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A HISTORY OF BORON NEUTRON CAPTURE THERAPY OF BRAIN TUMOURS

POSTULATION OF A BRAIN RADIATION DOSE TOLERANCE LIMIT

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SUMMARY

Boron neutron capture therapy (BNCT) is a form of radiation therapy mediated by the short-range (less than 10 μm) energetic alpha (^{4}He) and lithium-7 (^{7}Li) ionizing particles that result from the prompt disintegration by slow neutrons of the stable (nonradioactive) nucleus boron-10 (^{10}B). Recent advances in radiobiological and toxicological evaluation of tumour-affinitive boron-containing drugs and in optimization of the energies of neutrons in the incident beam have spurred interest in BNCT. This article presents a history of BNCT that emphasizes studies in the USA. A new dosimetric analysis of the 1959–1961 clinical trials of BNCT at Brookhaven National Laboratory is also presented. This analysis yields an acute radiation dose tolerance limit estimate of ~10 Gy-Eq to the capillary endothelium of human basal ganglia from BNCT. (Gy-Eq: Gray-equivalent, or relative biological effectiveness of a radiation component multiplied by the physical dose of the component (Gy), summed over the component kinds of radiation.)

INTRODUCTION

The existence of the neutron, an electrically neutral atomic particle with a mass equal to that of the nucleus of hydrogen, the proton, was first postulated in Great Britain (Rutherford, 1920). Experimental verification of the concept originated from discovery of radiation with strange properties 10 years later in Germany (Bothe and Becker, 1930*a*, *b*). When alpha particles (energetic helium-4 nuclei) bombarded certain light elements (most effectively, beryllium), electrically neutral radiation with unprecedented penetrability in lead was detected by a Geiger counter. This so-called 'beryllium radiation', at first considered to be ultra high energy gamma radiation, was found to eject protons with energies of up to 4.5 million electron volts from hydrogen-containing materials (Curie and Joliot, 1932). James Chadwick, Rutherford's student and colleague, finally explained the puzzling kinetics of the ejected protons when he suggested that the beryllium radiation was a stream of neutrons (Chadwick, 1932, 1937). He held that the protons resulted from elastic collision of neutrons with hydrogen nuclei. Such collisions are comparable with those of billiard balls. A collision of a fast neutron with a hydrogen nucleus imparts some (on the average, half) of the kinetic energy of the neutron to the nucleus, which recoils as a proton. Enrico Fermi and his associates in Rome discovered that neutrons slowed by passage through paraffin or water are more likely to be absorbed by atomic nuclei than are fast neutrons. The capacities of boron

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and lithium nuclei to absorb slow neutrons were greater than those of any other elemental nuclei examined (Fermi *et al.*, 1934; Amaldi *et al.*, 1935; Fermi, 1939; Stranathan, 1942).

The first observation of charged particles from slow-neutron irradiation of boron was made at Cambridge University on December 10, 1934 (Goldhaber, 1986). Charged particles, including protons, alpha particles and tritons (energetic tritium nuclei), are produced during bombardment of specific stable isotopes of boron, lithium and nitrogen with slow neutrons (Chadwick and Goldhaber, 1935; Taylor and Goldhaber, 1935; Burcham and Goldhaber, 1936).

$$^{10}B + {}^{1}n \rightarrow {}^{7}Li + {}^{4}He$$
$$^{6}Li + {}^{1}n \rightarrow {}^{4}He + {}^{3}H$$
$$^{14}N + {}^{1}n \rightarrow {}^{14}C + {}^{1}H$$

Nuclear reactions such as these were discovered in elegant experiments. Fast neutrons were produced at the rate of about 1×10^6/s when ~100 mg of radium, an alpha and gamma emitter, was mixed with beryllium powder. The mixture was surrounded by lead plates that transmitted most of the fast neutrons so generated and attenuated gamma rays. The neutrons were slowed by multiple elastic collisions with the light nuclei (most effectively, with the hydrogen nuclei) in a layer of paraffin. The slow-neutron target was either a powder applied thinly to part of the inner wall of an ion detection chamber or a gas that filled the chamber. The electrodes of the chamber were connected to an amplifier and an oscilloscope to detect pulses of ionization from reactions between slow neutrons and their targets. The energies of charged particles emanating from a solid target could be estimated by shielding the target with various layers of aluminium and noting the suppression of pulse intensities.

