THE EXPERIMENTAL APPLICATION OF NEUTRON CAPTURE THERAPY TO GLIOBLASTOMA MULTIFORME

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The rapid development of the field of atomic energy during the past few years now permits the exploration of applications to medicine involving new concepts in the treatment of cancer. One such has been the study of neutron capture therapy which is being developed at the Brookhaven National Laboratory.

Neutron capture therapy is a procedure for achieving selective irradiation of a diseased tissue by inducing throughout that tissue radioactivity of high biological efficiency. The radioactivity is induced *in situ* through the capture of thermal neutrons by a suitable target element. To develop the most efficient system, one chooses a target element which upon thermal neutron capture decays immediately through emission of energetic heavy particles such as alpha particles. Since the range of heavy particles of 2 to 4 million electron volts energy in tissue is very short, of the order of 8 microns, the resulting radiation effects are limited to the region of origin. Since the radioactive decay is practically instantaneous and results in a stable element, physiological dispersion from the site of origin is prevented. Only those elements are useful which have a high thermal neutron capture cross section or capacity to capture thermal neutrons. As has been reported in a previous communication, only three elements have the requisite characteristics : boron of mass 10, lithium of mass 6, and uranium of mass 235 (1). For various reasons we selected boron as the initial target element.

The reaction between boron[10] and thermal neutrons can be represented thus :

$$_5B^{10} + {}_0n^1 \rightarrow {}_5B^{11*} \rightarrow {}_3Li^7 + {}_2\alpha^4 + 2.79 \text{ Mev}$$

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As a result of this reaction two energetic heavy particles arise, namely Li^7 and an alpha particle. These traverse pathways from the origin at about 180° from each other. The alpha particle resulting from this reaction travels 9 microns from its site of origin in tissue while the lithium has a range of 6 to 7 microns. These heavy particles produce intense ionization all along their paths. This phenomenon may be taken advantage of to destroy cancer cells if the target element be distributed throughout the malignancy.

To achieve the desired uniformity of distribution of the target element it became apparent that for most purposes the vehicle must be the circulatory system rather than local injection. This in turn makes imperative a precise knowledge of the kinetics of boron distribution through normal and malignant tissues. This is both a difficult and a complex problem since it requires a body of general knowledge of kinetics of distribution which has not yet been developed. However, from extensive studies which we have carried on during the past few years we have been able to develop certain working hypotheses which were sufficiently well founded to permit exploration of the therapeutic potentiality of neutron capture therapy.

In this procedure the atomic population of the tissue in question becomes of the greatest significance. Not only must there exist a significantly greater concentration of the target element in the malignancy than in adjacent normal tissue, but also the absolute concentration must be great enough to develop the desired quantity of radiation within a reasonable time span of neutron exposure. Further, it must be borne in mind that attenuation of the numbers of neutrons is great, the half value layer for thermal neutrons in tis-

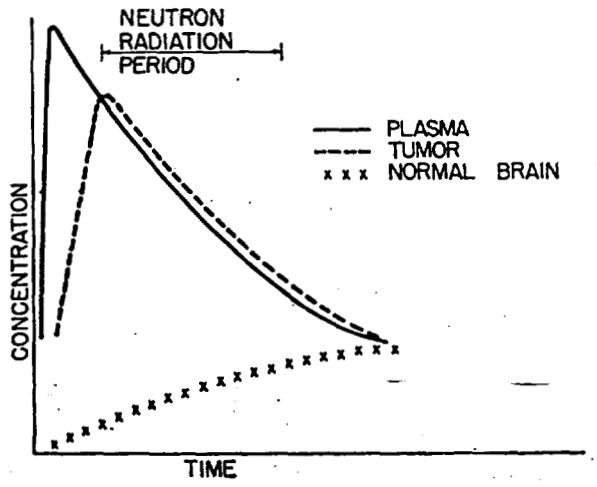

Figure 1. — Schematic probable relationship with time between plasma concentration, tumor concentration and normal brain concentration of boron following intravenous injection of boron. The maximum tumor concentration is shown at approximately twelve minutes post-injection and a neutron irradiation period of forty minutes is indicated.

