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NEUTRON CAPTURE THERAPY WITH BORON IN THE TREATMENT OF GLIOBLASTOMA MULTIFORME*†

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IN 1940 Kruger[6] reported some *in vitro* experiments of thermal neutron capture by boron-10 (B^{10}) on the survival of transplants of mouse sarcoma, mammary carcinoma and lymphoma, and concluded that the results indicated that "neoplastic cells can be destroyed *in vivo* if sufficient boron in some suitable form can be applied to the tumor *in vivo*." Later the same year Zahl, Cooper and Dunning[15] reported on effects on transplantable mouse sarcomas injected with boron or lithium preparations and exposed to a thermal neutron source. They concluded that a significant increase in tumor regression followed the exposure and could be attributed to localized ionization resulting from the nuclear disintegration products of the capture process. In 1941 Zahl and Cooper[16,17] reported studies on the localization in tumors of lithium and certain lithium salts of dyestuffs as possible neutron capture agents for tumor therapy. They published data showing that lithium compounds injected intravenously into mice concentrated to a degree in spontaneous mammary tumors and implanted tumors of the sarcoma strain and that the concentration of elemental lithium within the tumor mass some four hours after injection was sufficiently great to provide a significant source of radiation through thermal neutron capture. Neither Li^6 nor adequate neutrons were available at this time to permit extension of this work. They also computed the possible effectiveness of B^{10} as compared to Li^6 and discussed to some degree the possible advantages of thermal neutrons over roentgen rays and fast neutrons for tumor therapy. With a selective localization factor of only 2 times for the tumor over other tissues in the mouse and a concentration of 0.03 per cent lithium in the tumor, they estimated a gain of 43 per cent in radiation dosage to the tumor over the other tissues. In 1948 Tobias, Weymouth, Wasserman and Stapleton[14] reported studies on biological effects induced in animals by thermal neutron radiation following administration of uranium. They, however, reported no studies of uranium distribution in tumors.

Also during 1940 there appeared a preliminary report by Stone, Lawrence and Aebersold[10] on the use of fast neutrons in the treatment of malignant disease. Subsequently in 1942 a fuller report on fast neutron therapy was made by Stone and Larkin[11] and a follow-up report by Stone[12] on late effects was published in 1948. It was Stone's conclusion that the results with fast neutron therapy were not encouraging because of the severity of the late reactions. It must be emphasized that the present study deals with thermal or slow neutrons, the fast neutrons having been screened out, and that the effects are mediated by providing a target substance, B^{10}, which becomes an alpha radiation source by virtue of slow neutron capture. The direct effects of slow neutrons on tissue are not depended upon for results in the present study, as was done with fast neutrons in the earlier work.

In 1951, with the completion of Brookhaven's large nuclear reactor designed for

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experimental studies, thermal or slow neutrons became available in sufficient quantity to permit certain biological investigations. The development of procedures to achieve neutron capture therapy was among the first projects of the Medical Department. While engaged in studies of the kinetics of distribution of solutes through body water and a search for a suitable carrier for a capture element, we learned of the significant work of Sweet and associates[5,13] since published on boron distribution in brain tumors and normal brain of patients. The work herein reported is a collaborative effort beginning in 1951 of the group at Brookhaven and the group at the Massachusetts General Hospital to apply in a practical manner the advantages of neutron capture to therapy of glioblastoma multiforme. These studies, involving a very considerable effort by a large number of people, could not have been done without the generous assistance of members of the Reactor Science and Engineering, the Health Physics and Instrumentation, and the Chemistry Departments of Brookhaven, and members of the technical and nursing staffs of the Medical Department at Brookhaven. It is a pleasure to acknowledge the vital assistance received from these groups.

During the past two years 10 patients with proved glioblastoma who had been operated upon at the Massachusetts General Hospital were transferred to the Brookhaven National Laboratory for neutron capture therapy. Glioblastoma has to date proved refractory to treatment surgically or by means of conventional radiation therapy and therefore a new approach to control is justified in this surely fatal disease. On each patient studies were done at operation on boron distribution between tumor and normal brain. The patients were then observed for a preirradiation period at Brookhaven, followed by neutron capture therapy at appropriate intervals.

A limited number of elements have the capacity to capture thermal neutrons with subsequent disintegration by emission of an alpha particle. B^{10} is one of the most favorable to select because it has a large thermal neutron capture cross section of 3,990 barns.[8]

Commercial boron is composed 81 per cent of B^{11} and 19 per cent of B^{10}. The B^{11} has a cross section of 4.5 millibarns and a neutron capture results in a neutron-gamma reaction which is unsuited to our purposes. This makes imperative the use of B^{10} as the only suitable boron isotope for thermal neutron capture therapy of the type we have envisaged. We obtained from the Atomic Energy Commission Laboratory at Oak Ridge an enriched preparation containing about 96 per cent B^{10} and only 4 percent of B^{11}. From this enriched mixture of metallic boron, borax was synthesized at first in the Chemistry Department at Brookhaven by Dr. H. A. Finston[3] and later in the Medical Department.

The alpha particles resulting from the B^{10} reaction ($B^{10}+n^1 \rightarrow Li^7+\alpha^4$) have an energy permitting penetration of tissue to a depth of only 9 microns.[1] Therefore if the boron distribution be limited to the tumor area highly selective local radiation of great biological effectiveness can result. This, if sufficient in intensity, may result in annihilation of the tumor structures while leaving surrounding normal tissue intact because of the very limited penetration of the alpha particle radiation.

The physiological assumptions made by us in this therapy are few and simple. When a soluble substance is injected intravenously it will distribute in a characteristic manner throughout the body water. Its distribution may be limited to extracellular fluid or it may distribute between intracellular and extracellular fluid in a distinctive way. The concentration of the material in any given tissue water at any given time will be determined by qualities of that tissue and of the injected substance. In the central nervous system most substances pass through the capillary walls slowly, exhibiting an effect of what has been termed the blood-brain barrier. In glioblastoma there occurs within the tumor a destruction or disappearance of the blood-brain barrier, thereby permitting certain solutes to distribute through the tumor mass at a more rapid rate than through normal brain. Eventually equilibrium will obtain but during the pre-equilibrium period there will exist for a variable but short interval of time a significantly greater concentration of such an agent in tumor water than in normal brain tissue water (Fig. 1). Exposure of this volume to neutrons during this pre-equilibrium period permits neutron capture to proceed in the tumor with resulting radiation to its structure, while surrounding normal tissue is unaffected because of the low concentration of capture element. Thus a precise knowledge of the time-concentration relationship existing among components of what may be designated as a three-compartment system may make possible selective radiation of a given type of tissue beyond its radiation tolerance. These bases are discussed more fully elsewhere.[2]

Calculations which have been made at Brookhaven and data which have been obtained by Sweet at the Massachusetts General Hospital suggest that in the case of boron administered intravenously a maximum concentration is reached in tumor tissue about ten to fifteen minutes after injection.[13] It is estimated that thereafter for a period of at least forty-five minutes the concentration differences between tumor and normal brain are such as to permit effective neutron radiation for capture therapy.

