PHYSICS AND PHYSIOLOGY OF NEUTRON-CAPTURE THERAPY*

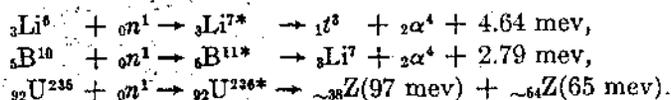BY L. E. FARR, J. S. ROBERTSON, AND E. STICKLEY

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Neutron-capture therapy is an experimental procedure for achieving selective irradiation of a diseased tissue by inducing radioactivity throughout that tissue.

The radioactivity is induced *in situ* by the capture of thermal neutrons by a suitable target element.   For best effects the target element is so chosen that decay of the excited isotope is immediate and results in energetic heavy particles, for example, alpha particles.   The advantages of heavy particles are that they have short

ranges in tissue and that they have high relative biological effectiveness. A high thermal-neutron capture cross-section is another essential requirement in selection of the target element. Only three elements decaying by heavy-particle emission have adequately large cross-sections. These are lithium 6, boron 10, and uranium 235, having cross-sections of 950, 3990, and 549 barns.[†]

The nuclear equations representing these reactions and the energies involved are

$$_3Li^6 + _0n^1 \rightarrow _3Li^{7*} \rightarrow _1t^3 + _2\alpha^4 + 4.64 \text{ mev},$$
$$_5B^{10} + _0n^1 \rightarrow _5B^{11*} \rightarrow _3Li^7 + _2\alpha^4 + 2.79 \text{ mev},$$
$$_{92}U^{235} + _0n^1 \rightarrow _{92}U^{236*} \rightarrow _{\sim 38}Z(97 \text{ mev}) + _{\sim 54}Z(65 \text{ mev}).$$

The asterisk in the above equations denotes the excited intermediate state of the compound nucleus formed by neutron capture.

In 1936 Locher[1] suggested the possibility of irradiation by neutron activation *in situ*. The first studies pertaining to the suitability of the boron 10 reaction were reported by Kruger in 1940,[2] and in the same year Zahl, Cooper, and Dunning[3] reported studies involving both boron 10 and lithium 6. In 1948 Tobias, Weymouth, Wasserman, and Stapleton[4] reported studies on biological effects induced in animals by thermal-neutron radiation following administration of uranium, using a reactor as the neutron source.

When the research reactor at Brookhaven National Laboratory began full power operation early in 1951, the clinical program for the treatment of malignancy by neutron-capture therapy was initiated in the medical department. There being no obvious first choice among the three possible capture elements, the availability of highly enriched boron 10 and the extensive medical literature dealing with the toxicology of boron led us to select this element for the first studies of the physiological problems involved in neutron-capture therapy.

From the physiological standpoint the first problem is to achieve a significantly greater concentration of the capture element within the volume to be irradiated than obtains in the surrounding areas, and the absolute concentration must be great enough to permit sufficient irradiation to be achieved in a reasonable time span.

These conditions would be met if a compound were available for which the tumor had a preferential uptake. Such a compound would contain the capture element and would be greatly concentrated from the blood by the tumor. By "preferential uptake" we mean the type of uptake which is seen in the case of iodine when it is concentrated by normal thyroid tissue. However, no such compound is known for tumors today. For this reason, we have developed an alternative approach, which we have termed "selective kinetics." In the application of selective kinetics we capitalize upon the transient differences in concentration resulting from differing rates of transfer of the target element from blood to the several tissues of immediate interest. When this concept is used, we are primarily concerned with concentration differences which exist before equilibrium is reached and are not concerned with final distribution.

The hypothetical relationships between time and changing concentration can be demonstrated in Figure 1, which shows the situation presumed to exist during the experimental application of slow-neutron-capture therapy to glioblastoma multiforme, a malignant tumor affecting the brain.[5] With time plotted from beginning

of the injection, the concentration in plasma rises quickly and then decreases as the borax is taken into various tissues or is removed from circulation by normal eliminative processes. The curve typifying concentration in the brain tumor is seen to follow the rise quickly and then follows the same general decreasing function. In normal brain tissues, however, the concentration of borax comes up quite slowly and reaches equilibrium only after an hour or more. The administration of the radiation treatment is accomplished by application of slow neutrons during this temporary state when a greater amount of the capture element is present in the disease area than in the normal tissues. In the first series of experiments the neutrons were used in the interval from ten to forty minutes after injection.