When the neutron capture nuclear reactions became known in the USA, it was proposed that they be applied to radiation therapy by the selective uptake of a suitable isotope into a patient's tumour, followed by slow-neutron irradiation of the tumour-bearing tissue (Locher, 1936). Of the readily available nuclei that can react with slow neutrons to produce short-range ionizing particles and that can be incorporated into a variety of tumour-affinitive drugs, the stable isotope boron-10 (^{10}B) is the most likely to react with a neutron in a slow-neutron irradiation field (Farr and Robertson, 1971).

The first radiobiological studies using the neutron-^{10}B reaction were performed at the University of Illinois in 1938 (B. V. Hall, M. Goldhaber and P. G. Kruger, cited in Kruger, 1940). Within the next few years, several articles described reduced viability of mouse tumour transplants after their exposure to boric acid and irradiation by slow neutrons in vitro (Kruger, 1940) and regression of mouse sarcomas infiltrated with a paste of boric acid powder in sesame oil after their irradiation by slow neutrons in vivo (Zahl *et al.*, 1940). It was realized that there would be clinical advantages to irradiation with neutrons of intermediate energies that could be slowed down further ('thermalized') in the brain, where the slower neutrons would be more likely to react with ^{10}B (Zahl, 1941). Although the use of uranium-235 for slow-neutron capture therapy was foreseen (Zahl and Cooper, 1941), a radiobiological study of the ^{235}U-fission reaction was not reported until the late 1940s (Tobias *et al.*, 1948). It was also suggested that a vital dye, appropriately labelled by ^{10}B or ^{235}U, might be useful in BNCT (Zahl and Cooper, 1941).

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After World War II, studies in radiobiology and medical physics were begun at institutes in the USA such as Brookhaven National Laboratory (BNL), which were established by the United States Atomic Energy Commission (AEC) primarily for nonmilitary nuclear physics research. In 1947, William Herbert Sweet, a neurosurgeon at the Massachusetts General Hospital (MGH) and professor at the Harvard Medical School, began collaborations with physicists at BNL and elsewhere to search for techniques to improve diagnosis and therapy of brain tumours. By 1949, these collaborations led to ^{32}P-labelled phosphate being used at the MGH as a radioactive tracer to localize brain tumours during neurosurgical operations. Working with the physicist Gordon Brownell, Sweet was among the first clinical investigators to image brain tumours with positron-emitting isotopes. However, no radiolabelled substance was known that would concentrate adequately in a brain tumour after its injection into a patient so as to deliver therapeutic doses of radiation to the tumour while sufficiently sparing normal brain and radiation-sensitive haematopoietic and gastrointestinal tissues. Sweet's search for a proton beam to be used for human brain tumour therapy eventually led to the establishment of a proton radiation therapy unit at the Harvard University cyclotron, but most malignant cerebral gliomas were considered to be too large and their margins too irregularly demarcated for proton therapy. The first clinical trial of fast-neutron therapy (radiation therapy mediated by fast recoiling protons in neutron-irradiated tumours), which had been carried out between 1938 and 1943 in California, was deemed to have failed 10 years after it began (Stone, 1948). Thirteen patients with brain tumours were among those treated with fast neutrons, without much success. By the late 1940s circumstances in the USA were thus appropriate for a renewal of interest in neutron capture therapy. Although the potential importance of BNCT was recognized by the British radiobiologist Douglas Lea in the 1940s (Lea, 1956), to my knowledge there were no British studies on BNCT published until the late 1970s (Constantine *et al.*, 1986, 1989; Mill *et al.*, 1986; Morgan *et al.*, 1986).