A facility for medical neutron radiation has been provided in the reactor at Brookhaven. By removing a part of the shielding over the top of the reactor it was possible to provide a radiation port of presumably sufficient flux without undue exposure of the whole body. The general details of this facility are shown in Figure 2.

Effective irradiation of the tumor is dependent upon the neutron flux, the concentration of capture element and the time of exposure. Rather extensive studies reported in detail elsewhere[9] have been

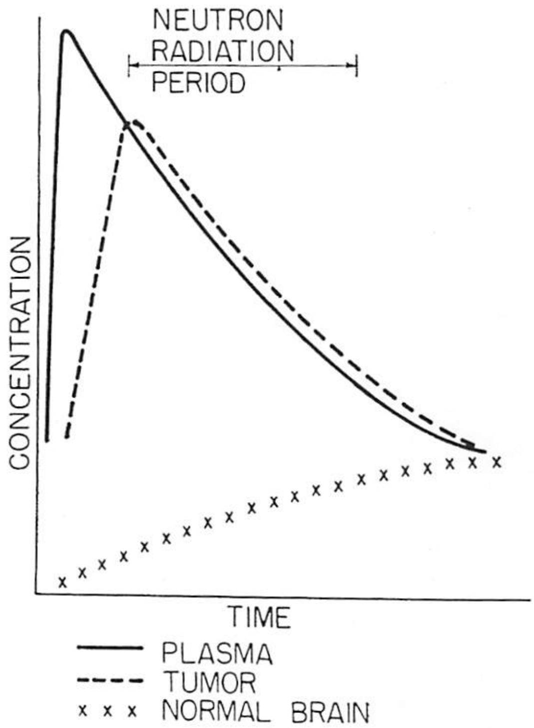

Fig. 1. Relationship with time between plasma concentration, tumor concentration and normal brain concentration of boron following intravenous injection of boron. The maximum tumor concentration is shown at approximately twelve minutes post-injection and a neutron irradiation period of forty minutes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

done with phantoms made of tissue equivalent plastic and tissue equivalent liquid, together with observations of activation of gold wires placed externally on the patient's head and inserted within the head at various levels about the tumor. From these data it has been possible to construct a first approximation of isodose curves. A summary of this is shown in Figure 3.

Immediately prior to irradiation the borax solution was injected intravenously in a volume of 100 milliliters. The dose of borax averaged 20 grams, which provided from 19 to 46 milligrams of boron per kilogram of body weight. Injection time averaged about seventy-five seconds and, immediately upon completion of the injection, the patient's head was fixed in the proper position over the radiation port with cotton web straps weighted by lead

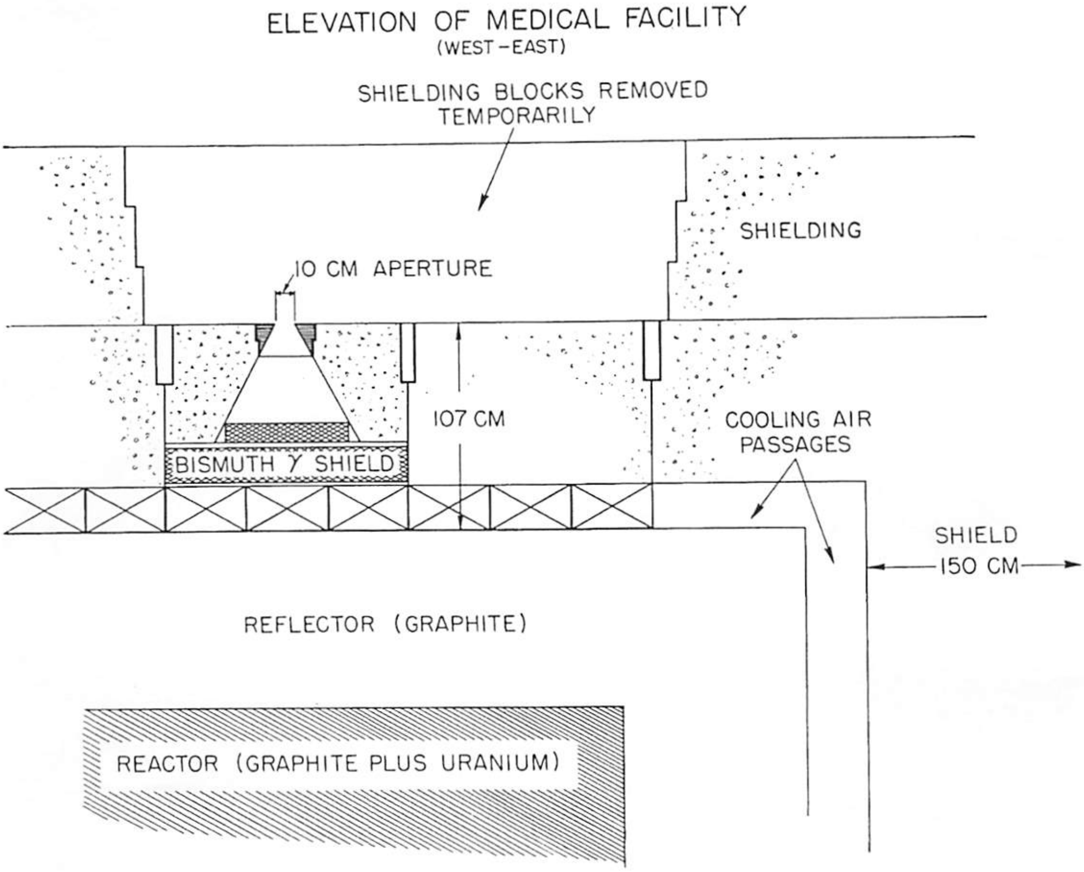

Fig. 2. Schematic diagram of facility at the reactor showing relations of shielding to source of radiation.

bricks. The reactor was then brought to full power as rapidly as could be done with safety. About eight to ten minutes were required for this operation. Our estimations of the occurrence of maximum concentration of boron in the tumor were also ten to twelve minutes postinjection. Approximately a thirty to forty minute period of neutron radiation was then given, with the major exception of the first patient who received only seventeen minutes of irradiation.

The treatment of the patients is divided into two series—the first, comprising 5 patients receiving only a single neutron irradiation followed by a period of observation to determine if any untoward effects developed, and the second, comprising again 5 patients who received from two to four irradiations.

