only: photons and neutrons or neutrons alone;

(c) palliative studies in patients too advanced for cure; testing of single shot palliation and effects of graded doses and varied fractionation schemes upon multiple skin nodules or isolated metastases.

The follow-up procedure and methods for assesing end-results in both tumor and normal tissues traversed by the beam have been designed. Referring physicians have undertaken to facilitate long-term follow-up procedures and to provide periodic reports on follow-up of state of disease and early and late reactions. Follow-up defaults will be investigated and special provision will be made to ensure autopsy examination of all neutron irradiated patients dying from any cause at any future date after treatment.

There are a number of possible choices for treatment schedules. Some of them are:

(a) The standard low-LET treatment which will in general consist of the best curative regimen for the appropriate tumor site delivering a high biological dose. Programs will involve delivery of doses approximating 5000 rads in five weeks to the primary site and areas of microscopic extension. This will be supplemented with a reduced volume boost including only areas of known gross tumor in the primary and clinically involved regional spread areas. This reduced volume boost will be to an additional 1000 to 2000 rads depending on the normal tissues encompassed in the treatment volume.

(b) A low-LET with neutron boost program which will be an identical treatment schedule to the low-LET large-volume procedure, except that the restricted volume of gross disease will be boosted with neutrons rather than low-LET photons.

(c) Neutron treatment only means neutron irradiation of the large volume of potentially involved sites to 3/4 of the total dose, and then the volume reduced as before with the restricted gross tumor volume receiving the last 25% of the dose. Basically this treatment option will be the best available fractionation schedule for neutrons known at that point in time. Where this information is not available, randomly assigned schedules will compare once-a-week treatment, twice-a-week treatment, and five times-a-week treatment.

(d) Undoubtedly, some patients will be referred for hope of miraculous response for significant symptomatic lesions in otherwise hopeless situations. Where such patients do not meet other protocol criteria, palliative treatment will be administered in either one or two treatment exposures in an effort to evaluate normal tissue response, tumor response, and "recovery" (demonstrable in two exposures as opposed to one exposure). Exposures will be in the order of 800 neutron rads.

1.4 Neutron Sources and Beams

There are three types of neutron sources from the point of view of the user: naturally radioactive sources, nuclear reactors, and charged particle accelerators. The neutrons from these various sources have very different physical and consequently, biological characteristics.

Radioactive neutron sources may be divided into two broad classes according to their constitution. In the first class, the radionuclide is mixed with a suitable target element such as beryllium, and the emitted particles or photons undergo nuclear reactions with the target material yielding neutrons. These sources are usually too bulky for implanation and too weak to be used externally.

The second class consists of radioactive nuclides which spontaneously fission and emit several neutrons per event. Suitable sources, such as californium, may be heretically sealed in small needles for

surgical implanation in patients. These two classes of neutron sources have significant gamma-ray fluxes in addition to the neutron fluxes.

Nuclear reactors provide beams of neutrons with poor penetration and high gamma-ray contamination as compared with accelerator produced neutron beams. Therefore, they are not now generally considered promising therapeutic tools.

Accelerators may create neutron beams in two different ways. In one case, the energy released in the nuclear reaction is the prime source of energy for the emitted neutron. The most common reaction is deuterons bombarding tritium. This requires low incident deuteron energies (a few hundred kilovolts is adequate) but large currents. The targets are gaseous or imbedded in a gaseous atmosphere, large, and somewhat hazardous due to the presence of tritium, a radioactive gas. Devices to produce neutrons by this mechanism are commonly called (d, t) neutron generators. So far their neutron dose output have been rather low in comparison with other accelerator produced neutron beams. However, this limitation may soon be overcome.

In the other case, the energy brought into the nuclear reaction by the charged particle, is the source of energy for the outgoing neutron. The incident particles are typically protons or deuterons and carry tens of millions of electron volts of energy. The targets are usually made of beryllium although under some circumstances lithium could be more advantageously used. These targets are solid and small. The protons or the deuterons may be accelerated in cyclotrons or linear accelerators.

It may be of interest to compare some of the characteristics of (d, t) generators and high-energy accelerators.

Beam power. The (d, t) generators use about 100 times more beam power than high-energy accelerators for equivalent dose-rate delivery.

Neutron energy. The (d, t) generators have essentially fixed energy while the high-energy accelerators have infinite flexibility in obtaining various average neutron energies and neutron energy spectra by the suitable choice of incident particle, its energy, target thickness, and material as well as target backing. Various physical properties of neutron beams such as skin sparing, depth dose distribution and collimation depend on their energy spectra, and different energies also produce different biological effects. Hence, the high-energy accelerator is potentially more interesting to the radiobiologist and the radiotherapist. Conceivably, different neutron energy spectra may be preferred for specific tumor types and locations. Finally, the targets used in high-energy accelerators tend to be smaller than those used in (d, t) generators, so that the neutron beams created by the former have narrower penumbrae.

Gamma-ray contamination. Both types have relatively low gamma-ray contamination.

Table I gives a comparison of various parameters of neutron beams from six accelerators now in use in clinical trials or about to

begin clinical trials. One American (d, t) generator is included. Several (d, t) generators are beginning to be used for clinical trials in various European installations.

2. THE FERMILAB INSTALLATION

The Fermi National Accelerator Laboratory is a high energy physics research facility operated by the Universities Research Association, Inc., for the Energy Research and Development Administration (ERDA) formerly the Atomic Energy Commission (AEC). The principal instrument at the Laboratory is a 400-500 billion electron volt accelerator. Because of the proximity to a large metropolitan population, Fermilab offers an outstanding site for the creation and operation of an accelerator-based medical facility. This facility could be used to perform initial clinical trials of high-LET radiation in cancer therapy, provide a national service in regard to neutron therapy, and possibly explore other medical applications of high-energy protons.

2.1 Beam Line and Targets

The Fermilab "accelerator" is actually composed of three accelerators in series forming the so-called "injector" providing a beam of 8 billion electron volt (GeV) protons and a very large, 6 km (4 mile) circumference, final accelerator, known as the "main ring". The main ring increases the energy of the injected protons to 400-500 GeV. It has a cycle of operations which include injection, acceleration, ejection of beam to the experimental areas, and resetting of conditions

for the next injection operation. This cycle takes from five to twelve seconds depending on the particular mode of operation required by the high energy physics research program. During the injection part of the main-ring cycle, the injector is needed to fill its vacuum chamber with protons. This takes about one second. The rest of the time, four to eleven seconds, the injector is kept on "standby" conditions. The Fermilab cancer therapy facility extracts protons from the second of these accelerators, a 200 million electron volt (MeV) linear accelerator (linac), during the standby periods.

The Fermilab linac has nine sections (tanks). For the cancer therapy facility (CTF) the protons are extracted with an energy of 66 MeV between tanks four and five. Between the end of the injection of protons to the main accelerator and the beginning of proton beam transport to the CTF, the linac beam is turned off, a 58° extraction magnet is turned on, and the linac beam is turned on again (see Fig. 2). The protons extracted from the linac are bent first through 58° and then 32° more. Seven quadrupole magnets focus the protons on a beryllium target on the far side of a 10-ft thick wall.

The protons are accelerated to 66 MeV, 15 times per second, by the linac in tightly bunched groups which may last from a few microseconds to a few tens of microseconds and may have instantaneous currents ranging from tens to hundreds of milliamperes. The pulse width and the instantaneous current vary depending on the demands of

the high energy physics research program. Average currents of 0.3 to 1 $\times$ 10^{14} protons/second may be expected.

The target material used during the initial radiobiological studies was beryllium. The thickness of the Fermilab beryllium target used is such that 66-MeV protons lose 50 MeV when traversing it. Another target material considered was lithium. In Fig. 3 energy spectra of zero degree neutrons due to 65-MeV protons on 50 MeV thick Li and Be targets are shown.[3] Various dosimetric studies confirmed the small differences to be expected from the different energy spectra.

2.2 Physical Characterization of the Neutron Beam

Some of the important characteristics of the Fermilab neutron beam created with the above beam energy and target thickness will now be discussed and illustrated.

Skin sparing. Figure 4 shows results of preliminary measurements of dose buildup. The neutron dose increases from the entrance to a maximum at a depth of 1.2 - 1.4 g/cm^2. The neutron depth dose distribution is compared with that of photons created by stopping 4-MeV electrons.

Central axis depth dose. Figure 5 shows results of neutron dose measurements made along the central-axis of collimated beams, 10 $\times$ 10 cm^2 in cross section at the entrance surface and at 153-cm target to skin distance. The neutron dose distribution is compared with that from 4-MeV photons (x rays).