These differences in concentration arise from differences in circulation and permeability. To establish the validity of these assumptions with regard to a target element it would be most convenient to use a radioactive isotope of that element as a tracer. For boron and lithium no suitable radioactive isotope exists. This difficulty might be obviated by placing the tissues in a neutron beam and determining the instantaneous concentrations of the target element by the use of alpha-particle detectors *in situ.* To date, we have not been successful in developing instrumentation for this purpose. Consequently, we have perforce resorted to the study of other radioactive elements to obtain certain data pertinent to this study and have related these data to chemical determinations of the target element in tissues removed at various time intervals after injection. We have studied boron behavior in transplantable mouse brain tumors induced originally with methylcholanthrene. With reference to selective kinetics, these serially passaged tumors behave apparently in a manner similar to glioblastoma multiforme in man. Representative data from such a study are shown in Figure 2. Equilibrium in the several tissues studied is attained at about seventy-five minutes after injection. The comparison of boron concentration in tumor and normal brain is seen to be well marked. Experimental difficulties due to the smallness of the experimental animal introduce some uncertainty that only undamaged brain is included in the sample, a factor which would serve to decrease the apparent preferential distribution.

In the case of brain tumors, the phenomenon of the blood-brain barrier, by retarding the appearance of boron in normal brain tissue, enhances the selective kinetics, or favorable concentration ratio, since this barrier does not exist in the tumor. If the blood-brain barrier is depended upon to retard distribution through normal brain, it is necessary to determine whether the barrier remains intact following radiation when more than one treatment is contemplated. Although we could not readily study the blood-brain barrier in our patients, we could study the blood-ventricular fluid barrier and have assumed that this would behave in the same manner. Thus far we have not been able to demonstrate any effect upon this barrier by the treatments.

In the first experimental series ten patients were irradiated with thermal neutrons at the Brookhaven reactor. The treatment facility is shown schematically in Figure 3. The upper layer of shielding was removed over an area four feet by eight feet, and a special block was inserted in the lower section. This block is a hollow cone which permits neutrons from a large area of surface of the graphite reflector surrounding the reactor core to be utilized at the two-inch-by-four-inch treatment port. Leakage neutrons escaping from this reflector are thus funneled through the
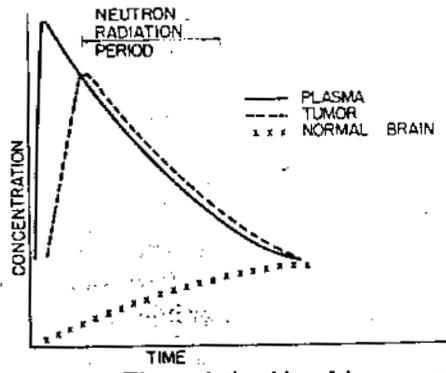
FIG. 1.—Time relationship of boron concentration in plasma, tumor, and normal brain following intravenous injection. The maximum concentration in tumor is shown at approximately twelve minutes postinjection, and a neutron irradiation period of forty minutes is indicated.
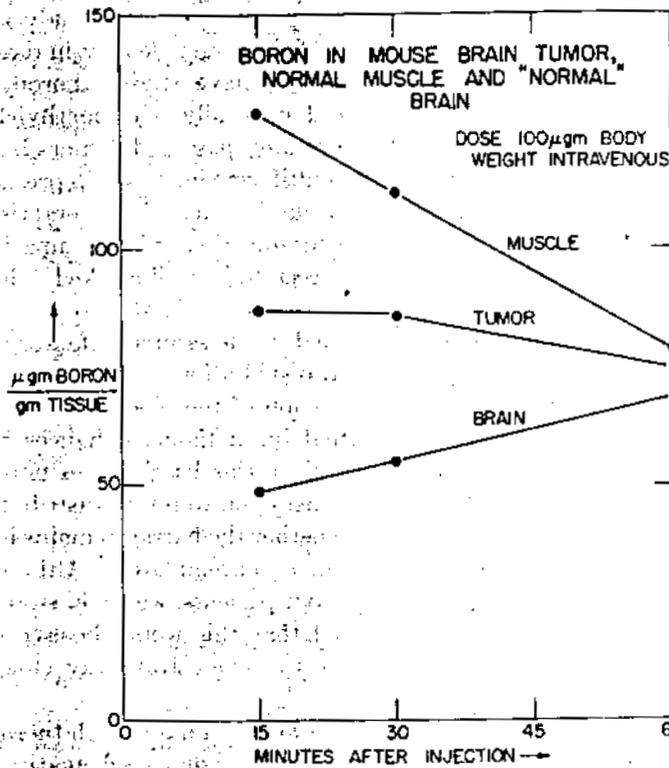
4-45-3