Since our hypotheses for conditions of treatment are predicated upon an intact blood-brain barrier, it became necessary to make observations upon the effect of neutron radiation upon this barrier. Observations made first upon dogs showed no demonstrable effect on the barrier by up to ninety minutes of neutron radiation. Subsequently we observed the effects on 3 patients through multiple irradiations measuring the blood-ventricular fluid barrier as a standard. The rate of appearance of radioactive sodium, chloride, bromide and phosphorus and the nonappearance of inulin and sucrose in ventricular fluid were observed. No significant changes occurred,

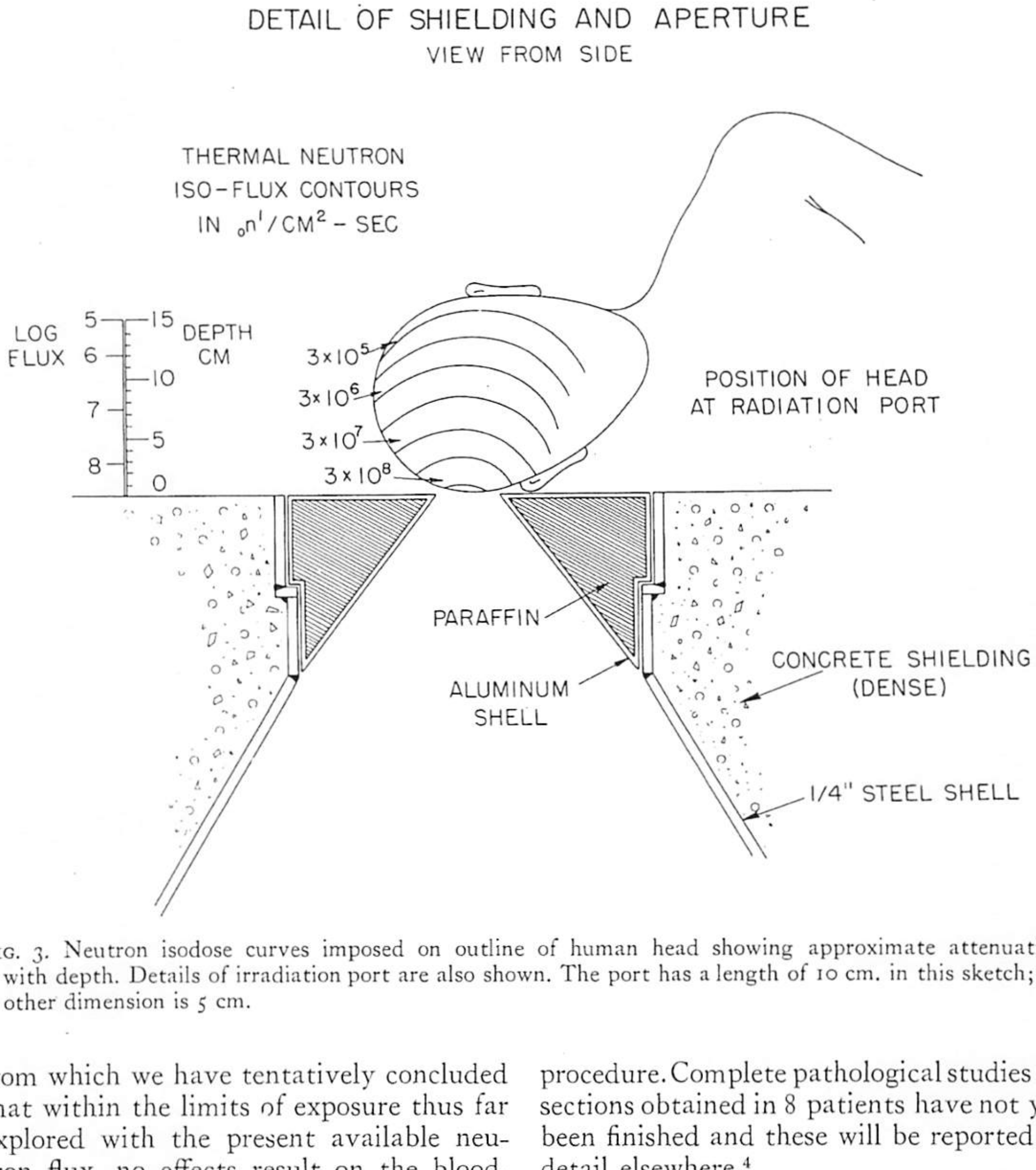

Fig. 3. Neutron isodose curves imposed on outline of human head showing approximate attenuation with depth. Details of irradiation port are also shown. The port has a length of 10 cm. in this sketch; its other dimension is 5 cm.

from which we have tentatively concluded that within the limits of exposure thus far explored with the present available neutron flux, no effects result on the blood-brain barrier. These studies are being reported in detail elsewhere.[7]

RESULTS

In the series of patients thus far treated by this method no conclusive results have been obtained and all 10 patients are now dead. However, rather uniform clinical responses were observed in our patients and all of these suggest that tumor growth was at least retarded to some degree by the procedure. Complete pathological studies on sections obtained in 8 patients have not yet been finished and these will be reported in detail elsewhere.[4]

In the first group of 5 patients, each receiving a single neutron treatment, the results will be discussed chronologically in the order of their treatment.

Patient No. 3977 (P. J.) was a fifty-one year old woman upon whom craniotomy three months previously had revealed an inoperable glioblastoma involving the temporal lobe. Prior to neutron capture therapy the patient's course appeared to be slowly progressive, most marked in deterioration of speech understanding, so

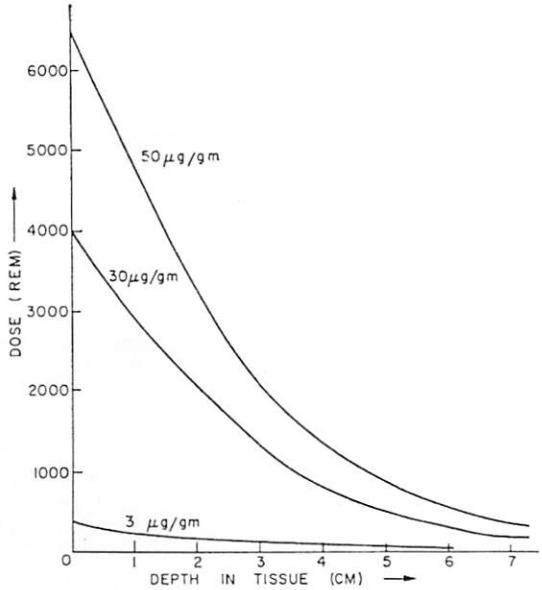

FIG. 4. Depth dose of radiation delivered by the B^{10} n alpha reaction assuming an incident skin flux of 3×10^8 n/cm²/sec., a radiation exposure of forty minutes and a relative biological efficiency of alpha particles of 20. The radiation dose for each of three concentrations of B^{10} is shown.