Collimator effectiveness and field flatness. Figure 6 shows preliminary dose distributions measured perpendicularly to the beam axis at two depths, 1.5 and 14 cm, in tissue equivalent solution for a 10×10 cm^2 neutron beam. The collimator, 120-cm long, is made of a mixture of portland cement and polyethylene pellets. The steep parts of the curves have widths comparable to the dimensions of the ionization chamber used in these measurements. Hence, the actual dose distributions must have narrower penumbrae. These curves also show what uniformity of dose delivery is possible in the "beam" without recourse to flattening filters.

Photon neutron dose ratio. Microdosimetric[3] studies show that in air the photon to neutron dose ratio is about 2% to 4% of the total dose. However, the measurement of the variation of this ratio as a function of depth along the central axis and perpendicularly to the central axis is still to be done.

3. PATIENT SETUP AND CONTROL SYSTEMS

An essential prerequisite to successful radiation therapy, and a major responsibility of the physicians, physicists, and technologists involved, is to ensure that the computed treatment plan is, in fact, executed precisely and reproduced exactly at each attendance. Since the horizontal neutron beam is fixed, it is a practical requirement that the patient be positioned in relation to the beam and immobilized in the correct alignment. It is also necessary to verify, at each setup, that

the beam traverses a rigidly defined path within the patient's tissues, encompasses a predefined target volume and avoids critically sensitive structures. For this purpose, errors in beam position can be no more than a few millimeters and little more than a fraction of a degree in angulation.

The horizontal beam and spatial limitations require that most patients be treated in the vertical standing or sitting position. Comfortably seated in a treatment chair (instead of the more conventional horizontal treatment couch), patients will be immobilized by light semi-rigid plastic bandage (Lite-cast^{R}) attached to a headrest on the chair. Alignment is then effected by four motions of the chair assembly. These include motorized vertical movement by means of the hydraulic elevator which forms the floor of the treatment area, two orthogonal translational movements of the chair on rails attached to its base, and rotation of the whole base and chair assembly around a fixed vertical axis. This axis of rotation intersects the central axis of the neutron beam at a fixed point in space termed the isocenter. In a typical treatment plan the isocenter is within the target volume, generally at the center of the tumor, and all anatomical areas of interest are defined in relation to this point.

3.1 Treatment Room Description

The following structural arrangements and setup procedures have been adopted. The treatment room is equipped for use at two levels

(Fig. 7). The lower level (Fig. 8) encompasses the path of the collimated neutron beam, the associated dose monitors, collimators, alignment devices, a television monitor, and an intercom system. The upper level (Fig. 9) supports a "simulator" with a diagnostic x-ray beam at the same source-to-axis distance and similar collimation as the proposed neutron field.

The thickness of necessary shielding walls is much greater in neutron facilities than in photon facilities even though the walls of the former are made with iron ore aggregate and the latter with ordinary stone aggregate concrete. The reason for this difference is due to the longer mean-free paths of neutrons with respect to photons. Access to the treatment room will be at the first floor level. The entrance will be closed by means of the air door before neutron irradiation begins. The air door is a concrete block mounted on compressed air pads, hovercraft-style (see Fig. 9). When the floor is lowered to the neutron beam (treatment) level, access to the level is via a folding (ship's) ladder.

The upper isocenter (intersection of the x-ray beam central axis with the vertical axis of rotation) is uniquely identified by three laser beams (north, east, and south) as well as the defining optics of the x-ray system intersecting this point. At the lower level three identical laser beams as well as a laser beam coaxial with the neutron beam intersect at the therapeutic isocenter. Translation of the treatment

chair assembly and ancillary equipment between the two levels is effected by the hydraulic elevator platform which constitutes the floor of the treatment room.

3.2 Patient Setup Procedure

In the inital setup the hydraulic elevator is leveled to the upper floor. The treatment chair or alternative supporting device is placed on the adjustable base plate and the patient invited to sit or lean comfortably in an approximate treatment position. A "Lite-cast"^{R} shell with lead lining will have been prepared for the patient and the skin marked to indicate isocentric reference and beam axis entrance points for one or more portals. The position of these points will have been derived on the basis of a treatment plan which has been completed for that particular patient and relates his contour and internal structures to the skin reference points, beam entrance portals and the direction of the beam axis. The isocentric reference marks are covered with small squares of retroreflective tape. The cast is fixed to the supporting device and the assembly is moved using the described four degrees of freedom to bring the three isocentric reference marks into coincidence with corresponding laser beams. At this stage, the optical entrance pointer (a light beam with cross hairs simulating the x-ray verification beam) should coincide with the planned entrance point. At the same time, the retroflective laser beams would activate three photo cells (at the three laser sources) and corresponding indicator lights on the

control panel. A digital readout of the chair identification and position also appears on the control panel.

At this stage the x-ray collimator is set to match the proposed neutron field, a diagnostic x-ray film is mounted behind the patient, the technologist leaves the area, steps behind the shielding wall, and exposes the film. A second film may be similarly mounted and the chair or supporting device rotated to a second port position (without changing the anatomical isocenter) and a second exposure taken. These constitute the initial "planning" films. Exposed films will be developed at the site using an automatic rapid processor installed adjacent to the treatment area. Examination of the planning films indicates whether any positioning adjustments are necessary, and if so these are computed in terms of displacements on the four positioning scales. When all alignment factors have been corrected, subsequent setup at the lower level can be followed immediately by the neutron treatment procedure

The treatment cycle consists of the reception of the patient each day prior to treatment, entry of an identification code or number at the control console, attachment of the appropriate collimator in the beam port, and a setup on the upper level as described. At this point a microprocessor verifies that the retroreflective strips are in the laser beams, and that the treatment parameters agree within predefined narrow limits with those entered at the initial setup for that particular patient. The treatment parameters include chair identification, angulation and x-

and y-displacements, collimator identification and angulation, and proposed dose. Some or all of the parameters may be a function of particular portals. If this checkout is in order, the technologist can lower the platform to the beam level, aligning the skin marks with the lower set of lasers. The technologist returns to the control room. At this stage the position of the patient is observed on the television monitor (focused on the entrance port) and the three lower retroreflective beams confirm alignment at the treatment position.

The control panel should indicate an "enable" display, that is, all the parameters affecting the neutron exposure must have the appropriate values, namely those in the patient's file. At this point the beam can be turned on and the appropriate exposure would then be delivered automatically. If a second portal is required with the same collimator (with the same or a different collimator angle), rotation of the chair assembly can be effected from the control room without reentering the treatment room. When this rotation has been effected and the patient's position observed with a television monitor, a second exposure can be delivered.

The x-ray cassette support which will have been aligned in relation to the diagnostic beam will now be in place in a corresponding position in the therapeutic beam so that a film placed in this position could be used from time to time to verify that the neutron beam traverses the correct anatomical pathway.

At the completion of the exposure, the technologist will enter the treatment area, descend from the upper level to the elevator (at the treatment level) using the retractable ship's ladder provided, release the patient from the treatment chair, adjust or replace the collimator prepared for the following patient, and ascend on the lift to the upper level at which point both the technologist and patient can leave the treatment area. All technical factors including the date, exposure time, dose delivered, and cumulative doses in the tumor and at specified points in the target volume, will be retained in the computerized clinical record.

All the treatment parameters as well as a portion of the patient's medical records will be in floppy disks. Each patient will have one floppy disk bearing his/her photograph and name. At the end of each portal, all the relevant parameters will be recorded automatically on the floppy disk.

4. NEUTRON BEAM CONTROL AND SAFETY

The controls for turning the beam on and off delivering a requested dose to the patients are based on microprocessors. The arrangement of the control room and the design of the safety system is explained in general terms below.

The controls and system status lights are divided into two sets. One set has information that may require action from the radiotherapy technologist. The other set has information necessary to an accelerator operator for tuning up and trouble-shooting the system.

The systems that assure safety to patients and personnel have been designed with redundancy and are inherently fail-safe. When a component must turn the beam off, it will turn off at least two critical devices in two different ways each.

Some examples of the above will help clarify their meaning. The radiotherapy technologist is expected to be in control of collimators, beam shaping, safety, patient positioning, immobilization, and dose delivery. Hence, status messages on a large TV screen and means to control each of these variables are provided in the treatment area. The legends are explicit, e.g., safety door: "open/closed"; patient positioning (laser beams): "OK/moved"; collimator ID: "correct/wrong"; dose requested: "OK/wrong", etc. Abnormal operating parameters produce a status message which essentially directs the technologist to ask for help from the accelerator operator. The messages for the accelerator operator are given via a video terminal. They include critical operating parameters like target temperature, transmission chamber ratio, vacuum valve status, and so on. These are presented either as a ratio of the present value to the standard or as a message (0 or 1) indicating status conducive to no-operations or operations respectively. The absolute values of the parameters are also available on request.

