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USE OF THE NUCLEAR REACTOR FOR NEUTRON CAPTURE THERAPY OF CANCER

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Neutron capture therapy is an experimental procedure for achieving selective irradiation of cancer (1, 2, 3). The selective irradiation is accomplished by utilizing nuclear reactions to generate short-range energetic heavy particles within and throughout the malignancy. The energetic heavy particles are produced by the immediate disintegration of unstable nuclear complexes which are formed when slow neutrons are captured by suitable target nuclei.

The procedure for neutron capture therapy begins with the intravenous injection of a suitable target or neutron capturing material and is arranged to provide, at least transiently, a concentration of this target material much higher in the cancer than in the surrounding normal tissues. While this favorable concentration difference exists, the area is exposed to slow neutrons, resulting in irradiation of the area by energetic heavy particles. Localization of the radiation depends on the short range of such particles and on the relative concentration of the target isotope in the disease tissue.

This radiotherapeutic modality is in distinct contrast with other uses of high energy machines or large radioactive sources for radiation therapy. Other methods in use are properly described as teletherapy, in that the radiation originates at a target or source external to the subject being irradiated. Neutron capture therapy uses the external source only to supply the slow neutrons, relatively ineffective in their own right, while the therapeutic radiation actually originates throughout the tumor tissues being treated. In this sense, the modality is one of interjacently originating radiation and the methods for determining dosage from internally administered radioactive isotopes are applicable. This modality is also in contrast to those methods depending primarily upon radiation sensitivity to achieve differential effects.

The accepted applications of radiation therapy in wide use for the treatment of malignant disease rely chiefly on penetrating electromagnetic radiation, that is, x-rays and gamma rays. In addition, there are instances in which irradiation with light particles such as beta rays or electron beams is used. Except for very recent developments which employ narrow

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beams of protons or deuterons of extreme energy, the application of heavier particles has been restricted to wholly superficial sites, since the penetration of alpha and other such particles is quite limited at energies hitherto generally available. Neutron capture therapy involves an importan physical difference in the approach to radiation treatment of disease in that the malignancy is treated in depth and presumably in a uniform manner with heavy particle radiation. The kinetic energy of these particles is transferred to the tissues within a very short range from their point of origin. This range is of the order of 10 microns for the nuclear reaction used in our work. Such intensive transfer of energy along a short path in contrast to the lesser linear energy transfer along the path of an x-ray or gamma ray might be expected to produce qualitative as well as quantitative differences in the results observed.

Nuclides desired for this work must have large capture cross sections for slow neutrons and must provide an instantaneous disintegration into massive particles with high energy. Consideration of the neutron capture cross sections and the heavy particle production characteristics narrows the choice of target elements to three: lithium-6, boron-10, and uranium-235. For our work, boron-10 was selected because of its availability and because certain specific data had been obtained by Sweet (4) indicating a satisfactory physiological behavior of boron.

From the physiological standpoint, the problem is to achieve, at least transiently, a significantly greater concentration of the capture element within cancer tissue than in the surrounding normal structures, with an absolute concentration great enough to provide tumoricidal radiation in a short interval. Infiltration or injection by mechanical means cannot provide the uniform distribution of target element which is required. The use of boron-containing dyes known to localize to a degree in tumors is limited by toxicity problems and unavailability. There is no known compound for which tumors have a significantly preferential uptake to the degree exemplified by the iodine uptake behavior of thyroid tissue. We have, therefore, developed an alternative approach to this problem which we have termed "selective kinetics". This is based on the phenomena of transient differences in concentration of the target-carrying substance which result from differing rates of transfer from blood to the several tissues of immediate interest. In working with glioblastoma multiforme, a rapidly infiltrating tumor, we are able to use to advantage the so-called blood-brain-barrier characteristic to retard entrance of the target element into the normal brain structures while rapid permeation of the tumor occurs, since no barrier exists here.

The first practical opportunity to apply the slow neutron capture principle to therapy of malignant disease in patients was provided by the high flux of slow neutrons available from the Brookhaven research reactor. A treatment facility was constructed in the top shielding of this reactor from which a flux of about 2×10^8 neutrons/cm^2·sec. was delivered to a presenting skin surface area of 5 by 10 centimeters in the first series of experiments. The patient was prepared by intravenous injection of borax, with maximum differences in concentration of boron between tumor and normal brain being assumed at about 10 minutes postinjection. The advantageous difference gradually decreases, disappearing at some time after an hour.

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For best effect, these conditions indicated that the procedure follow a schedule of neutron irradiation of roughly from the 10th to the 50th minutes.

Measurements of the neutron exposure were carried out by using the slow neutron activation of gold foils on the treatment port and on the patient's skin. In some instances, intracranial measurements of neutron flux were made by activation of gold wires which were inserted through the treatment area. Direct measurement of the heavy particle radiation which provides the therapeutic effect was not possible. Potential radiation doses delivered were computed from the experimentally determined values of neutron flux and selected values of boron concentration in the tissues.

Following the conclusion of the first experimental series of ten patients, the reactor medical facility was redesigned to provide several needed advantages. Most important was the increase of slow neutron flux to the presenting skin surface. This can now be as high as 3×10^9 neutrons/$cm^2 \cdot sec$. and is now presented through a treatment port 10 by 10 centimeters. A second major advantage of the new facility is the incorporation of a shutter mechanism sufficient to protect the patient and attending personnel during the preparatory stages without requiring that the reactor be shut down. In constructing the new facility, the bismuth gamma-ray shield was relocated to provide better neutron economy and the customary aluminum coating was removed from the top layer of bismuth to eliminate unnecessary exposure of the patient to the induced radioactivity of the aluminum.