that for four weeks prior to therapy she was unable to communicate except for indication of body needs to the nursing and medical attendants. On February 15, 1951, after intravenous injection of 1.59 grams of B^{10} as borax, she was irradiated for seventeen minutes during which period a total of 0.44×10^{12} neutrons per square centimeter reached the presenting skin surface. Within several days after treatment she could speak effectively, relate incidents which had occurred prior to treatment, and could respond to requests effectively. Motor incapacities in the right arm changed little but the patient desired to be and was ambulatory contrasted with previous unwillingness to get out of bed. Approximately six weeks post-treatment, progressive and definite deterioration set in; the patient became bedridden; the capacity for speech was lost and motor function of the right arm disappeared. Sixty-three days after irradiation, papilledema was noted and the patient suffered a series of jacksonian seizures. On the sixty-fifth day after irradiation she became comatose and died on the sixty-seventh day with signs of increased intracranial pressure. This was approximately fourteen months after beginning of initial symptoms and five months after the diagnosis had been made.

Patient No. 4055 (W.L.), a thirty-eight year old man, developed first symptoms one month prior to surgical exploration which revealed an aggressive glioblastoma involving the left temporal lobe. Only 75 per cent of the tumor was excisable. For thirty-seven days postoperatively the patient had shown rather rapid deterioration with signs of increased intracranial pressure despite decompression, and one week before irradiation survival for more than a few days appeared very doubtful. Immediately prior to irradiation, insertion of beta probe counters used to localize the lesion resulted in total aphasia. A dose of 1.7 grams of B^{10} as borax was given intravenously and the patient was irradiated for thirty minutes and received a total neutron dose of 1.42×10^{12} neutrons per cm.[2] at the skin surface. For the first twenty-four hours following irradiation an increase in pre-existing right-sided weakness and in the size of the decompression was noted. Thereafter there was progressive improvement so that within several days he was able to stand unaided, could speak a few words, understood clearly commands given and showed a return in size of the decompression to pre-treatment levels as evidenced by cephalic circumference. For the next three weeks there was no increase in head circumference, after which increase in size of the decompression was noted and deterioration in performance developed. Because of increasing intracranial pressure, he was returned to the Massachusetts General Hospital for re-exploration, which was done. No further improvement resulted from removal of a large mass of tumor sixty days after irradiation, and the patient died ninety-three days after irradiation.

Patient No. 4045 (G.F.), a sixty year old man, was operated upon one month prior to admission and extensive resection of the right parietotemporal and occipital lobes was carried out with residual tumor existing. Prior to irradiation, and following operation, the patient improved generally for one month but without specific neurological betterment. During the two weeks before irradiation he developed severe headaches and showed increased cerebrospinal fluid pressure. He was treated on March 22, 1951, receiving 1.47 grams of B^{10} borax intravenously followed by irradiation for thirty minutes, receiving 1.46×10^{12} neutrons per cm.[2]

at the skin. Treatment was uneventful. No change in the gradual deterioration was noted following irradiation and the patient developed clinical signs of tumor in the left hemisphere. Increased cerebrospinal fluid pressure became more prominent and death occurred forty-three days following irradiation. Gross autopsy findings showed extensive tumor extension to the left side.

Patient No. 4202 (J.M.), a fifty-four year old man, was operated upon 125 days prior to irradiation and one month following onset of symptoms. A very extensive excision of the right temporal, parietal and occipital lobes was carried out. Postoperative recovery was uneventful and, except for a hemianopsia and minimal impairment of the left extremities, the patient was admitted to Brookhaven in good condition. On June 14, 1951, he was given 1.69 grams of B^{10} as borax intravenously, irradiated with neutrons for thirty minutes for a skin dose of 1.42×10^{12} neutron per cm.^{2} The procedure was well tolerated but on the fourth postirradiation day the onset of lethargy was noted which progressively increased rapidly. Lumbar puncture yielded bloody fluid at increased pressure and withdrawal of fluid resulted in relief of symptoms. Within twelve hours a second tap was required and thereafter repeated taps were necessary to control the increased cerebrospinal fluid pressure. Blood gradually disappeared from the fluid but the patient slowly became progressively worse and died 126 days postirradiation.

Patient No. 4227 (A.R.), a forty-seven year old man, was operated upon 152 days prior to admission and one month after onset of symptoms. A large cystic tumor involving the parietal and occipital lobes was removed but P^{32} studies at the time of operation indicated remaining tumor in the thalamic area. On admission to Brookhaven Ntaional Laboratory Hospital the day before irradiation the patient showed only left-sided impairment of sensation and an incomplete left-sided hemianopsia. Speech, reading, thought and memory were unimpaired and he had successfully been carrying on his profession of college teaching. Following pneumoencephalography, 1.69 grams of B^{10} borax given intravenously, he received thirty minutes' irradiation for a total skin neutron dose of 1.42×10^{12} neutrons per cm.^{2} He had exceedingly severe headache persisting for six days. Ten days after irradiation he appeared unchanged from admission. No elevation of cerebrospinal fluid pressure was found before treatment. Immediately following discharge the patient left on a trip to South America. On August 15, 1951, two months postirradiation, he suffered recurrence of headaches and underwent a retrogressive course to death 100 days after radiation treatment.

To recapitulate the results in the first 5 patients, each of whom was given a single neutron irradiation: In one patient, No. 3977 (P.J.), there had occurred a striking clinical improvement to the observers at the bedside which was maintained for approximately six weeks. In a second patient, No. 4055 (W.L.), there was a temporary cessation in enlargement of the decompression area lasting about three weeks. In the third patient, No. 4045 (G.F.), in whom no improvement was recorded, the unsuspected tumor growth contralaterally, in an area where attenuation of the neutron flux precluded any possibility of therapeutic effect, provided an excellent control on immediate effects and susceptibility of the observers to suggestion. In patients four, No. 4202 (J.M.), and five, No. 4227 (A.R.), no assessment of treatment was possible. It was obvious at this time that more than one thermal neutron irradiation would be required.

The second group of 5 patients each received multiple neutron irradiations.