As an example of a safety system, one may examine the dose delivery monitoring system. The beam is turned on by the simultaneous operation of two single-purpose switches. Then the proton and neutron

beams are monitored by a proton current integrator, two neutron transmission chamber flux integrators, and finally a timer. The technologist needs to type only a "dose" to set up the irradiation. Then, the microprocessors will set the corresponding limits to the four integrators. An irradiation may be requested if the microprocessors have successfully verified the accuracy of all the treatment parameters set versus those in the patient's files. After the irradiation begins whichever of the first three integrators (proton current and both neutron fluxes) reaches the preset value first will terminate the irradiation. The fourth integrator (timer) is an emergency backup set for perhaps 20% higher than the prescribed dose, and is mechanically adjusted so that the dose could never exceed 500 rads assuming the highest dose rates that can be achieved. If activated the timer would terminate the exposure and display a warning that the dose monitoring system was in error. Further treatment would not become possible without operator intervention. Any number of malfunctions may also terminate the patients' irradiations: opening the door to the treatment room, too high a target temperature, variations in the ratio between the two neutron flux monitors and between one neutron flux monitor and the proton current integrator outside preset limits.

5. PRETHERAPEUTIC RADIOBIOLOGY

Initial radiobiological experiments were designed to confirm that the intensity (absorbed dose rate in rads per minute) and quality (LET,

RBE, and OER) were sufficiently close to measured and calculated values to permit these values to be used with confidence. Since these experiments were required to confirm expected results, rather than break new ground, they were completed in a relatively short time using well-established radiobiological test systems.

5.1 Broad-Beam Radiobiology

Preliminary studies included Chinese hamster cell tissue cultures irradiated in vitro under aerated and anoxic conditions. Similar studies were carried out with Vicia faba (bean-roots) and E. coli suspensions. In vivo systems included whole body irradiation of mice constrained in small containers. As controls, the same test systems were irradiated with low-LET photons (x rays or cobalt-60 gamma rays) or high-energy electrons.

These experiments were designed to provide estimates of the relative biological effectiveness of the neutron beam and to test the effects of changing oxygen tension (so as to derive estimates of the oxygen enhancement ratio) under the various experimental conditions described.

5.2 Narrow Beam Mammalian Radiobiology

When a sufficiently well collimated beam is available to provide treatment portals of the order of 1- or 2-cm diameter, one could obtain specific data on the response of animal tumors and normal tissues to neutrons in the energy range provided. This is a research area which

has not been fully explored, and would provide valuable new data in the field of fundamental radiation biology. It would also provide the data required for testing several proposed models of radiation lethality and cell population kinetic systems as they are perturbed by high- and low-LET irradiation.

Under these conditions, RBE and OER would depend on neutron energy, dosage, fractionation, and the specific cell population kinetic parameters in the tissue of interest. Since there are at least four significant unknown parameters in the cell population kinetic equation, it is necessary to test at least four distinct fractionation schemes on specified experimental tumors and normal tissues. A typical experiment is likely to include single exposures, equal-pair split doses, multiple large daily fractions, and either many small fractions or continuous irradiation. A good experimental system for this purpose is an inbred strain of laboratory mice to supply both spontaneous and transplanted tumors as well as a variety of normal tissue for experimentation. Median effective doses will be established for cure of the tumor in situ, radiation injury to the lung, skin, spinal cord, and bowel, using the four fractionation schemes described, with neutrons in the experimental system and high-energy photons or electrons for the controls.

These radiobiological studies would provide several independent estimates of RBE and OER for specific tissues from which appropriate coefficients could be obtained so that RBE and OER values can be

estimated for various human tissues and tumors. These parameters can also be used to generate iso-effect functions for the clinical situation.

5.3 Initial Radiobiological Results

The preclinical radiobiological operation to characterize the beam was initiated in terms of the NCI supported research programs. Our first objective was to determine the relative biological effectiveness (RBE) and oxygen enhancement ratios (OER) for mammalian cells cultured in vitro and mammalian tissues irradiated in situ (mice) of the neutron beam compared with low-LET standards. The formally approved program was conducted by Dr.'s M. M. Elkind and Michael Fry at the Argonne National Laboratory. Additional scientific support came from research workers in various centers who were interested in irradiating several other organisms with this relatively high energy neutron beam, and in so doing incidentally provided valuable comparative data on RBE and OER with a variety of biological systems. These contributors included Dr. J. L. Redpath of the Michael Reese Medical Center who conducted studies with two bacterial strains to be described below as well as with C3H mice; Dr. Eric Hall of the Radiological Research Laboratories at Columbia University, New York who provided data on two completely independent systems, namely Chinese hamster cells in tissue culture irradiated under oxygenated and anoxic conditions and bean roots (Vicia faba) also under oxygenated and hypoxic conditions;

George H. Harrison, University of Maryland, with additional data on Vicia faba; and Dr. John H. Levan, Veterans Administration Hospital, Hines, Illinois using human lymphocyte cultures.

Studies with normal and leukemic lymphocyte (J. H. Levan) are under way. Cellular lethality parameters, and hence observed RBE values for these cells, are expected to be somewhat different from the other systems tested but are not yet available for publication.

Radiobiological parameters derived by the five independent investigators are listed in Table II and appear to be self-consistent. In general their magnitudes are in line with what might be expected by comparison with other neutron installations operating at somewhat lower energies.

The Argonne hamster cell culture results (by F. Q. H. Ngo, A. Han, and M. M. Elkind) indicated an RBE for the Fermilab neutrons ranging between 3.8 at low doses (surviving fraction 70%) down to 1.8 at high doses (surviving fraction 1%). These results were obtained by comparing 250-kV x rays delivered at a dose rate of 165 rads per minute at the Argonne National Laboratory with neutrons produced by 66-MeV protons of a 50 MeV thick beryllium target (see section 2.2) at a dose rate of about 15 rads per minute. The cells were exposed in flasks under ambient temperature conditions. It should be noted that these measurements were carried out before absolute physical calibration of the beam had been completed, so that estimates are tentative and may have to be adjusted when more accurate dosimetry is available.

Delivered doses are reproducible within 1 to 2% but the accuracy of absorbed doses may be no better than about ±20%. Consequently, while the measured cellular survival and estimated RBE values are precise, absolute accuracy still depends on exact determination of actual absorbed doses in the tissues concerned.

Estimates of RBE for 4 tissues irradiated in situ were provided by the experiments of Hanson and Fry using B6CF1 mice. The LD-50/6 (50% lethality within 6 days after exposure) represents critical depletion intestinal crypt cells, and the associated RBE of 2.1 relates to relatively large single doses. Similar RBE values were derived for the LD-50/30 and survival of colony forming units (CFU) both of which measure the sensitivity of hemopoietic stem cells. A somewhat lower value (RBE = 1.65) was derived for the regenerative cloning capacity of surviving intestinal crypt cells. Split-dose and multifraction experiments (smaller individual dose-per-fraction leads) are under way and are expected to yield RBE estimates for higher cell-survival levels and information on repair and recovery processes.

The E. coli experiment (J. L. Redpath) was conducted with two strains of bacteria. Results in Table II relate to the E. coli B/r strain which had been previously shown (Alper, 1969) to be quite sensitive to differences in the ion-density of the beam, oxygen tension in the medium, and incubation temperature. A second study was carried out with E. coli strain AB 2463 which has been reported to have an exceptional insensitivity

to radiation quality (RBE approximately unity for Hammersmith neutrons compared with x rays Alper, 1969) and which could consequently serve as an LET-independent biological dosimeter at least for beams where most of the absorbed dose occurs at LET values below the overkill region (< 20 keV/μ) and hence lend some confidence to the physical intercomparisons required with different systems. An RBE determination could therefore be obtained for E. coli B/r, relating it both to the physical and biological dosimeters, comparing the Fermilab neutron beam with a 25-MeV electron beam as a reference standard. Under these conditions, the RBE for this strain varied from 2.9 for 50% survival to 1.9 at 1% survival under normally oxygenated conditions at 30° C post-irradiation temperature.

The RBE for gastrointestinal death (J. L. Redpath) in C3H male mice irradiated with Fermilab neutrons compared with 25-MeV electrons suggests an approximate RBE of 2.4 under these conditions.

Two accurate estimates of the OER for the Fermilab neutron beam were also obtained from the well-established mammalian cell culture and vicia systems developed at Columbia (E. J. Hall). These studies indicated the OER to be about 1.6 for the Vicia faba experiment and 1.7 for the mammalian cells. An analogous but independent Vicia faba experiment (G. H. Harrison) yielded an estimated OER of 1.6 ($\pm$0.2).

The OER of Fermilab neutrons for E. coli B/r was estimated to 1.6 $\pm$ 0.1 at a post-irradiation incubation temperature of 30° C.

6. SUMMARY

Neutron-beam therapy has been shown to be efficacious in treating certain radioresistant tumors, presumably because of the relatively greater effect of heavily ionizing particles on hypoxic (oxygen-deficient) tumor cells. The Fermilab Neutron Therapy Facility will allow more far-reaching clinical studies to be conducted along the following lines.

