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BORON-SLOW NEUTRON CAPTURE THERAPY OF GLIOMAS

by

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The type of radiation following capture of slow neutrons presents a possible method for destroying tumor rootlets which remain after surgical extirpation of cerebral neoplasms.

$$\text{BORON}^{10} + \underset{\text{NEUTRON}}{\text{THERMAL}} \longrightarrow \left[\text{BORON}^{11}\right] \longrightarrow \text{LITHIUM}^{7}\ (0.87\ \text{mev}) + \underset{\text{PARTICLE}}{\text{ALPHA}}\ (1.52\ \text{mev})$$

$$B^{10} + n_{th} \longrightarrow [B^{11}] \longrightarrow Li^{7}\ (0.87\ \text{mev}) + \alpha^{++}\ (1.52\ \text{mev})$$

[ ] = *Symbol for unstable compound nucleus*

When the isotope boron 10 captures a slow neutron the ensuing compound nucleus disintegrates at once into a lithium atom and an alpha particle. These share between them the huge energy, 2.4 million electron volts, which is also evolved. But because of the relatively enormous size of the particles they travel only about 8 microns in tissue. Hence, the destruction they cause is confined to the site of the disintegrating atom. The greater the concentration of boron 10 in tumor than in brain, the greater the differential injury to the tumor.

During the last 8 years 140 boron compounds have been studied by SOLOWAY (1, 2, 4, 5, 6) in mice, bearing gliomas, re the differential tendency of the compounds to enter the tumors, and in larger animals as well for their toxicity.

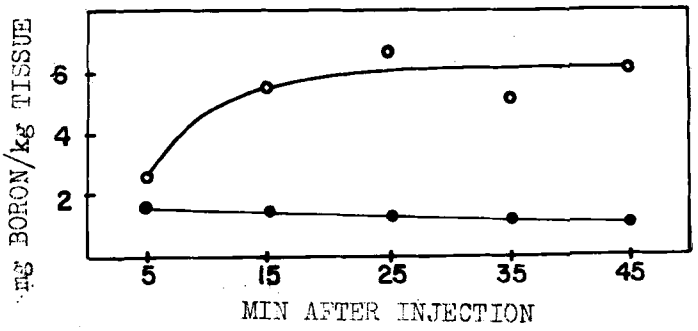


Fig. 1. Boron concentration in man, intravenous injection of 3 mg/kg p-carboxyphenylboronic acid. The curve marked with empty circles represents 17 biopsies in 7 patients with glioblastoma. The curve marked with filled circles represents 15 biopsies in 6 patients with 'normal' brain.

The 6 most favorable of these have then been given intravenously in small doses to patients while they were undergoing craniotomy for tumor. The tumor and any normal brain necessarily removed with it were assayed for boron. Fig. 1 is a plot of boron concentration against time for glioblastoma and for normal brain in man when the compound given was paracarboxybenzeneboronic acid. The tumor to brain ratio 15 to 45 minutes after injection rises slowly from 3 to 1 up to 5 to 1.

De Rougemont and Soloway have demonstrated that the barrier mechanism between blood and normal brain in the dog recovers from the insult of cerebral lobectomy within three weeks.

Hence, we seek in our patients to carry out the irradiation from the boron-slow neutron capture 2 to 3 weeks after the grossly total resection of the tumor. The original wound is completely re-opened in a special operating theatre (Fig. 2) beneath the core of the nuclear reactor of the Massachusetts Institute of Technology. Scalp, muscle and bone, which like tumor take up much boron, are widely reflected in order to minimize radiation injury to them (Figs 3 and 4). We place thin gold foils on cerebral surfaces and tiny gold wires into the depths of the brain.

Following the irradiation, we measure from the radioactivity induced in the gold the slow neutron dose. From these analyses and those for boron uptake obtained at the first operation on each patient, we arrive at a first approximation of the dose due to heavy particles. Moreover, since the slow neutrons penetrate matter poorly we also remove the cerebrospinal fluid at the lobectomy site and if necessary replace it by an air-filled balloon. A tube to the bottom of the field is connected to suction for preventing accumulation of cerebrospinal fluid during the 30 to 105 minute period of irradiation. The patient is elevated to the ceiling portal; we leave the room, but give anesthesia and check the vital signs from the adjoining area outside the concrete shield.