Patient No. 4653 (A.B.), a fifty-eight year old man, suffered an attack with loss of consciousness for a few minutes, twenty-four days prior to craniotomy at the Massachusetts General Hospital on October 26, 1951. No symptoms preceded this first attack. At operation a resection of the frontal lobe extended medially to the falx and included all but the precentral, inferior frontal and posterior part of the orbital gyri. Postoperative recovery was good and he was admitted to Brookhaven National Laboratory Hospital on December 11, 1951. At this time speech and intellectual facilities were not impaired. Weakness was present in the left arm and leg and the patient complained of pain in the left upper arm. On December 13, 1951, he was given 2.02 grams of

B^{10} as borax followed by thermal neutron irradiation for a neutron skin dose of 1.47×10^{12} neutrons per cm.[2] No pneumoencephalography was done. Following irradiation the patient was alert, had less arm pain and walked about during the day. Three days after exposure a mild dermatitis over the area exposed to the irradiation was noted. He was discharged home December 18, 1951, in good condition.

He was readmitted January 7, 1952, and during the intervening three and a half weeks had grown much weaker, was not able to walk without assistance from two people and had suffered increasingly severe pain localized in the left upper arm. On admission there was now marked weakness on the left side and the patient was not oriented as to time or place. Speech was markedly slurred. Patient had great difficulty in concentration. On January 8, 1952, he was given 2.12 grams of B^{10} as borax intravenously and received a neutron skin dose of 1.93×10^{12} neutrons per cm.[2] A pneumoencephalogram was not done prior to treatment. Following therapy the patient became alert and briskly cooperative. By January 16 he was walking without assistance and with only a slight shuffle in his gait. He was discharged home on January 25 with evidences of definite skin reaction over the neutron exposure area over which epilation of second growth hair was now seen.

He was readmitted March 10 and it was evident that the postirradiation improvement in sensorium and muscle strength on the left had been maintained during the interim. Pain in the left arm had grown more severe and the patient still had seizures, but infrequently. He had continued throughout on dilantin therapy. On March 11, without antecedent pneumoencephalography, he was given 2.12 grams of B^{10} as borax intravenously followed by his third neutron irradiation for a neutron skin dose of 0.93×10^{12} neutrons per cm.[2] On discharge he was alert, cheerful, witty and enjoying life. The severe pain in the left arm had disappeared by the third postirradiation day so that demerol previously given, 50 mg. t.i.d., to control the arm pain, was discontinued and no analgesic therapy was required. The patient was discharged March 18 and for at least four to five weeks remained as above while journeying about Florida.

He was readmitted on April 24, 1952. At this time the patient was retarded in thought and speech. Neurological examination showed no change from the previous admission except for continued absence of pain in the left arm and the recent occurrence of episodes of hypesthesia of the left heel. On April 25 the patient was given his fourth neutron capture therapy, again without antecedent pneumoencephalography. For this treatment he received 1.69 grams of B^{10} as borax intravenously and a neutron skin dose of 0.98×10^{12} neutrons per cm.[2] The patient was lethargic after treatment and became somnolent with generalized weakness developing over the following ten days. Psychic depression was marked. A rise in temperature to 39° C. on the fifth postirradiation day was seen without ascertainable cause. On discharge May 9 the patient showed considerable generalized weakness, lethargy, hypesthesia and hypalgesia on the left, a definite left lower facial weakness and a distinct retardation of thought and speech. During the next month the course was retrogressive and the patient died on June 15, 1952. An autopsy was done.

Patient No. 4737 (T.F.), a fifty-nine year old man, was first operated upon June 20, 1949, when a temporo-parieto-occipital lobectomy for glioblastoma multiforme was done at the Massachusetts General Hospital. Symptoms of severe headaches began about April 25, 1949. Following operation, which was presumed to be total extirpation of the neoplasm, the patient was able to carry on his work and felt well. He had a left homonymous hemianopsia, an absent left ankle jerk and a positive left Babinski. The patient did well until September, 1951, when headaches recurred. He was operated upon November 14 and a cystic cavity containing 50–60 ml. of fluid was aspirated. This occupied the volume of the previous resection. In the posterior inferior part of the right temporal lobe remnant frank neoplasm was removed. On January 10, 1952, further removal of cystic wall and tumor was carried out.

The patient was admitted to Brookhaven National Laboratory Hospital on February 8, 1952. At this time he had an unsteady gait, was rather confused; his memory was poor and some neurological changes were noted on the left side. He received 2.12 grams of B^{10} as borax intravenously on February 12, 1952, and was irradiated for thirty minutes with thermal neutrons for a skin dose of 0.86×10^{12} neutrons per cm.[2] No encephalography was done. He was discharged home February 19 essentially unchanged from admission neurological examination.

He returned to the hospital on May 9, 1952. During the intervening period he had appeared improved to his family, being more self-reliant and responsive for seven weeks, and then in the subsequent three weeks had failed rapidly to the point where he was no longer able to walk, to sit up without support or to use his left arm or hand effectively due to sensory deficits. He had become somnolent and devoid of initiative. Significant admission findings were poor articulation of speech, almost complete sensory loss on the left side and generalized weakness. Coordination was particularly weak on the left and was also imperfect on the right. On May 2 he was given 2.12 grams of B^{10} as borax intravenously and irradiated with thermal neutrons for a neutron skin dose of 0.70×10^{12} neutrons per $cm.^2$ He improved rapidly after treatment and on discharge seven days later was able to stand alone, walk with assistance, feed himself, and made effective use of his left hand in manipulating matches, cigarettes and newspapers. At home he continued to improve as above until the end of the month when over a two day period he became weak and ataxic with headaches and was unable to sit up even in bed. Nausea became prominent and he was hospitalized in Concord, New Hampshire, on June 2. A large dose of demerol was given and after sleeping twenty-four hours the patient awoke refreshed, alert and with no headache. Subsequently, speech, movement and coordination improved but periods of mental confusion persisted. The patient then gradually deteriorated to death on June 27, 1952. Autopsy was obtained.

Patient No. 4709 (P.P.), a fifty-four year old man, developed memory loss and mental confusion at the end of December, 1951. He was operated upon January 11, 1952, and a left anterior temporal lobectomy with subtotal removal of glioblastoma multiforme was carried out. Recovery from operative procedures was satisfactory and on January 22, 1952, he was admitted to Brookhaven National Laboratory Hospital. His general condition was poor. During the next two months there was little change in the patient's condition. He was semicomatose most of the period but for short intervals on occasion could comprehend requests and demands. A right hemiparesis was present. Increased intracranial pressure required frequent taps. On February 14 and 25 radioactive argon (A^{41}) was injected into the tumor area after removal of fluid. There was no change noted in his slowly progressive course. Preneutron therapy examination on April 8 showed a stuporous, hemiparetic man with normal vital signs and good vegetative functions. On this date 2.12 grams of B^{10} as borax were injected followed by thirty minutes of neutron irradiation for a neutron skin dose of 0.93×10^{12} neutrons per $cm.^2$ During the first two weeks following this treatment the patient appeared to lose his usual lethargy and to be alert and agitated. He made jaw movements suggestive of talking. Increased intracranial pressure again demanded frequent taps to prevent excessive pressures. This did not appear to be exaggerated nor decreased following treatment.