FIG. 2.—Boron concentration in mouse tissues following injection. The normal brain samples might have included some tumor tissue.

4-259-4

volume to be treated. A bismuth shield is interposed to reduce the amount of gamma radiation which accompanies the neutrons.

Studies of the neutron flux were made at this facility, using a phantom. In order to get valid data for the neutron flux, it is necessary that the phantom match tissue not only in its density but also in the atomic population. This was done with special plastic materials and with liquid solutions contained in a thin plastic box. Gold foils were employed as neutron detectors, using the neutron activation technique.[6] The results are shown in Figure 4, superposed on a sketch of the treatment situation. These figures have been substantiated also by intracranial measurements made during treatment with gold wires inserted through the treatment area.[7]

In this study the results obtained were encouraging clinically but were far from definitive. Assessment of the conditions under which multiple radiations were carried out indicated that boron concentration in the tumor area was low and that the attenuation of thermal neutrons was so great as to preclude the possibility of effective treatment in areas approaching the midregion of the head, where effective tumor control is imperative. Two objectives became immediately apparent: (1) to increase the thermal-neutron flux and (2) to increase the boron dose.

During the past year we have redesigned our reactor facility so that now the flux has increased from 2×10^8 to 3×10^9 thermal neutrons per square centimeter per second at the skin surface. Figure 5 shows the new treatment facility. A shutter is included to permit setting up the patient for treatment without requiring the reactor to be shut down. This compound shutter consists of a thin layer of boron carbide to absorb the slow neutrons, several inches of paraffin and lithium fluoride to thermalize and capture the fast neutrons, and two inches of lead as additional gamma-ray shielding. The shutter is also of great value in carrying out the extensive small-animal irradiations which are an important part of the research program. A second major improvement is the increase in neutron flux. This has been achieved by making the treatment level lower, widening the angle of the funnel block, and minimizing the amount of structural material in the path of the neutrons. Also, a treatment port as large as four inches square can now be used. The gamma-ray contamination in the beam has been lessened by removing the aluminum covering normally used on bismuth. We have also carefully evaluated the toxicity of intravenously administered boron in mice and believe we can safely increase the dose over that previously given. During April, 1954, a new series of experiments was begun in which the patients are treated with the higher flux and with larger doses of borax. It is too early to make any statement of the results, but the immediate treatments were successful.

DECK

ELEVATION OF MEDICAL FACILITY
(WEST—EAST)

SHIELDING BLOCKS REMOVED
TEMPORARILY

SHIELDING

10 CM APERTURE

107 CM

COOLING AIR
PASSAGES

BISMUTH γ SHIELD

SHIELD
150 CM

REFLECTOR (GRAPHITE)