6.1 Study Objectives

The objectives of these studies is to explore: first, the efficacy and safety of neutron-beam therapy in tumors normally unresponsive to conventional radiotherapy, determining what response rates can be obtained with specific radioresistant tumor types and the tolerance limits of key organ systems in which the tumors arise; and second, the feasibility of optimizing the treatment schedule, identifying particular combinations of dose-per-fraction, number of fractions, and interval between fractions (and overall treatment time) yielding the best prospect of cure without excessive normal tissue injury.

6.2 Cancer Therapy Facility

A source of neutrons is provided at Fermilab by extracting a beam of 66-MeV protons from the linear accelerator and focusing them on a beryllium target. The protons are available during the time that the linear-accelerator beam is not used for injection into the booster synchrotron. This available time is currently about eight out of every ten seconds. At the expected operating intensity of some 10^{14} protons

per second, the 66-MeV proton beam striking a beryllium target will produce a neutron beam, at 153 cm in the forward direction, of about 30 rads per minute. The neutron spectrum, RBE (relative biological effectiveness), and OER (oxygen-enhancement ratio) are essentially similar to the neutron beams used for patient treatment in other centers.

Studies are in progress to optimize the techniques for monitoring, collimating, and measuring the properties of the neutron beam. Included in this work are the development, calibration, and intercalibration with other neutron facilities of dosimeters for the measurement absorbed doses.

Radiobiological experiments are under way using either broad-beam conditions (for irradiation of samples in vitro or whole-body irradiation of experimental animals) or with a collimated narrow beam suitable for in vivo irradiation of localized tumors and specific organs. These initial radiobiological experiments are designed to confirm that the intensity and quality (RBE and OER) are sufficiently close to calculated values and to other measurements to permit clinical use of this neutron beam with confidence.

After satisfactory progress has been made in the physical and radiobiological operations described, it is intended that the facilities be upgraded for patient studies by the provision of:

(a) an adequate set of neutron-beam collimators;

(b) refurbishing and furnishing the protected area to provide a treatment room of acceptable standards;

(c) a control room near the treatment area;

(d) offices for staff, records, medical physics, planning and computing facilities;

(e) an area for patient handling.

6.3 Optimization Studies

Optimal treatment factors will be determined in four phases: (1) Radiobiologic characterization of neutron beams over the energy range 10 to 66 MeV, determining the trade-off between OER, RBE, and depth-dose to yield the highest therapeutic ratio for a hypoxic tumor at some depth below a relatively sensitive normal tissue; (2) Computer simulation and prediction of cellular responses in various tumors, normal tissues and organs to neutron beams; (3) Design of treatment protocols that will offer patients the best prospect of cure with currently available data and, at the same time, provide new clinical data on both tumor response and normal-tissue reactions with different dose-time combinations; and (4) Analysis of results so as to permit updating parameters, revising protocols appropriately, and identifying statistically significant trends that may lead to optimization of treatment procedure.

7. ACKNOWLEDGMENT

The work reported here has been possible due to the efforts of enthusiastic volunteers, mostly from the Fermilab Accelerator Division and the Chicago radiotherapy community, as well as several Chicago foundations, private benefactors, the American Cancer Society (Illinois Division), the Illinois Cancer Council, and the National Cancer Institute. We hope that their valuable cooperation will continue in the future.

8. REFERENCES

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[3] H. Amols, M. Awschalom, L. Coulson, J. Dicello, S. Johnsen, R. Theus, to be published.

Table I. Comparison of Some Parameters of Accelerator Produced Neutron Beams and a ( ) Neutron Generator

Parameter \ Institution	Fermilab	Hammersmith (1)	University Washington	NRL (2)	M. D. Anderson T. A&M U. (3)	(d, t) Generator (4)
particle	p	d	d	d	d	d
target	Be	Be	Be	Be	Be	^{3}H
incident energy (MeV)	66	16	21.5	35	50	.180
beam power (kw)	.53	1.3	.64	.35	.35	72.
mean neutron energy (MeV)	25±2	7.6	8	15	21	14.2
TSD (cm)	153	116	150	125	140	125.
depth of Dmax (g/cm^2) (5)	1.2-1.6	0.23	0.30	.55	1.07	.50
depth of 50% Dmax (g/cm^2) (5)	14.9	8.8	10.2	12.8	13.8	12.
beam current (mA)	.008(6)	.080	.030	.010	.007	400.
tissue dose rate at Dmax at stated TSD (rad/min)	16 (6)	43	34	66	60	25

(1) Hammersmith Hospital, MRC
London, England

(2) Naval Research Laboratory
Washington, D. C.

(3) M. D. Anderson Hospital and Texas A & M University
Houston, Texas

(4) Under construction by the Cyclotron Corp.,
for the Hospital of the Univ. of Penn.

(5) 10 cm × 10 cm field at stated TSD

(6) Linac pulse modulation for
High Energy Physics

Table II. Fermilab Neutron Therapy Facility

(a) RBE Data

Contributor	System	End-Point	Reference Beam	R. B. E.
Ngo, Han and Elkind	V-79 Chinese Hamster Cells	70% survival 50% " 10% " 1% "	250 kV X rays	3.8 2.6 2.2 1.8
Hanson and Fry	B6CF1 Mice	LD-50/6 LD-50/30 Spleen CFU Gut clones	Cobalt-60 Gamma rays	2.1 2.1 2.3 1.65
Redpath	E. coli B/r	50% survival 10% " 1% "	25-MeV Electrons	2.9 2.1 1.9
	C3H Mice	LD-50/5	25-MeV Electrons	2.4

(b) OER Data

Contributor	System	End-Point	Reference Beam	Reference OER	Neutron OER
Redpath	E. coli B/r	D_o ratio	25-MeV Electrons	3.0	1.6
Hall	Vicia faba	Growth Reduction	250 kVp X rays	2.8	1.6
	V-79	Cell Survival	^{60}Co-γ	3.2	1.7
Harrison	Vicia faba	Growth Reduction	250 kVp X rays	2.6	1.6

FIGURE CAPTIONS

Fig. 1. Dose response curves for normal tissues and tumors. The upper lines represent the local control rate for human breast cancer nodules (a) and the computed probability of significant skin damage (b). The conditional probability of uncomplicated cure (c = a - b) displays a well defined optimal value and depends critically on the shapes and separation of the two functions.

Fig. 2. Plan view of the beam line showing tanks 4 and 5, beam transport system, collimator holder, and target. The shielding walls shown are those in use during the first phase of dosimetry and radiobiology.

Fig. 3. Energy spectra of neutrons created by 65-MeV protons on Be and Li targets in which protons lose 50 MeV.

Fig. 4. Dose buildup and attenuation near the entrance to tissue equivalent plastic due to neutrons from 66-MeV protons incident on a semithick Be target, and due to 4-MeV x rays. Two neutron buildup curves are shown, one for a 10×10 cm^2 beam and another one for a 30-cm diameter beam.

Fig. 5. Depth-dose distribution in tissue equivalent fluid (ρ=1.065 g/cm^2) along the central axis of a 10×10 cm^2 neutron beam (TSD = 153 cm) and a 4-MeV x-ray beam of same dimensions. 4-MeV x-ray data was corrected for TDS and phantom density.

Fig. 6. Neutron dose distributions in tissue equivalent solution ($p = 1.065\ g/cm^2$) at depths of 1.5 and 14 cm in a direction perpendicular to the central axis.

Fig. 7. Elevation through the proton beam line showing the relative locations of the diagnostic x-ray tube and neutron target as well as the two isocenters defined by the laser beams. The new permanent shielding configuration is shown.

Fig. 8. Plan view of the facility at the neutron beam level. The permanent shielding configuration is shown. The TV camera monitor and associated mirrors are shown. This arrangement will allow a single panning camera to monitor the patients from four different directions.

Fig. 9. Plan view of the facility at x-ray level. The permanent shielding configuration is shown. The air door is used to close the shield and protect linac workers from neutron fields. The opposite side of the door leads to the linac enclosure. In an emergency this exit may be used.