On April 22 he was given his second neutron treatment. For this he received 2.12 grams of B^{10} as borax intravenously and a neutron skin dose of 0.70×10^{12} neutrons per $cm.^2$ The third post-treatment day the patient appeared very toxic with elevation of the white blood cell count, decreasing hemoglobin and marked increase in intracranial pressure with low blood pressure. Transfusions, ventricular taps and supportive therapy carried him over a difficult three week period. On May 12, because of further deterioration, ventricular taps were discontinued and the patient went into deep coma. Following the second irradiation an infection of the area of dermatitis over the exposure field had developed and was treated locally. Healing, though slow, was steady. Despite clear evidences of extension of the tumor contralaterally it was decided to treat the patient a third time with neutrons and this was done on June 20. Before treatment the patient showed shallow, rapid respirations, gray color, and several times during the day required stimulants. Borax injection of 2.12 grams of B^{10} and treatment that evening were, however, well tolerated, and following treatment he appeared in unexpectedly good condition with satisfactory vital signs. The neutron skin dose for this treatment was 0.72×10^{12} neutrons per $cm.^2$ However, the patient declined steadily and on July 11 was noted to be deeply jaundiced. A diagnosis of serum hepatitis was made. The patient's condition grew rapidly worse and death occurred July 14, 1952. An autopsy was obtained.

Patient No. 5227 (J.H.), a fifty year old woman, in April, 1952, noted that she was failing and seemed tired and apathetic. In August, 1952, she had a seizure, again in September, and several in the next few weeks. She was admitted to Baker Memorial Hospital, Boston, on October 2, 1952. The patient was diabetic and also had rheumatoid arthritis. On October 4, 1952, a partial left frontal lobectomy was carried out to remove a glioma. The tumor was over 6 cm. in diameter. Postoperative recovery was satisfactory and she was discharged on October 20.

She was admitted to Brookhaven National Laboratory Hospital for the first time on November 4, 1952. Her general condition seemed good except for a severe mixed aphasia, slight right hemiparesis, moderately severe diabetes and chronic rheumatoid arthritis. Her first boron-neutron treatment on November 7 was well tolerated. She received 2.12 grams of B^{10} as borax intravenously and a neutron skin dose of 0.91×10^{12} neutrons per $cm.^2$ It was noted on the seventh postirradiation day that her general condition was about the same as on admission except for the impression that she was brighter and mentally more alert. There was a slight residual edema about the left side of the head associated with erythema and pigmentation. She was discharged on November 19 with no clear change in her neurological status. On December 1 she was readmitted. During the intervening three weeks she had developed increased weakness on the right and frequent urinary incontinence. She appeared more alert than on the previous admission, was cheerful and communicative and although her aphasia was severe her vocabulary seemed to have increased and she was speaking in more coherent phrases. On December 5 she was given her second treatment despite belief that her neurological condition was rapidly deteriorating. For this treatment she received 2.12 grams of B^{10} as borax intravenously and a neutron skin dose of 0.82×10^{12} neutrons per $cm.^2$ On the sixth postirradiation day it was noted that she was somnolent most of the time. On January 7, 1953, thirty days after treatment, she was in precarious condition. This was believed due to thalamic invasion by the tumor and atelectasis at the base of the left lung. After slight improvement in general condition following hemotherapy on January 9 she was given her third neutron irradiation. For this she was given 2.02 grams of B^{10} as borax intravenously and received a neutron skin dose of 0.80×10^{12} neutrons per $cm.^2$ The treatment lasted thirty-five minutes and was well tolerated. Subsequently hemotherapy, digitalization and oxygen were required but without avail and the patient died on January 12. Autopsy was obtained.

Patient No. 5144 (A.H.), a thirty-three year old woman, developed diplopia, severe headaches and left-sided weakness in April, 1952. On May 12 a right parietal craniotomy was done with removal of a large cerebral glioblastoma multiforme. On June 27 a second craniotomy was done to remove all additional identifiable neoplastic tissue. Following this second extensive resection the patient made a postoperative recovery and was admitted for the first time to Brookhaven National Laboratory Hospital on September 10, 1952. The patient had no specific complaints and was cooperative although almost totally helpless with a left hemiplegia, a left homonymous hemianopsia and an indwelling catheter because of bladder hypertonia and poor control. Her recent memory showed gross impairment. The large decompression area was soft.

On September 12 she was given 2.12 grams of B^{10} as borax intravenously and irradiated for forty minutes. Neutron skin dose was 0.96×10^{12} neutrons per $cm.^2$ By discharge on October 8 she was alert (for her) and well oriented. This had developed within the first two days after treatment. She could partially feed herself and could smoke a cigarette by herself. The left lower extremity could be adducted and the fingers of the left hand extended. Epilation began fourteen days after irradiation and a definite dermatitis, dry and scaly, was seen at the time of discharge.

She was readmitted on November 5. Her condition was essentially unchanged except for increase in weakness on the left side, less vision and increased sensory loss. On November 7 she was given her second neutron capture therapy; 2.12 grams of B^{10} as borax were given intravenously and a neutron skin dose of 0.91×10^{12} neutrons per $cm.^2$ By November 10 erythema of the exposed area was marked and later this area broke down, became infected and healed slowly. Assessment on December 11 showed improvement. Tests were performed better than before, an equivocal Babinski had disappeared, right abdominal reflexes had returned, there was less facial weakness and reflexes on the right side were more normal. The patient continued to be more alert. On January 9, 1953, she was again treated with 2.12 grams of B^{10} as borax given intravenously and a neutron skin dose of 0.96×10^{12} neutrons per cm.[2] Little change was noted in the patient following this treatment. On February 6 she received her fourth neutron radiation after a similar B^{10} injection. The neutron skin dose on this occasion was 0.90×10^{12} neutrons per cm.[2] The treatment was well tolerated but no change in the patient's condition could be firmly detected. On the afternoon of February 11 the patient suddenly became stuporous with elevation of blood pressure to 170/90 but no elevation of intracranial pressure. She remained semi-stuporous, failed to respond to drugs and died that evening. Autopsy was obtained.