The shielding pieces which cover the treatment facility when not in use were simplified and fitted with access doors, so that auxiliary experiments on small animals, tissue sections, or bacterial cultures can be put into position and irradiated at any time without disturbing other experimental work at neighboring locations. This unique facility has accelerated many phases of the contributory research program of the Medical Department and has been used to advantage in the work of other Brookhaven departments as well. It is used extensively to investigate experimental approaches to the problem of dosimetry by means of special ionization chambers made of entirely tissue-equivalent materials and by the development of dosimeters based on the biological response of selected systems.

The first clinical study of neutron capture therapy was begun in February, 1951, and was completed in February, 1953. Ten patients with glioblastoma multiforme were given one to four capture therapy irradiations. Details have been reported in the literature (1). Survival in this series ranged from 43 days postirradiation to 184 days postirradiation. The two patients in this group who received four irradiations survived longer than the others. The average survival time was 107 days. In this group, the skin surface neutron flux was approximately 2×10^8 neutrons/$cm^2 \cdot sec$. A second clinical study began in April, 1954, with the enhanced neutron flux of 3×10^9 neutrons/$cm^2 \cdot sec$. To date, nine patients have been treated in this facility. Three patients have received two treatments and six a single treatment. Five patients have died, but average survival time postirradiation of these was 169 days with a range of 93 to 337 days. Four patients are surviving whose survival postirradiation as of June 1, 1955, ranged from 42 to 279 days. As of this writing, no prediction can be made

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of the expected survival of this group. It appears, however, that the increase in boron dose and slow neutron flux was accompanied by a significant lengthening of survival span. On the basis of calculations and experience, until a slow neutron flux of 10^{11} neutrons/cm^2·sec. at the skin surface can be obtained, adequate penetration to optimum depth cannot be achieved.

New problems arose when treatment with the higher intensity neutron beam was begun. It should be noted that at this same time we had discovered means allowing the safe injection of greater quantities of boron. Thereby, the potential amount of radiation delivered to the tumor was increased considerably. One problem of first importance which has developed following use of the higher neutron flux is a severe skin reaction which requires detailed care so that the patients had to remain in the hospital much longer than their clinical condition otherwise indicated. This skin effect was due at least in part to the more intense neutron beam which, along with the high energy gamma rays, was able to release energetic protons, electrons, and perhaps other massive particles from the shielding materials and intervening air. An additional thin filter of material of low atomic weight (3 mm. plastic) eliminated part of this difficulty. The area of adverse reaction of the skin was also limited to a degree by the use of strong neutron absorbers to define the treatment area more closely. Both of these changes were made at a sacrifice of a fraction of the neutron intensity but with unquestionably desirable results.

Many other aspects of the program require further study. Among those of considerable immediacy are the pharmacology involved in delivering adequate boron target element concentrations to the tumor site, the physiology of selective kinetics which provides the differences of concentration necessary for localization of the irradiation, the toxicology of the target element and its vehicle compound, and the physics of neutron energy selection and control for optimum penetration at the tumor depth. Following any new development in any of these directions, a careful clinical assessment of effect of the modification is absolutely essential and, on the clinical side, it is also necessary to improve the means of analysis employed in establishing the state of the disease and its changes.

From our experience with the neutron capture therapy experiment and with other biological investigations utilizing the nuclear reactor, specifications have been detailed for a proposed reactor to be built exclusively for our medical applications. This reactor should be capable of providing external thermal neutron beams at intensities of 10^{11} neutrons/cm^2·sec. at the presenting skin surface. This intensity is about thirty times the flux we are now using. Fast neutron and gamma ray contaminations must be maintained well below tolerable limits. To continue and extend our investigation, the medical research reactor should provide a patient irradiation facility with a widely adaptable treatment port incorporating both gamma-ray and neutron shutters and with an auxiliary preparation room. Means should be provided for modifying the character of the neutron flux, in order to explore the enhanced penetration of epithermal neutrons. A similar exposure facility should be provided for animal irradiations. In addition, a large cell directly exposed to a bare face of the reactor should be available. A collimated neutron-beam hole should be included for irradiation of microbiological specimens and for study of radiation effects or neutron depth

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dosimetry in tissue or equivalent media. Our work also includes the application of radioactive materials of very short half life, for which an irradiation tube inside the reactor should be arranged with direct delivery into the treatment rooms or laboratories. A reactor so designed will permit adequate exploration of the field which has been touched upon in the studies mentioned in this report.

SUMMARY

A brief resume of clinical experience to date with neutron capture therapy has been presented. On the basis of this experience and the collateral studies carried out, it is possible to establish operating performance characteristics for a nuclear reactor for medical purposes which will provide an adequate thermal neutron flux at depth in human tissues. This reactor must provide a variable energy neutron spectrum through the epithermal range for satisfactory depth effects. Other facilities desirable in such a reactor have been mentioned. Physiological theory and practice to provide suitable environmental characteristics for neutron capture therapy have been presented in outline.

The present statistics of survival time of patients with glioblastoma multiforme show a significant lengthening following the increase in boron dosage and in thermal neutron flux provided by our latest facility. This is objective evidence supporting the basic tenets advanced in explanation of neutron capture therapy.

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