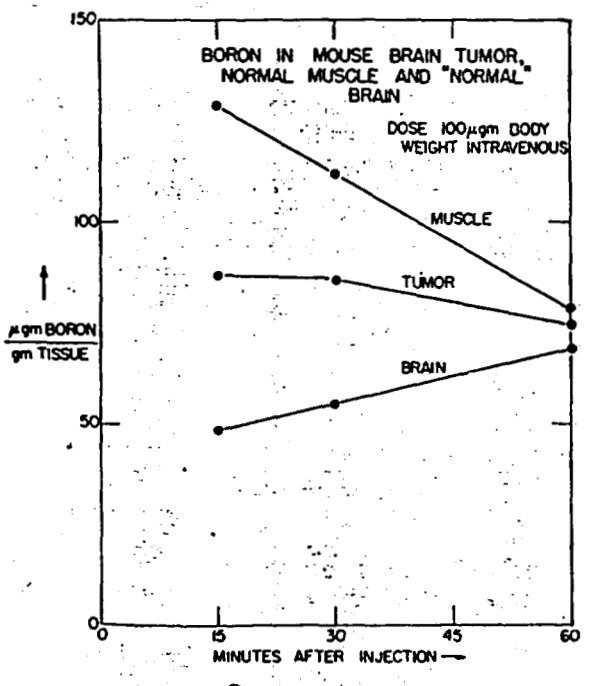

Figure 2. — Concentration of boron in « normal » brain, brain tumor and muscle of mice following intravenous boron injection providing 100 micrograms boron per gram body weight. Each point represents the average values for analysis of specimens from ten animals. The injection was done at time zero.

sue being only 1.9 cm. (2). Hence very high thermal neutron fluxes at the site of entry are requisite for an adequate flux at a depth of 7 to 10 cm.

For the target element, requisite conditions would be fulfilled if a substance were available for which the tumor tissue had a very large preferential uptake such as that of the normal thyroid for iodine. Since we do not have such a target compound an alternative approach termed *selective kinetics* has been developed. In this concept, capital is made of the differing rates of transfer from the blood to the several tissues of immediate interest. If the target element be present in requisite concentration for a reasonable interval during which sufficient numbers of neutrons can be brought to that tissue, the subsequent movements of the target element are no longer of concern for the radiation selectivity. One deals with transient concentration differences existing prior to final equilibrium. These relationships are demonstrated in *Figures 1 and 2.*

These general considerations have been and are being treated more fully in other publications (1) (3) (4).

Beginning in February 1951, a series of five patients with glioblastoma multiforme were given single exposures to thermal neutrons followed by another series of five patients who were given three to four treatments at four to six week intervals. The results of this study have been published (3). From this experience it was possible to state that technically the procedure is feasible and that although some temporary but definite clinical ameliorations of the disease were seen, radiation dosage given these patients had been inadequate for a definitive result.

We have therefore over the past year redesigned and rebuilt the medical facility at the Brookhaven reactor to provide a greater neutron flux as well as to incorporate other technical changes which increase the usefulness of that facility. The neutron flux at the skin surface in the original facility was 3×10^8 thermal neutrons per cm^2 per sec. The present facility provides 3×10^9 thermal neutrons per cm^2 per sec. We have also increased the size of the treatment port from 5×10 cm to 10×10 cm to permit greater exposure of tumor masses.

On April 2, 1954, after extensive phantom tests to establish the ratio of fast to thermal

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neutrons as well as the gamma contamination, the first patient was treated in the new facility. In the present series of treatments not only have we increased the neutron flux but also we have increased the dose of the target element, boron. This is still administered as a borax synthesized with boron of mass 10 and given to the patient intravenously in a concentrated solution of 100 ml. containing 20 to 30 grams of borax. The dose has been adjusted to each patient on the basis of surface area which, from pharmacological studies to be reported shortly, appears to provide a better standard than weight alone. The dose in the present series of patients has ranged from 32 mg B^{10} per kilogram body weight to 42 mg B^{10} per kilogram body weight. In the original series of patients, the dose on a weight basis ranged from 19 to 46 mg per kilogram body weight. Radiation time has been reduced from a 40 minute period to a 20 minute period. In both procedures neutron radiation is begun 8 to 10 minutes following completion of the injection.

Because we have not yet been able to work out fully the kinetics of borate we cannot estimate with accuracy the radiation dose delivered to the tumor in roentgen equivalents physical or roentgen equivalents man. However, with a tumor concentration of 20 micrograms of boron-10 per gram of tumor and a brain concentration of 5 micrograms per gram of normal brain there should be developed at a depth of 4 cm a tumor dose of 178 rep and a normal tissue dose of 44 rep. This would correspond to a tumor dose of 3,600 rem and a normal tissue dose of 880 rem. This dose should be adequate to provide effective results in the tumor and yet be within acceptable limits for normal tissue.