Considering as a group the 5 patients who received multiple neutron capture treatments, it is our belief as observers of these patients at the bedside that in 3, No. 4653 (A.B.), No. 4737 (T.F.), and No. 5144 (A.H.), there was temporary evidence of improvement following one or more of the irradiations. In patient No. 4709 (P.P.), the results were equivocal but possible betterment may have occurred following treatments one and three, while in patient No. 5227 (J.H.) we observed no improvement following any of the three exposures. The best results were seen in No. 4653 (A.B.) who received the largest total neutron dose and at the highest rate. Statistically there was no evidence of significant prolongation of life in these patients, though particularly in No. 4653 (A.B.), who had a tumor with histopathological evidence of rapid growth at the time of operation, and with initially an apparently rapid retrogressive course, events during the period of treatment suggested a real prolongation of life in this individual. We are aware of the difficulties of immediate prognosis in these patients and for purposes of therapeutic evaluation have endeavored to require some definitely objective sign of improvement, such as relief of pain sufficient to permit discontinuation of analgesic drugs such as occurred in No. 4653 (A.B.), or marked improvement in muscular coordination without specific training such as occurred in No. 4737 (T.F.). The absence of conclusive results in this series of patients may well be explained by a consideration of probable dosage which is discussed in more detail later.

As yet we have not been able to determine with any degree of accuracy the dosage which was delivered to the tumor. Strenuous attempts were made to construct an alpha sensitive probe counter but satisfactory instruments were not developed. Nor do we have accurate analyses of blood during the runs since the patient could not be approached during the neutron exposure. Analyses of tumor tissues taken serially immediately after boron injections are available only for doses of 0.5 gram of B^{10} given as borax[13] and not in the amounts used during therapeutic trials. Since the neutron dose diminishes significantly with distance from the port, the effectiveness of irradiation is greatly dependent upon position.

Despite all these uncertainties presently existing, some parameters of dosage can be estimated. Relations between boron concentration, neutron flux and dose are shown in Figure 4. The radiation dose resulting from thermal neutron capture by the B^{10} has been calculated by us in REM (roentgen equivalent man). The REM as used herein is obtained by multiplying the energy absorbed in the tissue by the RBE (relative biological effectiveness) which is taken as 20 for the alpha radiation. If one assumes the tumor tissue to lie at a depth from 3 to 7 cm. from the surface of the head, an incident flux of 3×10^8 n/cm^2/sec. will have decreased to 10^8 at a depth of 3 cm. and will be approximately 10^7 at a depth of 7 cm. The radiation dose resulting from thermal neutron capture by the B^{10} at these fluxes will therefore vary from 1.2 REM per minute per microgram B^{10} per gram of tissue at 3 cm. depth to 0.12 REM per minute per microgram B^{10} per gram of tissue at a 7 cm. depth. For each thirty minute treatment period there will then be delivered 36 REM per microgram of B^{10} per gram of tissue. The boron dose in our patients ranged from 20 to 46 micrograms per gram body weight and assuming an average tumor concentration of boron of these values during the treatment, a reasonable conservative assumption, the dosage delivered to the tumor structures from boron alone would amount to from 720 to 1,756 REM at a depth of 3 cm. with the flux available. At a 7 cm. depth the dose will decrease to one-tenth of this value. We believe from clinical considerations alone that the dose delivered to the tumor area in these patients was a minimal therapeutic dose and this is in agreement with the above considerations. The maximum probable radiation from B^{10} to normal structures would be one-third of that delivered to the tumor, and in some patients with a better than 3:1 tumor-brain distribution the normal tissue dose will be significantly less. Sweet and his collaborators have observed ratios of 12:1 and 24:1 to exist in these patients. It is apparent that both concentration and flux are critical in attaining satisfactory dosage and we are vigorously studying systems which will give us more information regarding the behavior of boron under these conditions.

The complications of therapy thus far have been few and of relatively minor significance. One group of effects was due to boron and a second to irradiation. The injections of borax were followed uniformly by vigorous retching for a few minutes and not infrequently evacuation of bowels and bladder. A short period of respiratory arrest was noted in 1 patient about one hour after injection and poor color of the patient was seen following the majority of injections. In 2 patients a papular skin rash was noted followed by desquamation in about five to ten days. No untoward effects on renal function were observed.

Following irradiation, erythema of the skin outlining the irradiation port was seen in the majority of runs. A single neutron exposure resulted in temporary epilation, while two or more exposures resulted in permanent epilation over an area somewhat larger than the exposure port. Pigmentation of the skin lying over the irradiation port was uniformly observed. Fragile, parchment epidermis has been seen in 3 patients after their second neutron exposures and, although this area is very susceptible to pyodermic infection after minor trauma, healing was uneventful but slow. Only topical treatment was used. Further irradiation did not aggravate the condition. Two patients who also received multiple irradiation did not show this type of skin response. None of the patients showed it after a single neutron exposure. In 2 patients capable of cooperation, slit lamp examinations of the lens were done and no changes suggestive of cataract formation were observed. Examination was carried out as much as 140 days following the first neutron exposure in 1 patient who received four irradiations. Ordinary ophthalmological examination showed no changes in any of the patients. The longest period of observation was 186 days following the first irradiation. In no patient were significant decreases seen in the number of circulating lymphocytes in the peripheral blood.

SUMMARY

(1) The feasibility has been shown of the use of a nuclear reactor to provide a neutron source for boron-10 capture therapy of glioblastoma multiforme.

(2) A series of ten patients were treated of whom five received a single irradiation; one patient received two irradiations; two patients each received three irradiations, and two patients each received four irradiations. Multiple irradiations were in general given at five to six week intervals.

(3) Temporary amelioration of clinical symptomatology suggestive of retardation of tumor growth was seen to occur following eight of twenty-one capture therapy efforts, questionable improvement in six of the remaining thirteen efforts, and no detectable change following seven of the treatments. Only one of five patients receiving multiple treatments registered no improvement at any time.

(4) Periods of observation of up to six months during which patients received up

to four capture therapy procedures have revealed no serious complications of this therapy.

(5) Further extensive exploration of neutron capture therapy is warranted.

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DISCUSSION

Paul C. Aebersold, Ph.D., Oak Ridge, Tennessee. I welcome the opportunity to discuss this very interesting paper by Dr. Farr and his associates. As one of the group at the Radiation Laboratory, Berkeley, California, who first investigated the biological effects of neutrons and later who attempted fast neutron therapy of patients, I had always hoped, and still do, that in some way neutrons may be used for therapy. Neutrons produce heavily ionizing particles either by collisions with nuclei or by nuclear reactions. They also have special absorption characteristics. Soon after the discovery of neutrons, just over twenty years ago, it was recognized that neutrons would have powerful biological effects and in unique ways. It is unfortunate that this powerful and unique radiation did not immediately lend itself to cancer therapy.