After 36 months under construction, the Brookhaven Graphite Research Reactor (BGRR) was commissioned in August, 1950. Lee Edward Farr, a paediatric research physician who was appointed chairman of the newly formed BNL Medical Department on September 1, 1949, became interested in new applications of the BGRR to slow-neutron radiation therapy (L. E. Farr, personal communication). Work on BNCT began at the BNL Medical Department in the summer of 1950 (Brookhaven National Laboratory, 1951). Independently, a proposal by Sweet for BNCT of brain tumours at the BGRR and for later development of a major intermediate ('epithermal') energy component in a neutron beam for BNCT was submitted to the AEC in 1950 (Sweet, 1986*a*, *b*) and published, in part, over 1 year later (Sweet, 1951; personal communication). Under the aegis of Donald Van Slyke, an eminent biochemist who was then BNL's Assistant Director for Biology and Medicine, A. Baird Hastings, a distinguished Harvard biochemist and BNL trustee, and Shields Warren, a noted pathologist who was the Director of the Division of Biology and Medicine in the AEC, plans by Sweet, Farr and others for BNCT of malignant gliomas at the BGRR were coordinated and quickly brought to fruition (Brookhaven National Laboratory, 1951). An irradiation facility with a 5 cm × 10 cm rectangular neutron port in its steel/lead/boron-shielded floor was built at the top of the BGRR, surrounded by concrete. The neutron port was at the apex of a 3½ foot high conical air space in the reactor shielding beneath

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the floor of the facility, with bismuth plates used as extra gamma shielding at the base of the cone. Preliminary experiments were performed at the MGH in which nontoxic doses of borax (~70 mg/kg) were injected intravenously into volunteers with brain tumours (Javid *et al.*, 1952; Sweet and Javid, 1952). Beginning early in 1951, some patients with glioblastoma multiforme were referred from the MGH to Brookhaven for BNCT at the irradiation facility of the BGRR.

About 15 vital dyes were screened in tumour-bearing mice at BNL for possible use, after their boronation, in BNCT (Brookhaven National Laboratory, 1951; Sinex *et al.*, 1953). Winton Steinfield, who joined the BNL group in February, 1952, announced his success in the boronation of the vital dye Bismarck Brown after about 1 year's work. Unfortunately, Steinfield died accidentally in 1953 and his notebooks on the technique could not be deciphered (L. E. Farr, 1990, unpublished). Steinfield also performed a preliminary in vivo study relating to uranium neutron capture therapy (Steinfield, 1952). Coincidentally, the untimely death of another scientist, Leslie McKlintock, prevented a method for preparation of uranium-binding tumour-affinitive antibodies developed at a US Army laboratory (McClintock and Friedman, 1945) from being repeated (Knock, 1959). Such antibodies were thought to be potentially useful for uranium neutron capture therapy.

About 20% of boron in the earth's crust is ^{10}B. The production of ^{10}B-enriched boron did not begin in the USA until 1943 when the first method for ^{10}B-enrichment of boron, equilibrium counter-current distillation of a boron trifluoride dialkyl etherate, was developed at Columbia University in New York under the leadership of Harold Urey. A distillation column 1 inch in diameter and 5 yards high could produce 500 mg of 95% ^{10}B-enriched boron per day. Methods of large scale production of ^{10}B are now well known as, for example, in a factory commissioned in 1954 that was capable of producing over 1 lb of 95% ^{10}B-enriched boron per day (Miller *et al.*, 1958).