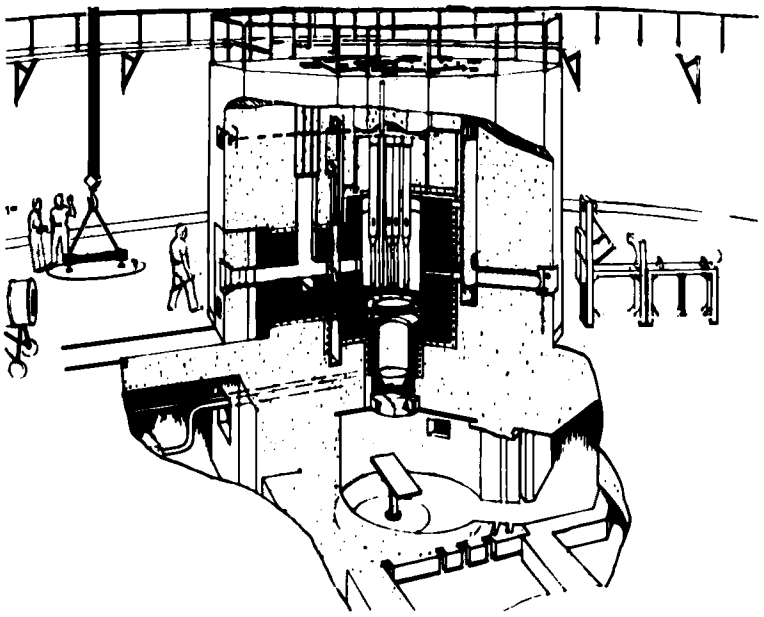


Fig. 2. Cut-away diagram of M. I. T. nuclear reactor. The operating room lies directly below the core of the reactor. A hydraulic lift on the operating table permits elevation of the patient to the ceiling when the wound has been reopened. Shutters above the ceiling portal in the operating room are independently controllable so that all other reactor studies proceed without interference.

Between mid-November 1960 and mid-August 1961 we irradiated 16 patients after intravenous injection of paracarboxybenzeneboronic acid made with boron 10. Eight of these have already died from 2 to 6 months after irradiation, and the post mortem material from 7 of them is still under study. Tentatively, however, we can say that our tactic has not given enough radiation to tumor cells. The dose to neoplasm at the surface of cut face of brain has been steadily increased from 4 000 to 16 000 rad. Normal brain received about 1/3 that amount. Among the 12 patients irradiated between 4 and 10 months ago there is but one excellent result. That we did achieve some destruction of tumor is suggested by a comparison between the next two pairs of figures. The radioarsenic scan of a patient with a glioblastoma just before operation, and the typical residual tumor seen 43 days after a grossly total removal via lobectomy, are seen in Fig. 5. In Fig. 6 are shown the scans of another patient just before operation and 56 days after similar surgery plus reactor radiation 34 days previously. Although almost no tumor can be seen here, it did recur and has since killed the patient.

Fig. 3. General view of the right frontal lobe prepared for radiation. A white circular boron-loaded ceramic cone surrounds the area of exposed brain. The anterior frontal zone of previous tumor removal is filled with an air-inflated balloon (at 8 to 10 o'clock near periphery of inner circle enclosed by cone). This facilitates access of the slow neutrons to the cerebral area containing tumor remnants. Another lithium-filled rubber balloon — 11 to 1 o'clock at periphery of inner circle — protects underlying temporal muscle from neutron radiation. The black flaps hanging down from the outer circumference of the white cone are a boron-loaded plastic to protect the remainder of the head and neck from this radiation.

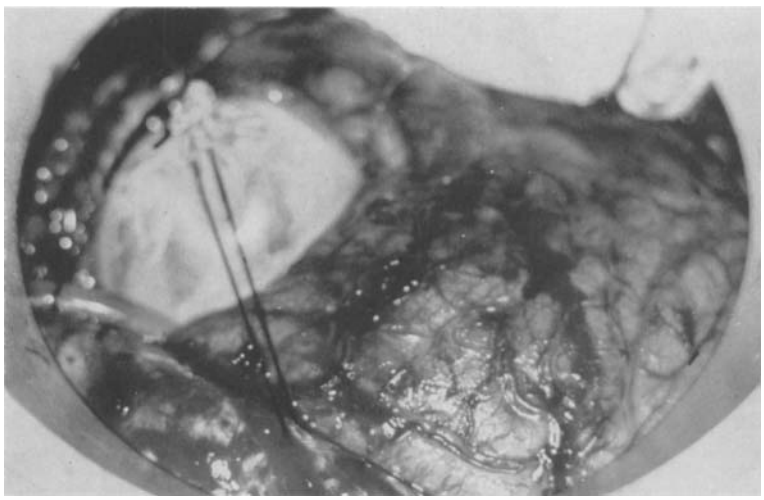
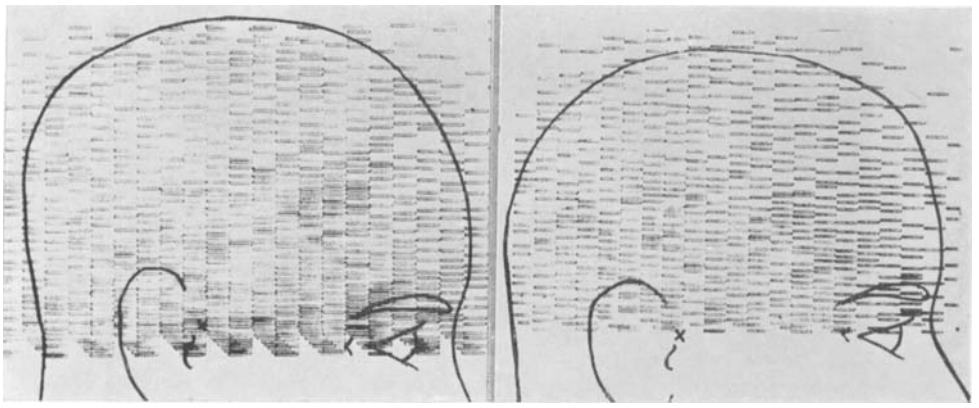