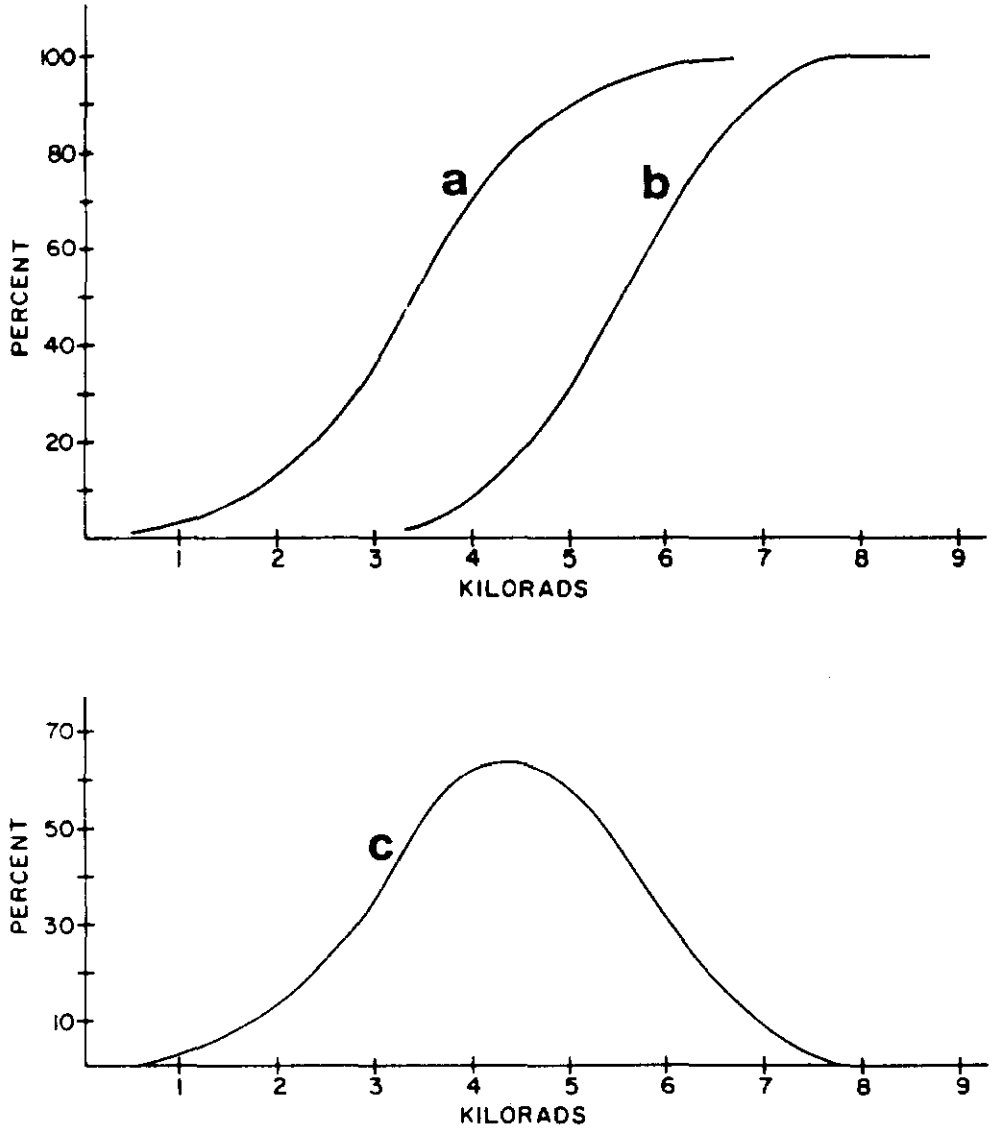
100
80
60
40
20
PERCENT
a
b
1
2
3
4
5
6
7
8
9
KILORADS
70
50
30
10
PERCENT
c
1
2
3
4
5
6
7
8
9
KILORADS

Figure 1

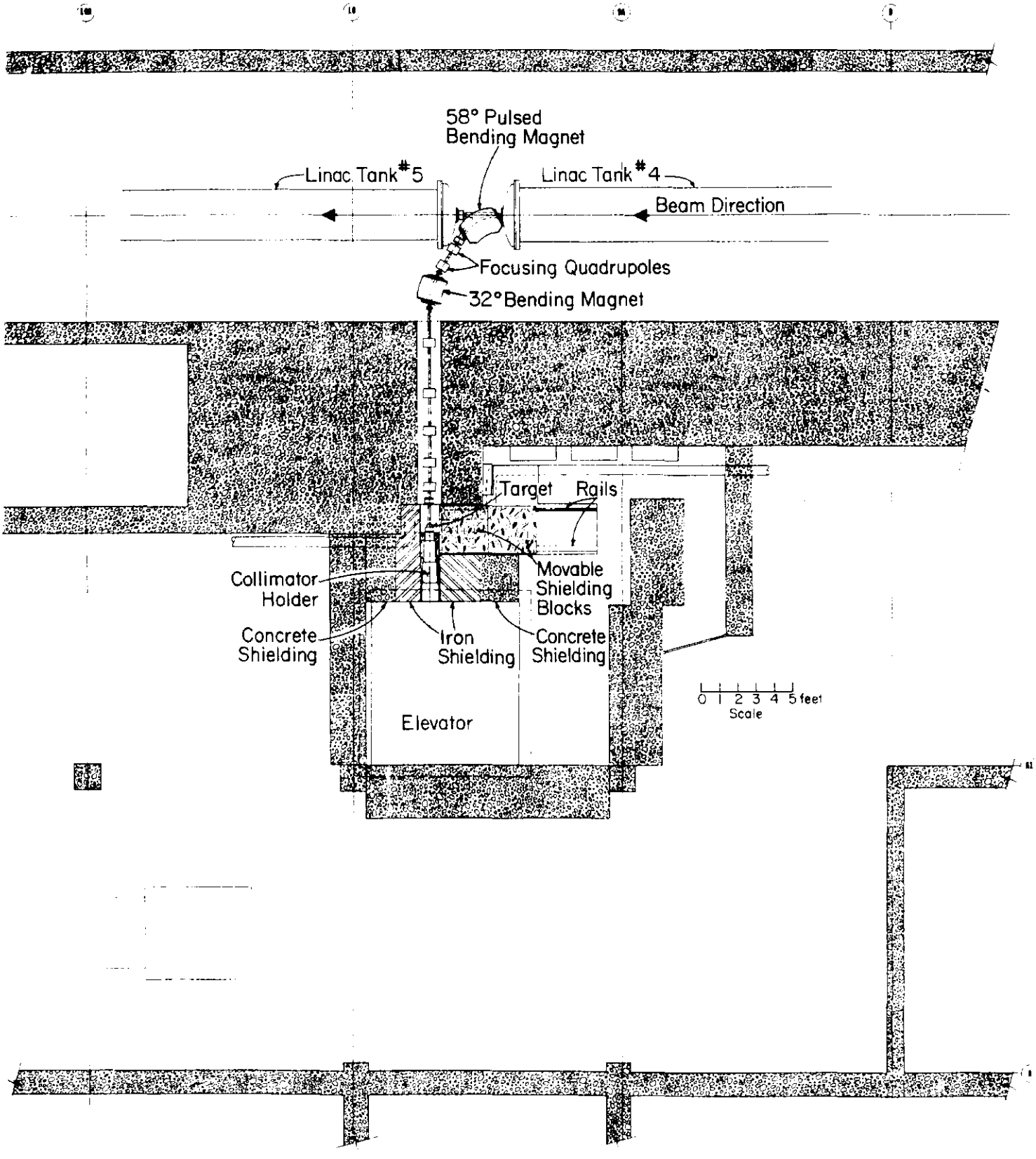
58° Pulsed
Bending Magnet
Linac Tank #5
Linac Tank #4
Beam Direction
Focusing Quadrupoles
32° Bending Magnet
Target
Rails
Collimator
Holder
Movable
Shielding
Blocks
Concrete
Shielding
Iron
Shielding
Concrete
Shielding
Elevator
0 1 2 3 4 5 feet
Scale