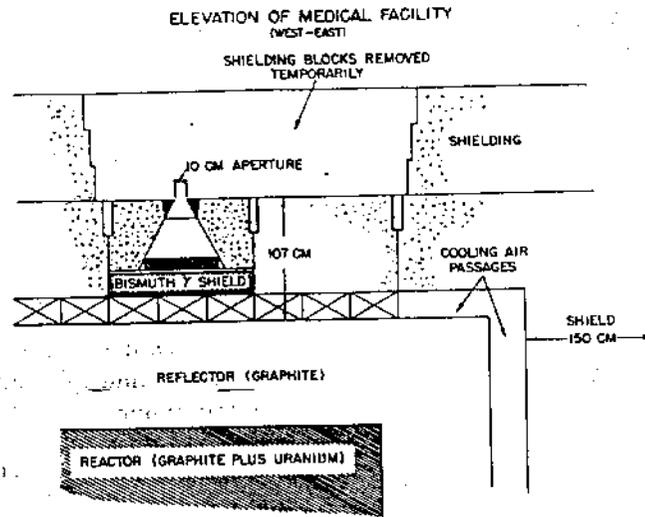REACTOR (GRAPHITE PLUS URANIUM)

4-47-3

FIG. 3.—Schematic detail of nuclear-reactor facility in cross-section, showing geometric relationship of treatment site, shielding, and radiation source.

DETAIL OF SHIELDING AND APERTURE
VIEW FROM SIDE

THERMAL NEUTRON
ISO-FLUX CONTOURS
IN $_0n^1$/CM^2 – SEC

LOG FLUX

5 — 15 DEPTH CM
6 — 10
7 — 5
8 — 0

3×10^5
3×10^6
3×10^7
3×10^8

POSITION OF HEAD
AT RADIATION PORT

PARAFFIN

ALUMINUM
SHELL

CONCRETE SHIELDING
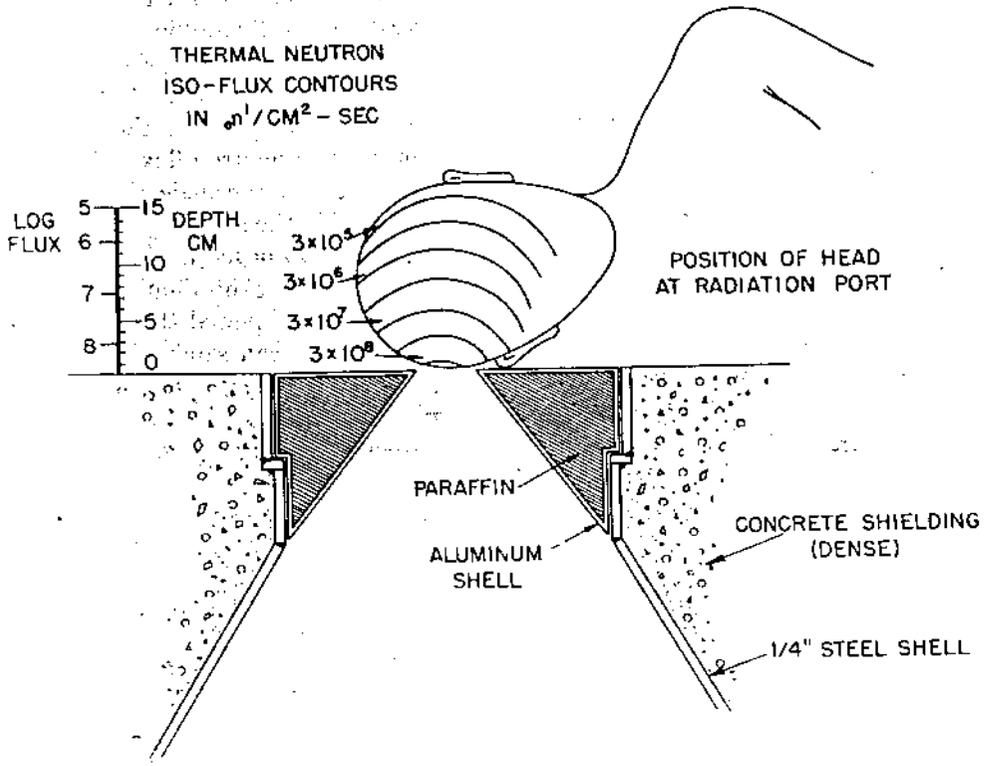(DENSE)