The first patient in Brookhaven's initial 24-month, 10-patient BNCT study (Farr *et al.*, 1954*a*, *b*, *c*; Godwin *et al.*, 1955; Robertson *et al.*, 1962; Farr and Robertson, 1971) was irradiated at the BGRR on February 15, 1951, just 6 months after the BGRR was commissioned. All the patients had undergone a neurosurgical operation for malignant cerebral glioma and showed clinical evidence of tumour recurrence. Eight of the patients had received conventional radiation therapy for their brain tumours. These advanced malignant cerebral gliomas were irradiated by thermal neutrons (and by the inevitable concomitant gamma, proton and fast-neutron radiations), after an aqeuous solution of 96% ^{10}B-enriched borax was administered intravenously over a period of several minutes. The patient was positioned horizontally with the tumour zone apposed to the neutron port. Since there was then no irradiation shutter, the reactor pile was shut down during the preirradiation infusion and alignment procedure, which took about 10 min. Critical reactivity of the pile was then reestablished and the reactor power was raised to 40 MW for irradiations of 17–40 min duration.

There were no serious side-effects of BNCT in the first 10 patients, although the large doses of borax infused before irradiation, ~200 mg/kg, were slightly toxic (Farr *et al.*, cited in Sweet and Javid, 1951; Conn *et al.*, 1955; Locksley and Farr, 1955). A 20-ton armour steel irradiation shutter was installed below the BGRR treatment port to allow a more rapid rise to full reactor power after the injection of borate without shutting

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down the reactor (Brookhaven National Laboratory, 1953). The neutron port was enlarged to 10 cm × 10 cm.

A second series, comprising 9 malignant glioma patients, was treated with a less toxic borate preparation, sodium pentaborate with D-glucose in the molar ratio 2:1 (Easterday and Farr, 1961; Easterday and Hamel, 1963), but at a higher ^{10}B dose than in the first series: 32 – 50 mg ^{10}B per kg body weight (median, 42 mg/kg) instead of 16 – 43 mg ^{10}B/kg (median, 26 mg/kg). Incident thermal neutron fluences were $2.34 - 3.84 \times 10^{12}$ per cm^2 (median, 3.38×10^{12} per cm^2), higher than the previous fluences, which were $0.44 - 1.93 \times 10^{12}$ per cm^2 (median, 0.93×10^{12} per cm^2). A troublesome side-effect of BNCT in the second series was intractable radiation dermatitis of the scalp (Archambeau, 1970), sometimes with ulceration, despite later efforts to prevent it by application of tight head bandages during borate infusion. The median survival time after BNCT for the second series was 147 (range 93 – 337) days, which was longer than that for the first series (median 97, range 43 – 185 days) (Farr *et al.*, 1958).

In the third series of patients treated by BNCT at the BGRR, in order to reduce the radiation dose to the scalp, the neurosurgeon H. J. Bagnall delivered the pentaborate (26 – 60 mg ^{10}B/kg, median 50 mg/kg) through a long warmed tube into the internal carotid artery of the tumour-bearing hemisphere while the patient was positioned at the irradiation port. Neutron fluences were reduced to $0.39 - 1.5 \times 10^{12}$ per cm^2 (median, 0.72×10^{12} per cm^2). Survivals after BNCT in the 9 patients of the third group (median, 96 days, range 29 – 158 days) were similar to those of the 10 patients in the first group and to those of patients in the north-east USA with similar cerebral tumours treated only by conventional postoperative therapies during the 1950s (Slatkin *et al.*, 1986*a*). None of the 9 developed severe radiation dermatitis, a fortunate outcome that sustained prospects for further clinical trials of BNCT at Brookhaven (Farr *et al.*, 1958; Farr, 1960).

Sweet was involved in the first two series of patients treated by BNCT at Brookhaven. Thereafter, he turned his attention to development of a brain tumour BNCT facility at the Massachussetts Institute of Technology (MIT) (Brownell and Sweet, 1958). To identify a ^{10}B-carrier that yielded more favourable tumour:brain boron concentration ratios than were obtainable with borates, the MGH chemist Albert Soloway investigated a series of monosubstituted derivatives of phenylboronic acid. Of 8 derivatives studied, the m-carbamido, the m-carboxy and the p-carboxy derivatives yielded tumour:brain ratios in the 2.5 – 9.0 range between 15 min and 3 h after their prompt intraperitoneal injection in mice bearing subcutaneous transplanted gliomas (Soloway, 1958). None of the other 5 derivatives yielded a tumour:brain ratio greater than 1.6. The p-carboxy derivative of phenylboronic acid was selected as a ^{10}B-carrier for 16 of the 18 brain tumour patients treated with BNCT by Sweet and his colleagues at the MIT reactor during 1959 – 1961. The outcome of the MIT trial of BNCT was unsatisfactory (Asbury *et al.*, 1972), with an average post-BNCT survival time of 6 months (Hatanaka, 1986).