The total single treatment thermal neutron dose in the old facility was 9×10^{11} neutrons per cm^2. In the present facility the total single treatment thermal neutron dose ap-

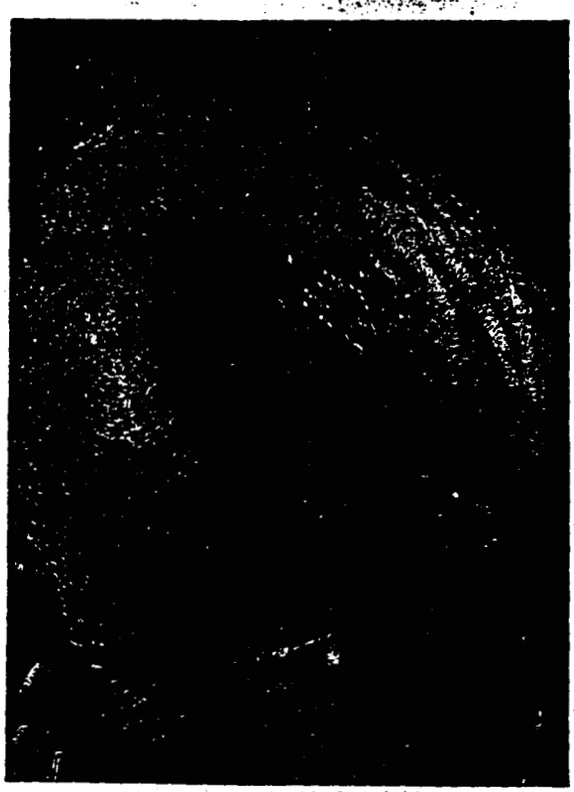

Plate I. — Radiation dermatitis of scalp after three exposures to thermal neutrons. Each exposure was of forty minutes duration. The total neutron irradiation per treatment averaged 9×10^{11} neutrons per cm^2 and was delivered through a 5×10 cm port.

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Plate II. — Severe radiation dermatitis, four weeks after 20 minute exposure to thermal neutron radiation. Total thermal neutron radiation was 3×10^{12} neutrons per cm^2. Boron-10 dose was 42 mg per kilogram body weight.

proximates 3×10^{12} neutrons per cm^2. The single dose in the new facility was carried out with the reactor operating at a lower power level than in the initial studies. By any standards, however, this is a large dose of thermal neutrons. One patient has received two such treatments and three patients one such treatment. While it is too early to discuss results in these patients, one can say at this time, some three to four months after treatment, that no evidence of resumption of tumor growth has yet appeared in any of these individuals and they are able to carry on normal tasks and assume normal responsibilities.

While the outcome of the treatment cannot be given yet, a complication can be described. With the very large neutron dose and the large boron dose a severe radiation dermatitis developed in our first patient in the latest series. Following a large area of skin breakdown, healing has been slow and infection very difficult to control. During the last three of the five treatments a pressure bandage was applied to prevent boron accumulation in the scalp. This appears to have been quite successful, since the last two patients have shown no significant radiation dermatitis and even only a minimal and not disfiguring amount of epilation. These results are shown in the accompanying photographs, *Plates I, II and III.*

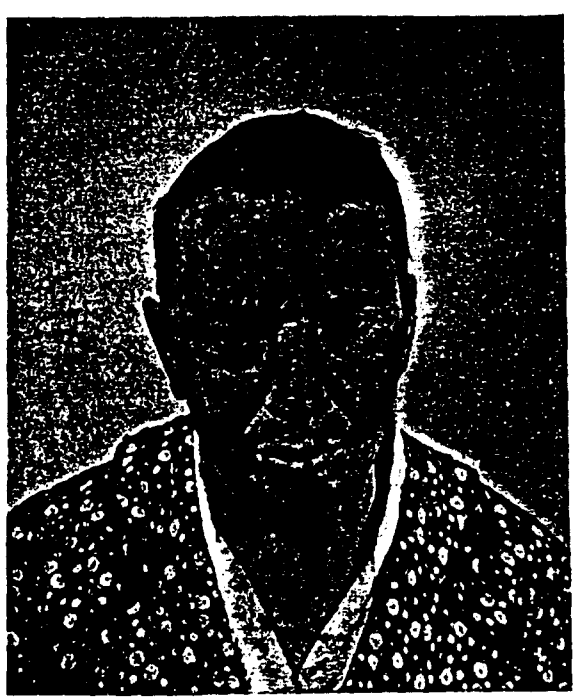

Plate III. — Absence of radiation dermatitis three weeks after 20 minute exposure to thermal neutron radiation. Total thermal neutron radiation was 3×10^{12} neutrons per cm^2. Boron-10 dose was 32 mgr per kilogram body weight. Pressure bandage to head was applied immediately before boron was injected intravenously.

In conclusion it can be said that neutron capture therapy of glioblastoma multiforme with thermal neutron fluxes up to 3×10^{8} is feasible ; results of treatment to date suggest an inhibition of tumor growth of at least four months following a single treatment, the final results will become apparent with further observation; radiation dermatitis of the scalp presumably caused by the capture reaction can be very sharply ameliorated by proper procedures.

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