Figure 2

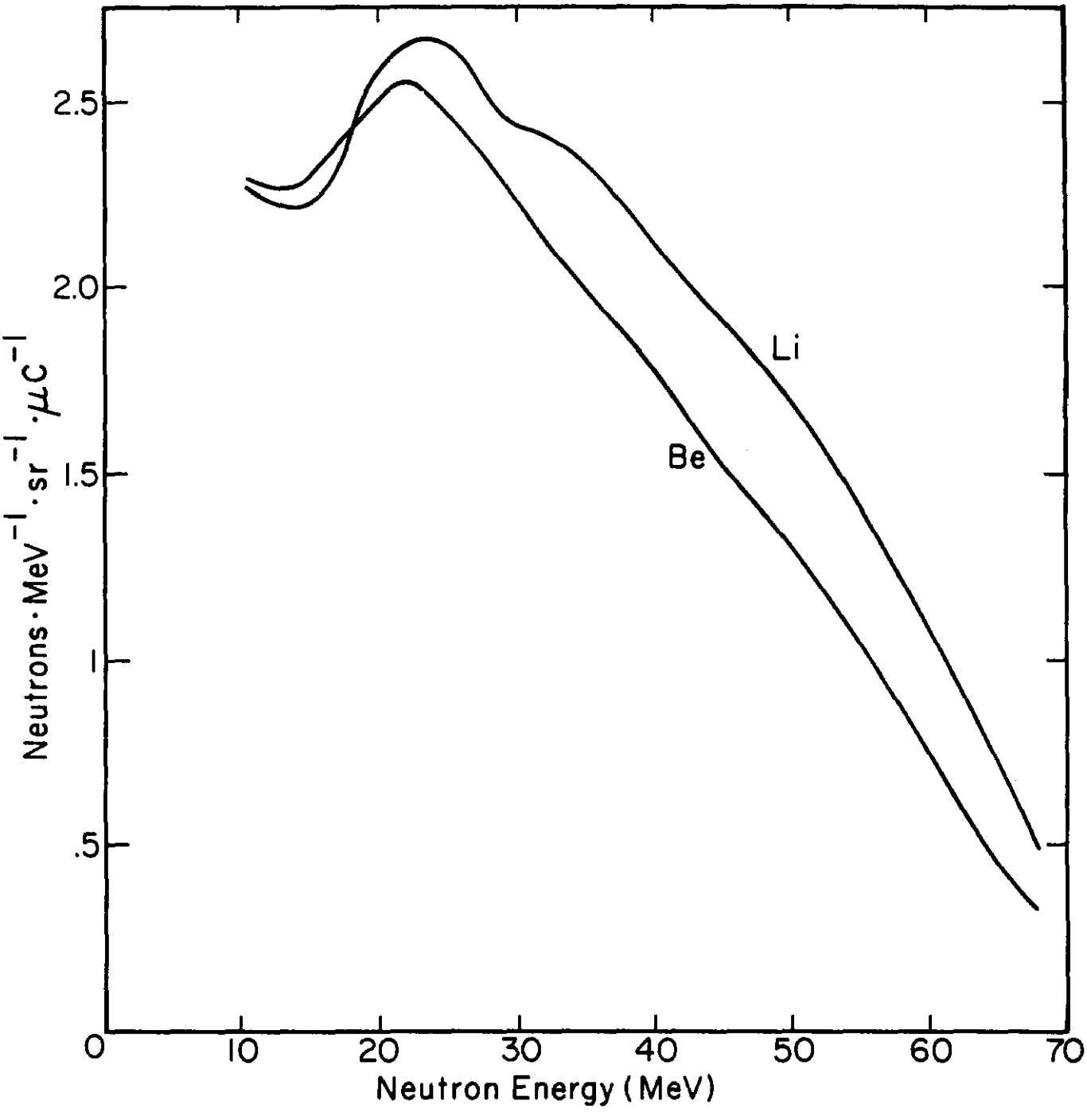
2.5
2.0
1.5
1
.5
0
10
20
30
40
50
60
70
Neutrons·MeV⁻¹·sr⁻¹·μC⁻¹
Neutron Energy (MeV)
Li
Be

Figure 3

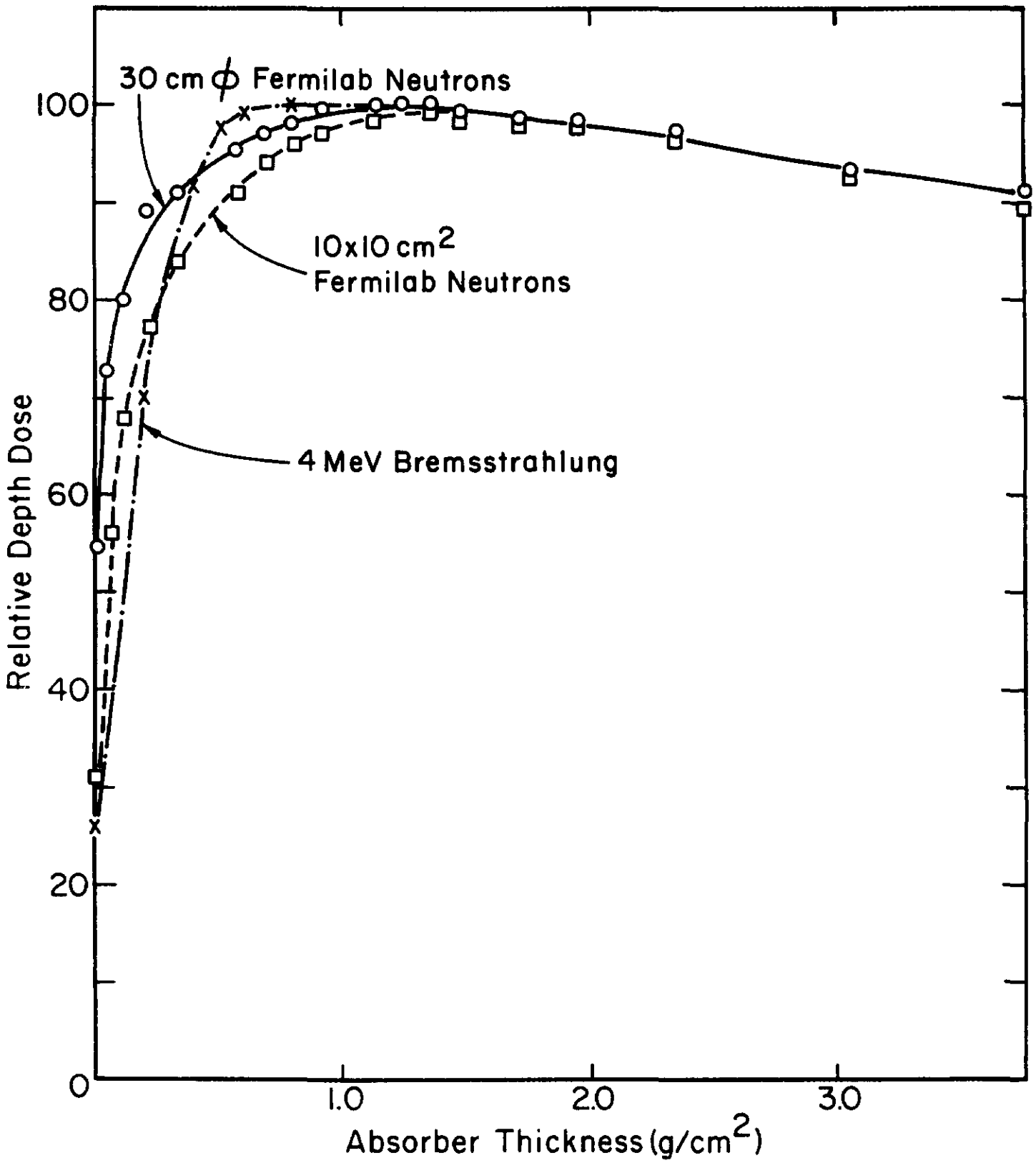
30 cm ϕ Fermilab Neutrons
10x10 cm2
Fermilab Neutrons
4 MeV Bremsstrahlung
Relative Depth Dose
100
80
60
40
20
0
1.0
2.0
3.0
Absorber Thickness (g/cm2)

Figure 4

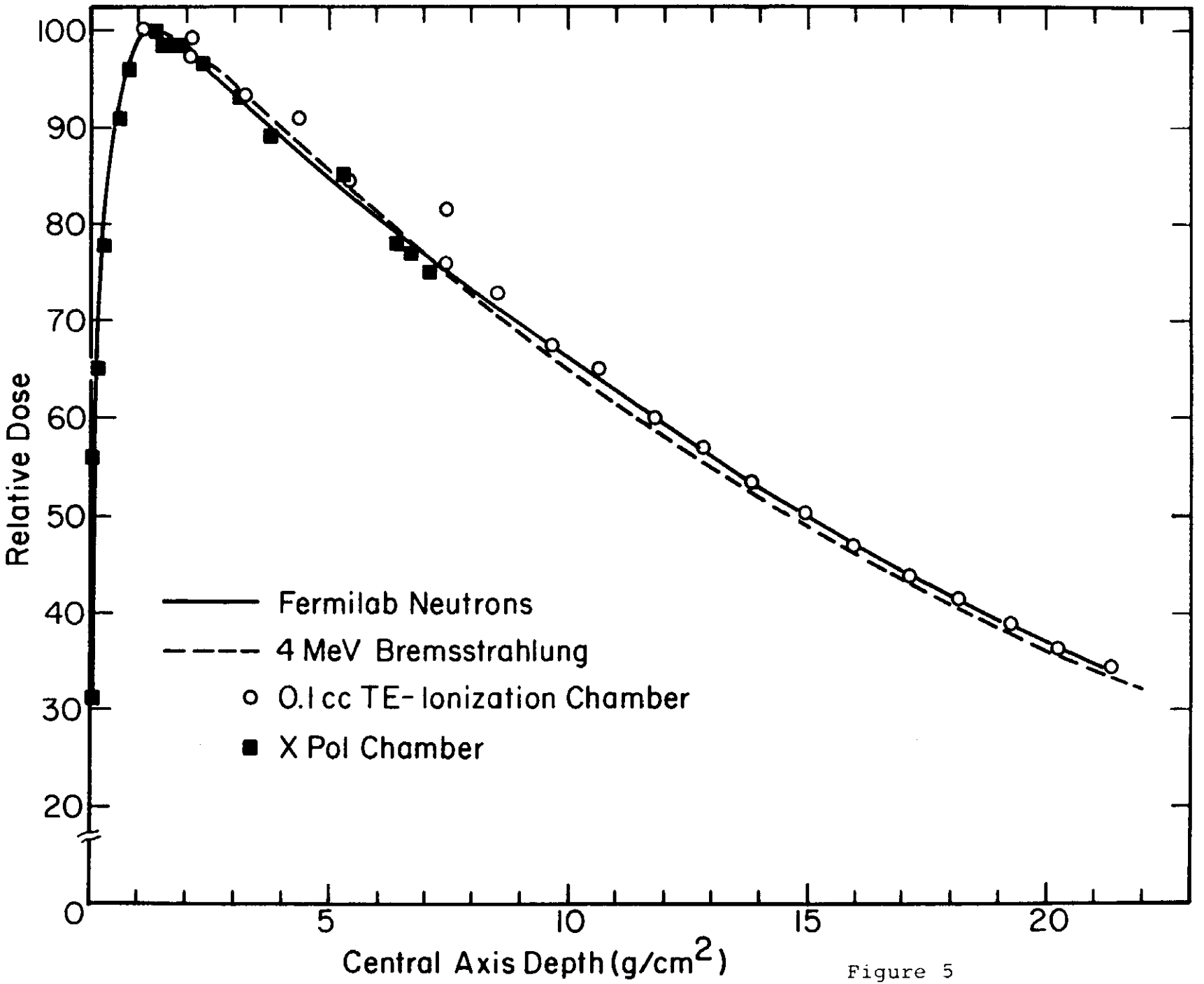
100
90
80
70
60
50
40
30
20
0
Relative Dose
5
10
15
20
Central Axis Depth (g/cm^2)
Fermilab Neutrons
4 MeV Bremsstrahlung
0.1 cc TE- Ionization Chamber
X Pol Chamber