While clinical trials of BNCT were in progress at the BGRR, a study in mice of the in vivo relative biological effectiveness (RBE) of heavy particles from the $^{10}B(n,\alpha)^7Li$ reaction was carried out at BNL (Bond *et al.*, 1956). Studies on BNCT of a mouse tumour were carried out by Farr and his laboratory assistant Tadeusz Konikowski during the 1950s and early 1960s at BNL. A methylcholanthrene-induced glioma was

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transplanted intramuscularly into the mouse thigh. BNCT could cure the transplanted tumour almost predictably with no visible residual effects on the mouse (Table 1) (Farr and Konikowski, 1967, 1976). The thigh tumour could also be eradicated by x-ray therapy, but this was only achieved with severe damage to the irradiated limb (Farr and Konikowski, 1964). These results were the first extensive experimental demonstration of the BNCT concept in vivo.

TABLE 1. BNL-10-584-89. SUMMARY OF TUMOUR REGRESSION DATA FROM FARR AND KONIKOWSKI (1967, 1976) ON 1587 MICE WITH A NONMETASTATIC GLIOMA TRANSPLANTED TO THE THIGH AND TREATED BY BNCT USING 96 ATOM % ^{10}B-ENRICHED SODIUM PENTABORATE WITH D-GLUCOSE (MOLAR RATIO 2:1) VIA PROMPT INTRAVENOUS INJECTION

	Injection-irradiation time interval (min)			
	7–23	*25–48*	*50–72*	*74–92*
	Average boron concentrations (μg/g)			
Sarcoma	25	28	28	28
Blood	34	26	21	18
Tumour diameter (mm)	*Fraction (%) with permanent regression*			
8–9	115/137 (84)	165/185 (89)	79/125 (63)	40/95 (42)
10–11	48/82 (59)	98/128 (77)	63/128 (49)	15/90 (17)
12–13	25/68 (37)	46/130 (35)	28/82 (34)	1/52 (2)
14–15	1/51 (2)	9/86 (10)	6/86 (7)	0/62 (0)

Surface fluence $1.41-1.67\times10^{12}$ n/cm^2: BMRR: 5 MW, 23 s.

It was suggested that untoward complications of BNCT for human gliomas might be avoided if adequate numbers of neutrons could be delivered to the tumour during the few minutes when the tumour:brain ^{10}B concentration ratio was considered most favourable. To achieve this, thermal neutrons would have to be generated at a much greater rate than was possible at any acccessible port of the BGRR. Accordingly, plans were made to build a compact, high-flux, broad-beam thermal neutron facility for BNCT at the BNL Medical Department (Robertson *et al.*, 1955). The 5-MW H_2O-moderated Brookhaven Medical Research Reactor (BMRR) became operational in 1959 (Godel, 1960). It was a great disappointment that BNCT of 17 cerebral tumours (all but 1, malignant gliomas) carried out at the BMRR during 1959–1961 was not nearly as useful as had been anticipated; the median post-BNCT survival was only 3 months (Table 2). Failure to show substantial extensions of lifespan resulted in suspensions of both the BNL and the MIT clinical trials of BNCT. There has been no patient treated by BNCT in the United States since 1961.