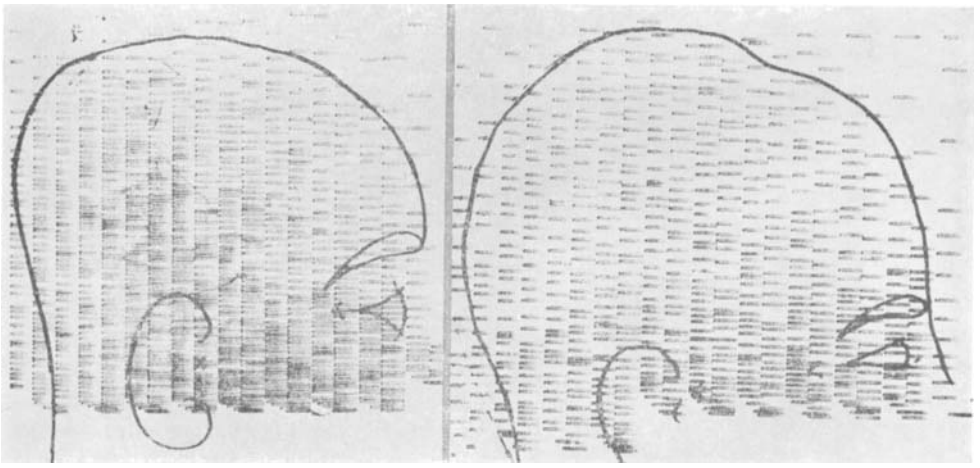
Fig. 4. Close-up view of site prepared for radiation. The air-filled balloon in the area of previous partial lobectomy is anchored in place by a silk suture through the dura reflected medially at the superior midline.



a b

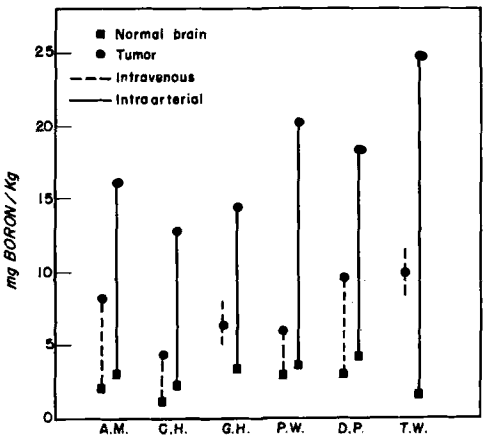
Fig. 5. Positrocephalograms in one and same patient. a) Pre-operatively, of a radioarsenic scan showing dense concentration in a posterior inferior frontal glioblastoma. b) 43 days after grossly total removal of the glioblastoma. Abnormal isotopic uptake in the original area is still recognizable.

In our next series, which has already started with one patient, we are giving sodium perhydrodecaborate, $Na_2B_{10}H_{10}$. Advantages over our previous compound are: (1) this molecule has a far greater percentage of boron, (2) it is less toxic and we have given it in doses up to 50 mg of boron per kg of body-



a b

Fig. 6. Positrocephalograms in one and same patient. a) Pre-operatively, of a radioarsenic scan showing dense concentration in a temporo-parietal glioblastoma. b) 56 days after grossly total removal of tumor and 34 days after boron-slow neutron reactor therapy. More striking reduction in abnormal isotopic uptake than in the non-irradiated patient in fig. 5.