It is gratifying to see this new attempt being made to use neutrons for therapy. Several factors now make for greater possiibilities of success than in the various pre-war attempts.

The first two factors are physical: (1) Enriched isotopes may now be obtained, permitting more tumor dose for a given chemical toxicity; and (2) very intense, highly collimated beams of thermal neutrons are now available from nuclear reactors, thousands of times more intense than from the cyclotron.

The other factors are biological: (1) Treatment in these cases is attempted on the basis of a very short-term, non-equilibrium selectivity, lasting for matters of minutes, rather than on a longer term selective uptake requiring hours to days: and (2) the type of tumor selected, both because of location and capillary characteristics, permits suitable neutron beam penetration and selective localization.

It should be pointed out that using an enriched isotope does not increase the selectivity; the isotope will have the same increased enrichment in all tissues. Using five-fold enriched B^{10} does, however, mean that the amount of boron required in the tumor need be only one-fifth as much as with normal boron. The enriched isotopes Li^6 and U^{235} have also been investigated by some experimenters as potential materials for neutron capture therapy. Should any other isotope look feasible, we could no doubt now concentrate it by methods developed during World War II.

The penetration in tissue of a slow or thermal neutron beam is fairly limited. Using a beam with an energy spectrum extending from thermal to higher energies would permit greater penetration. I would like to ask Dr. Farr what are the *optimum* as well as the *limiting* depths of treatment with the present Brookhaven beam, and to what extent these might be increased.

As Dr. Farr pointed out the alpha particle in the B^{10} reaction penetrates only 8 microns of tissue. This is less than cellular dimensions and means that for the B^{10} to be effective it must either get inside the tumor cells, on the surfaces of the cells, or in the intercellular fluid immediately surrounding the cells. Although ionic movement into cells can be rapid, I wonder whether the B^{10} in these cases gets into the tumor cells themselves in sufficient concentration to produce the destruction internal to the cells or whether most of the effect is from external bombardment. I would like to ask whether studies have been made of the detailed cellular distribution of the B^{10}.

In this connection, since there are no radioisotopes of boron to use for tracer studies, I wonder whether a secondary type of radioautograph would be possible for studying B^{10} distribution. The tissue sections containing B^{10} could be mounted next to a photographic emulsion as for a radioautograph and then irradiated with thermal neutrons; the alpha particles ejected from the B^{10} into the emulsion should show the B^{10} distribution.

It should be noted that an alpha particle and a lithium nucleus are released in the B^{10} reaction. If it requires release of only one of these particles in a cell to kill it and if considerable B^{10} gets inside cells, then the effectiveness of many of the released particles is lost and the effective dosage should not be figured solely on the total energy released. If most of the killing is due to particles impinging on cells from the surface or outside, then all the particles may be useful in killing and the effective dosage should be calculated from the total energy released. In the calculations of "roentgens equivalent man" given in the tables I wonder whether any such factor related to number of particles was considered and also what factor of relative biological effectiveness was ascribed to the released particles.

It is hoped that the studies mentioned by the authors to provide more accurate information of total integrated dose given to the tumor will soon be completed. These are essential to an understanding of what is happening and will no doubt indicate improvements in technique.

Although all the physical and biological factors have not been worked out and it is too early to discuss clinical results, I believe with the authors that the possibilities for neutron capture therapy are so attractive that further extensive exploration is warranted.

In closing, as a side remark, I wish to say that although the role of reactor thermal neutrons directly for therapy is still to be determined, indirectly these neutrons play a great role. Thermal neutrons in nuclear reactors produce the copious amounts of radioisotopes now so widely used in therapy. As contrasted with immediate use of the neutron reaction in the case of B^{10}, the neutrons in the radioisotope case are stored in an unstable nucleus and do not cause effects until the radioactive disintegrations which take place later.

Dr. Lee E. Farr. Thank you, Dr. Aebersold, for those very kind remarks.

This is an exceedingly complicated problem. We realize that there are very many areas in which our knowledge is sadly lacking, and we hope in the future we may be able to fill in some of these areas. The essential of our concept is that a nonspecific target substance, such as boron, lithium or any other capture element can be used under these circumstances if we know its precise physiological behavior, for then we can be reasonably certain it will be present in the treatment area in requisite concentration at the time of neutron exposure.

In regard to the optimal radiation dose, the optimal dose is higher than what we have been able to give. We are limited in part by the maximum available thermal neutron flux of our reactor. One should probably have a thermal neutron exposure throughout the tumor averaging, let us say, 10^9 neutron, which is higher than we can at present attain. However, by increasing the dose of boron which is given one can in part overcome this difficulty. We are giving 20 gram doses now. This is about 30 micrograms per gram of body weight. We have been able to give seven times this dose in mice, daily for five days, without untoward effects, and we now feel encouraged that we may be able to at least double the dose which may be given to the human.

If we can get a surely certain boron concentration of perhaps 50 micrograms per gram of tumor mass, then the treatment should be effective, even with the present flux.

I should like to ask two of my colleagues who are here to answer two other questions which you brought up, Dr. Aebersold.

Dr. James S. Robertson. Dr. Aebersold suggested the possibility of increasing the effectiveness of this treatment by including some fast neutrons in the beam and depending on the slowing which occurs in the tissue to provide a higher depth dose of thermal neutrons.

Our thinking along this line has been in the other direction; that we should try to keep out fast neutrons. Part of the reason has been the desire to avoid the skin damage from fast neutrons reported by Dr. Stone, Dr. Aebersold and others of the group in California,* although it is true some skin damage has occurred even with the present arrangement.

* Ref. 10, 11 and 12 in present paper by Farr *et al.*

The other factor to be considered is that the number of slow neutrons one can get from fast neutrons is rather small. The flux measures not the number of neutrons involved, but the number of times that they cross a certain barrier. Fast neutrons are counted much more often than slow ones, so you lose a great deal in terms of flux in thermalization.

We have thought that it would be much better to increase the initial dose of slow neutrons than to depend on any slowing down of fast neutrons for the depth dose. Perhaps the best depth dose effects would be attained by the use of epithermal neutrons, those with energies slightly above thermal.

Dr. E. E. Stickley. On the matter of relative biological effectiveness, the curve you have seen was based on a factor of 20, which may seem high, although it is accepted in the literature.

Two things help to justify the use of this factor. One is that we actually achieve a somewhat higher total neutron dose than the case which was reported as typical. Another is that a large part of the energy—or at least an appreciable part—is carried by a lithium recoil particle, which may have an even higher biological effectiveness, being heavier than the alpha particle, and thus giving a denser ionization.

Another question asked by Dr. Aebersold concerned the use of photographic methods to track the alpha particles. We are doing some of this in our depth dose work, but it is still in an early stage.