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TABLE 2. BNL-12-23-89. CLINICAL PARAMETERS AND INCIDENT THERMAL NEUTRON DOSES FOR 17 PATIENTS WITH MALIGNANT CEREBRAL TUMOURS TREATED BY BNCT AT THE BMRR DURING THE 1959–1961 STUDY. THE PATIENTS' SERIAL NUMBERS, ASSIGNED IN ORDER OF INCREASING NEUTRON DOSES, ARE NOT NECESSARILY IN CHRONOLOGICAL ORDER OF IRRADIATION

Serial no.	*Age at first operation (yrs)*	*Survival after first operation (days)*	*Survival after BNCT (days)*	*Previous radiotherapy*	*No. of major craniotomies*	*Incident thermal neutron fluence × treatment area ($\times 10^{14}$ neutrons)*
1	58	148	87	No	1	0.6
2	38	192	123	No	1	1.6
3	44	181	31	Yes	2	1.7
4	61	488	165	Yes	2	1.8
5	35	1128	98	Yes	2	1.8
6	44	68	19	No	1	4.6
7	65	~220	~170	No	2	5.6
8	57	144	87	No	1	5.9
9	43	313	153	No	1	6.8
10	56	1121	143	Yes	2	6.9
11	66	123	26	No	1	7.5
12	30	1750	57	Yes	2	16.0
13	51	425	151	Yes	1	20.0
14	35	636	12	Yes	3	25.5
15	32	50	4	No	1	26.2
16	66	36	6	No	1	26.7
17	50	312	3	Yes	1	29.7
Median	50 yrs	220 days	87 days	–	–	5.7×10^{14} neutrons

In the early clinical trials of BNCT, no technique was available that was fast enough to allow estimation of the patient's blood-^{10}B concentration in planning the duration of irradiation. In retrospect, this problem is seen to be important because radiation damage to the cerebral vasculature turned out to be a complication of the early BNCT trials and because there was considerable variation from one patient to another in the concentration of ^{10}B observed in the blood at a given time after administration of a standard dose of ^{10}B-carrier. Recently, a gamma spectrometry facility has been constructed at BNL to measure ^{10}B quickly and accurately in less than a gram of blood or tissue (Fairchild *et al.*, 1986). In this so-called 'prompt-gamma' method, the sample is irradiated with slow neutrons. Gamma photons in the narrow energy range (~478 keV) produced instantly by ^{10}B-neutron capture reactions are counted. The amount of ^{10}B in the sample is proportional to the net count. The ^{10}B analysis of one blood or tissue sample at the prompt-gamma facility of the BMRR takes only several minutes.

Another important aspect of the initial clinical trials of BNCT was the unavailability of boron-containing compounds that would enter glioma tissues freely and not cross the blood-brain barrier. Such boron compounds were first synthesized in the 1960s from polyhedral boranes (Miller *et al.*, 1963; Knoth *et al.*, 1964). The applicability of these compounds to BNCT was studied initially at the MGH (Soloway *et al.*, 1967). This led to the selection of sodium mercaptoundecahydrododecaborate ($Na_2B_{12}H_{11}SH$) for a trial of BNCT of brain tumours in Japan. The first BNCT irradiation of a human brain tumour in Japan took place in August 1968 (Hatanaka *et al.*, 1986*a*; Hatanaka and Urano, 1986).

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It is instructive to estimate radiation doses to the normal cerebral capillary endothelium in patients who underwent BNCT at the BMRR 30 years ago, and to review those doses in relation to post-BNCT survival. The capillary endothelium of a tissue receives doses from BNCT that reflect ^{10}B concentrations in blood and tissue parenchyma weighted in the ratio of about 1:2, respectively (Kitao, 1975; Rydin *et al.*, 1976; Slatkin *et al.*, 1988). Decreases of normal brain capillary endothelial cell radiation dose (*see* Appendix) with increasing penetration of neutrons are indicated in Table 3. As shown in the Appendix

TABLE 3. BNL-10-375-89. IRRADIATION PARAMETERS AND ESTIMATES OF CAPILLARY ENDOTHELIAL DOSE FOR 17 PATIENTS WITH CEREBRAL TUMOURS TREATED BY BNCT AT THE BMRR DURING 1959–1961