Figure 5

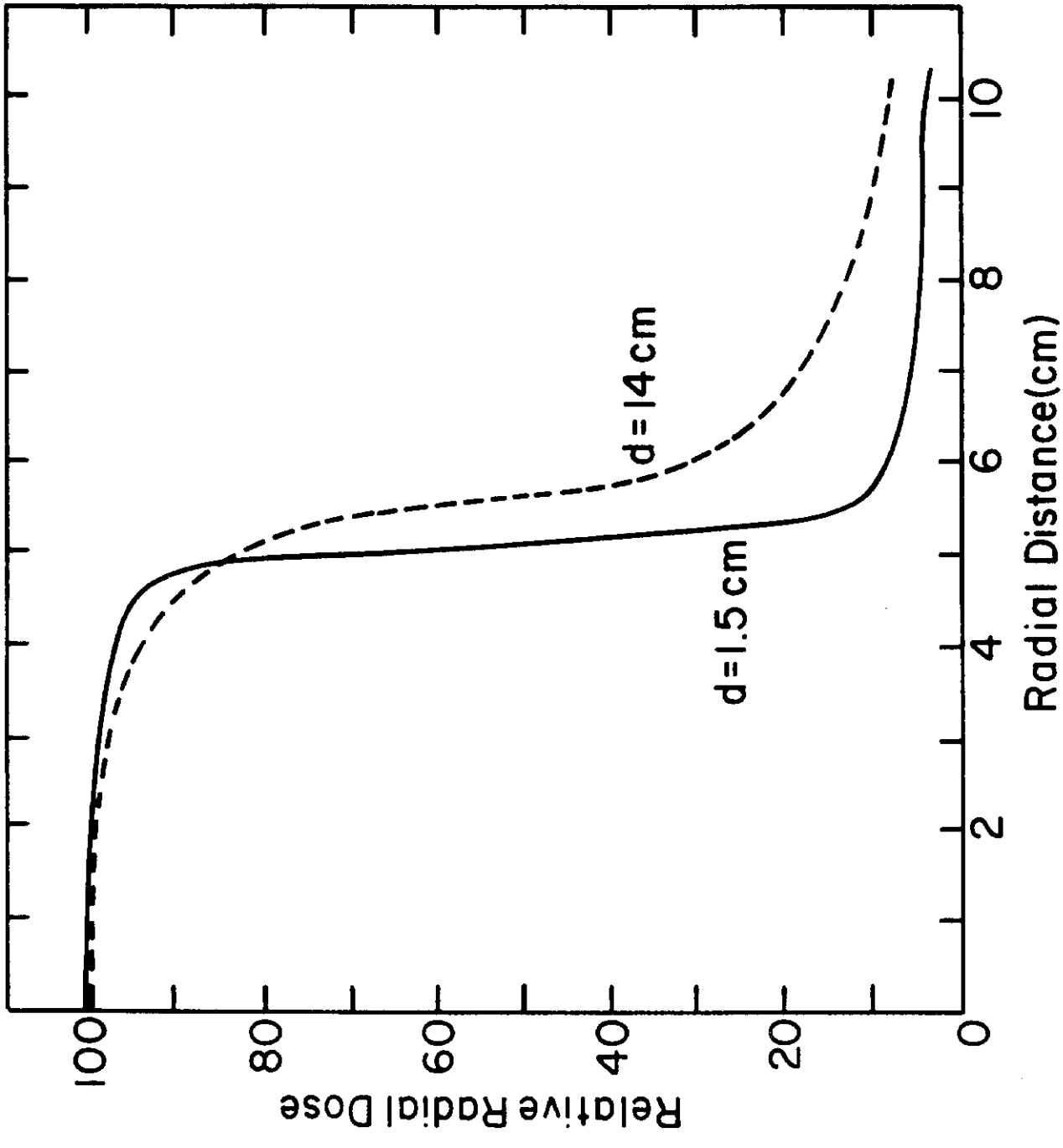
Relative Radial Dose
100
80
60
40
20
0
2
4
6
8
10
Radial Distance(cm)
d=1.5 cm
d=14 cm

Figure 6

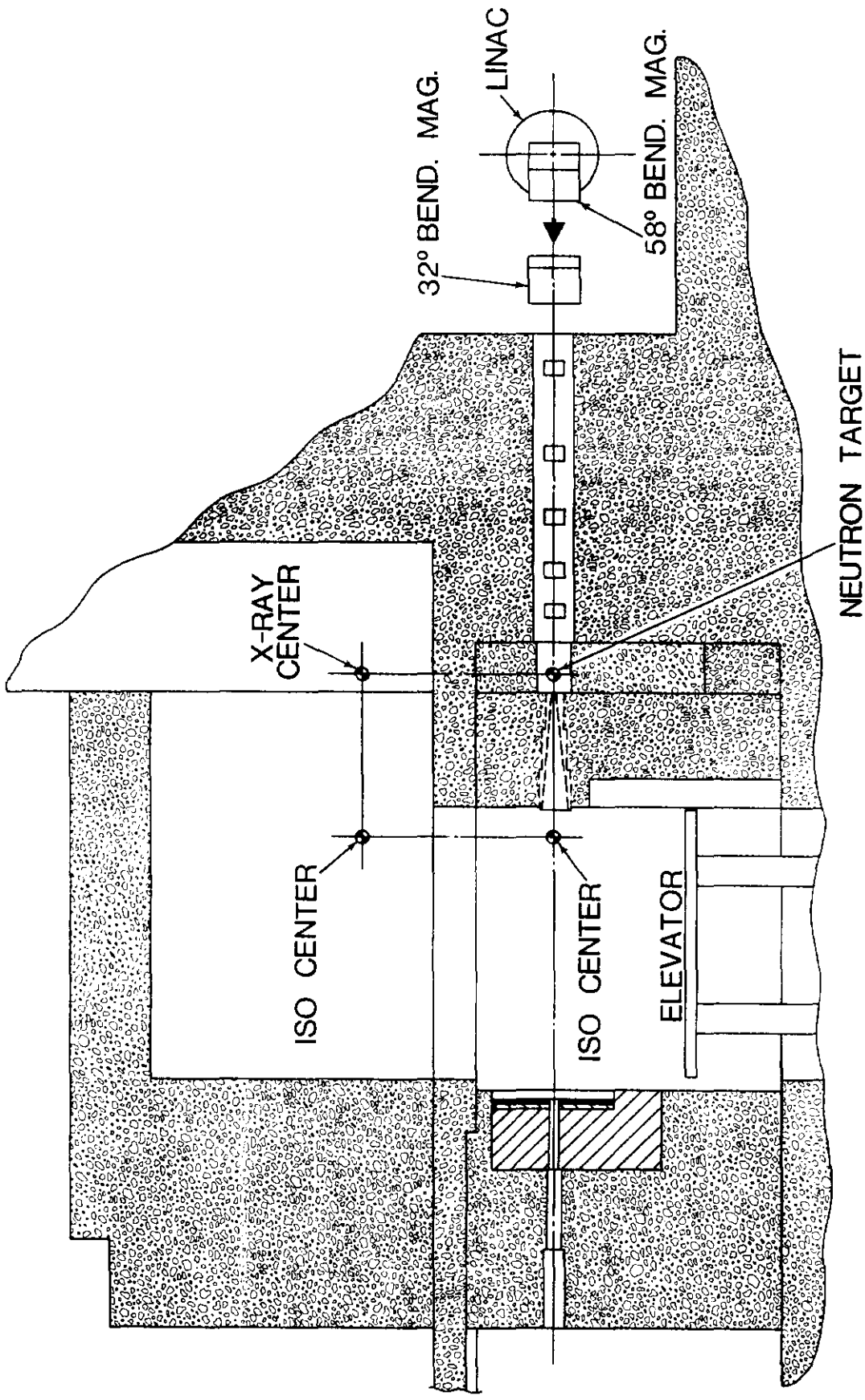
32° BEND. MAG.
LINAC
58° BEND. MAG.
NEUTRON TARGET
X-RAY CENTER
ISO CENTER
ISO CENTER
ELEVATOR