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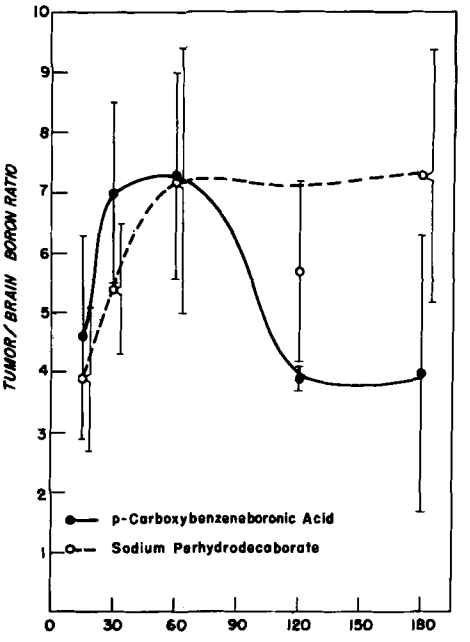

b

Fig. 7. a) Glioblastoma multiforme sodium perhydrodecaborate. Comparison between intravenous and intra-arterial injections of uptake in brain and tumor in human subjects. b) Mice studies with standard deviations. Uptake of two boron compounds by mouse brain and mouse gliomas.

weight without ill effect, (3) it maintains a high tumor to brain ratio of nearly 7 to 1 in mouse gliomas longer than the paracarboxy-compound (Fig. 7a), and (4) it is water soluble at pH 7.4 and can be injected directly into the common carotid artery distal to temporary occlusion of that vessel and with the external carotid tied off (Fig. 7b). In the 6 patients illustrated here, a portion of tumor and contiguous normal brain was removed following intravenous injection of 3 mg per kg of $Na_2B_{10}H_{10}$. Then about 1 hour later the same amount was injected directly into the proximally occluded ipsilateral common carotid artery and the extirpation of the tumor was concluded. We find an average of about 2 1/2 times as much boron in tumor after the second injection, contrasting with 1 1/2 times as much in normal brain thereafter. We have exploited this tactic still further by irradiating our first patient after an injection of $Na_2B_{10}H_{10}$ while both common carotid arteries were occluded. Another favorable change in our physical facility has occurred, namely a doubled output of the reactor from 1 to 2 megawatts, permitting a lowering of the unwanted gamma dose from the reactor core.

Aided by these two major changes we hope our next series of patients will show more satisfactory responses than the first group.

Acknowledgements

We are grateful to the supporters of this research: U. S. Atomic Energy Commission under contract No. At (30—1)—1093, National Cancer Institute, U. S. Public Health Service Grant No. C-3174 Rad., and a grant by the John A. Hartford Foundation on Isotopic Radiation Therapy of Neoplasms.

SUMMARY

The most favorable among 140 boron compounds studied in mice, bearing gliomas, have been checked for their toxity in larger animals, and of these the six best have been finally assayed in man for use in neutron capture therapy by analyses of tissue uptake during craniotomy and by toxicity and excretion studies in terminal glioma patients. An initial series of 16 patients were irradiated, using intravenous injection of paracarboxybenzene boronic acid made with boron 10. Dosimetric and operative techniques are described. Treatment of a second series has begun, using an even less toxic compound, containing far more boron and suitable for intracarotid injection following temporary occlusion of both the common carotid arteries.

ZUSAMMENFASSUNG

Die aussichtsreichsten der 140 Bor-Verbindungen, die an Mäusen mit Glioma studiert wurden, wurden an grösseren Tieren bzgl. ihrer toxischen Wirkung untersucht. Die 6 besten Verbindungen wurden schliesslich am Menschen zwecks Neutronenbestrahlung ausprobiert, wobei die Aufnahme ins Gewebe während einer Kraniotomie, die Toxizität und die Ausscheidungsverhältnisse bei Patienten mit terminalen Gliomen studiert wurden. Zu Beginn wurde eine Gruppe von 16 Patienten unter Anwendung von paracarboxybenzen Borsäure, aus Bor 10 hergestellt, behandelt. Die dosimetrische und operative Technik wird beschrieben. Es wurde eine Behandlungsserie begonnen, wobei eine geringer toxische Verbindung zur Anwendung kam. Sie enthält bedeutend mehr Bor und eignet sich für Injektion in die Arteria carotis im Anschluss an temporären Verschluss beider AA. carotis commun.

RÉSUMÉ

Parmi 140 composés du bore expérimentés sur des souris porteuses de gliomes, les plus favorables ont été testés au point de vue de leur toxicité sur des animaux plus gros. Les six meilleurs de ces composés ont été essayés sur l'homme en vue de leur utilisation pour un traitement par capture de neutrons; cette expérimentation faite sur des malades atteints de gliomes au stade terminal a comporté des analyses de fixation tissulaire au cours de craniotomies et des études de toxicité et d'excrétion. Une première série de 16 malades a été irradiée après injection intraveineuse d'acide paracarboxybenzène borique fait avec du bore 10. Les auteurs décrivent la technique du traitement et de la dosimétrie. Le traitement d'une seconde série a été entrepris avec un composé encore moins toxique, contenant beaucoup plus de bore et utilisable en injection intracarotidienne après occlusion temporaire des deux carotides primitives.

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