1/4" STEEL SHELL

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FIG. 4.—Slow-neutron penetration pattern, showing attenuation with depth. This figure is idealized from measurements in phantom and in vivo using gold-foil activation technique.
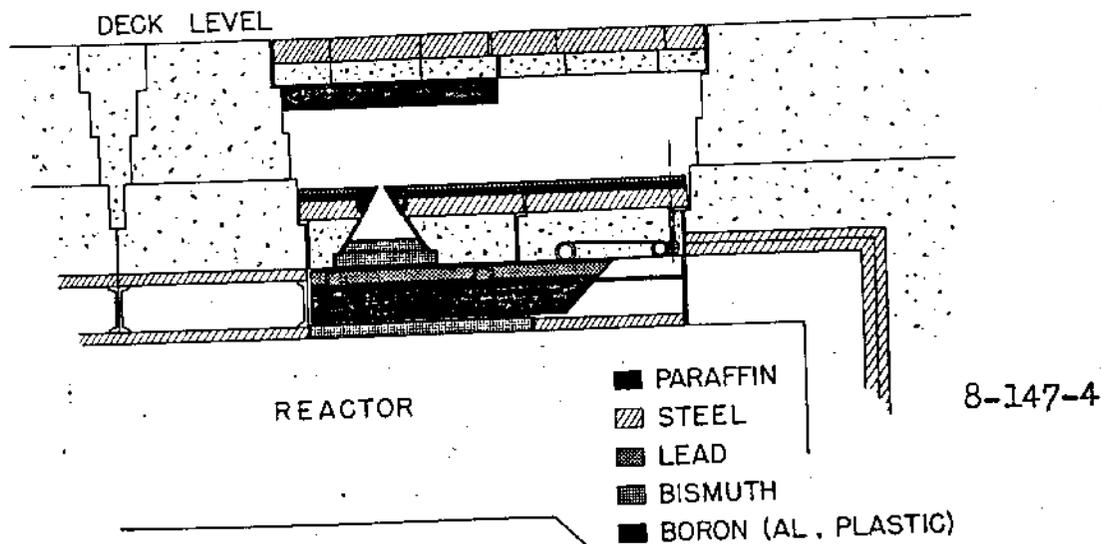
MEDICAL REACTOR FACILITY

Fig. 5.—New medical facility at the Brookhaven nuclear reactor. Vertical section through center of treatment cone, showing arrangement of shielding materials, compound shutter, and limitation of neutron flux.

Our experience to date points to the desirability of improving the neutron penetration of the deeper-lying tissues, a result which possibly can be achieved by developing a beam providing epithermal as well as thermal neutrons.

Summary.—We have utilized the phenomenon of thermal-neutron capture to develop radiation *in situ* in patients suffering from glioblastoma multiforme. We have applied our concept of selective kinetics to localize this radiation to the sites desired. The results to date have been encouraging and have suggested numerous other basic studies required for fuller development of this therapeutic approach.

† The barn is a unit of magnitude 10^{-24} cm^2. The neutron-capture cross-section expresses the probability of capture in terms of the effective target area which the nucleus presents to the neutron.

[1] G. L. Locher, *Am. J. Roentgenol. and Radium Therapy*, 36, 1–13, 1936.
[2] P. G. Kruger, these PROCEEDINGS, 26, 181–192, 1940.
[3] P. A. Zahl, F. S. Cooper, and J. R. Dunning, these PROCEEDINGS, 26, 589–598, 1940.
[4] C. A. Tobias *et al.*, *Science*, 107, 115–118, 1948.
[5] L. E. Farr *et al.*, *Am. J. Roentgenol., Radium Therapy, Nuclear Med.*, 71, 279–293, 1954.
[6] E. E. Stickley, *Am. J. Roentgenol., Radium Therapy, Nuclear Med.* (in press).
[7] H. B. Locksley and E. E. Stickley (in preparation).