Figure 7

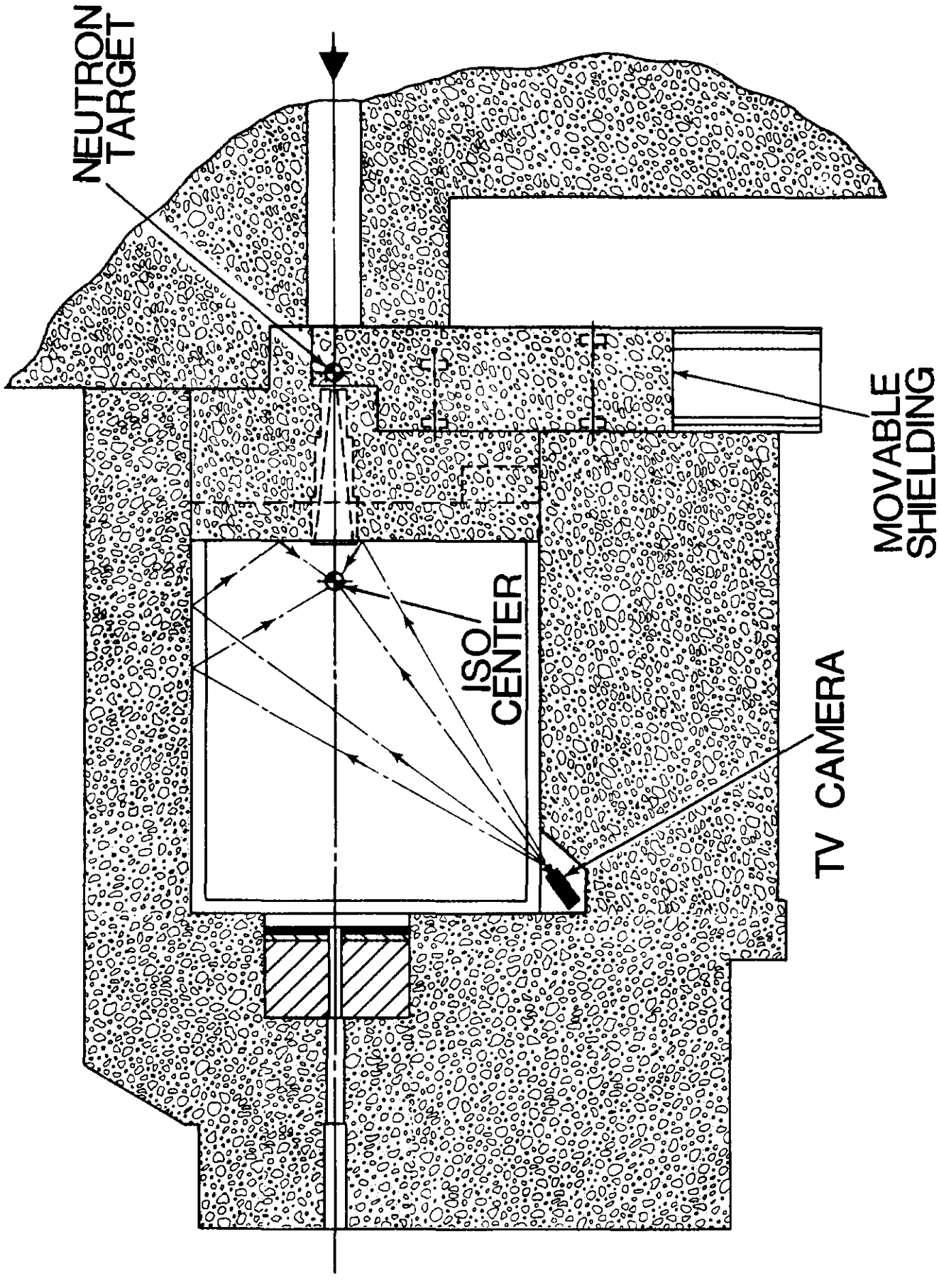

Figure 8

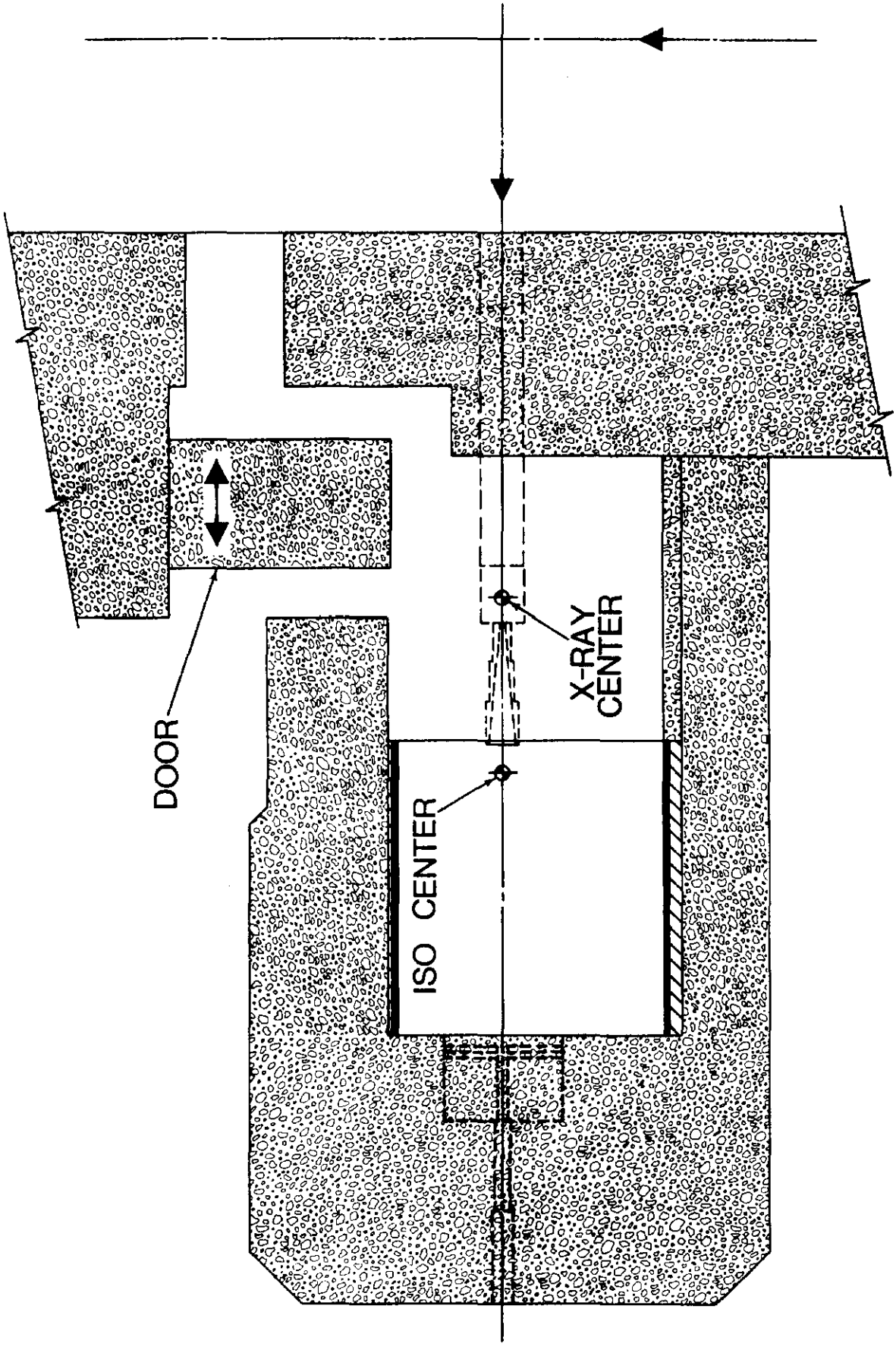

Figure 9