Serial no.	*Reactor exposure (MW-min)*	*Maximum surface thermal neutron fluence ($\times 10^{12}$ n/cm^2)*	*Maximum surface thermal neutron flux/MW ($\times 10^{10}$ n/cm^2-s)*	*Treatment area (cm^2)*	*Endothelial radiation doses at depth D cm (Gy-Eq)*				
					(D = 0)	*(D = 2)*	*(D = 4)*	*(D = 6)*	*(D = 8)*
1	0.83	0.6	1.28	100	5.0	2.2	1.0	0.5	0.3
2	3.50	1.6	0.76	100	13.3	6.0	2.9	1.5	0.9
3	3.33	1.7	0.87	100	14.3	6.4	3.1	1.6	0.9
4	2.33	1.8	1.31	100	14.4	6.3	2.9	1.4	0.8
5	2.50	1.8	1.22	100	14.5	6.4	3.0	1.4	0.8
6	8.33	7.4	1.48	62	57.1	22.4	9.4	4.4	2.4
7	9.67	7.1	1.22	79	55.8	23.4	10.4	5.0	2.8
8	8.33	9.5	1.89	62	71.6	27.6	11.3	5.0	2.6
9	9.67	8.6	1.47	79	66.1	27.5	12.0	5.6	3.0
10	10.42	8.8	1.40	79	68.1	28.4	12.4	5.9	3.2
11	11.08	12.1	1.82	62	91.8	35.5	14.6	6.5	3.4
12	8.33	9.5	1.90	168	74.0	35.3	16.9	8.1	4.3
13	10.92	11.9	1.82	168	92.8	44.3	21.2	10.3	5.4
14	12.50	15.2	2.02	168	117.8	56.0	26.6	12.8	6.7
15	12.50	15.6	2.08	168	120.7	57.3	27.3	13.1	6.8
16	12.50	15.9	2.12	168	122.9	58.4	27.7	13.3	6.9
17	13.42	20.6	2.56	144	125.5	71.8	33.0	15.4	7.8

and in Tables 4 and 5, BNCT also involves radiations other than those from the neutron-^{10}B reaction that, in principle, cannot be limited to the tumour even if ^{10}B were limited exclusively to the tumour. These non-^{10}B-related radiations increase in relative importance with increasing depth in the brain.

In retrospect, Case 13 (Tables 1–5) is of particular interest because BNCT apparently arrested the growth of his malignant cerebral tumour. An ~ 4 cm diameter carcinoma was removed from his anterior parietal region at a left temporoparietal craniotomy. Seven weeks later, a 6-week course of cobalt-60 gamma radiation therapy (51 Gy to the whole brain) was begun. Recurrence of neurological signs, including right hemiparesis, led the patient to undergo BNCT at the BMRR 6 months after the termination of cobalt-60 therapy. The patient developed right hemiplegia, acute increased intracranial pressure and a slight drop in systemic blood pressure (150/90–110/60 mmHg) about 10 h after BNCT. Following emergency treatment with intravenous urea, the patient slowly recovered and became ambulatory within 10 days. Before he left BNL 53 days

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TABLE 4. BNL-11-275-89. ESTIMATES OF DOSES TO CAPILLARY ENDOTHELIAL CELLS IN NORMAL BRAIN TISSUES FOR CASE 13 AT DEPTH D cm (Gy-Eq)

	D				
Source of radiation	*0*	*2*	*4*	*6*	*8*
43 μg ^{10}B/g (RBE = 2.0)	79.2	34.0	14.6	6.3	2.7
Fast neutrons (RBE = 2.0)	3.9	2.6	1.7	1.1	0.7
22 mg ^{14}N/g (RBE = 2.0)	3.7	1.6	0.7	0.3	0.1
Intrinsic gamma (RBE = 1.0)	4.1	4.4	2.7	1.4	0.7
Extrinsic gamma (RBE = 1.0)	2.0	1.7	1.5	1.3	1.1
Total endothelial dose	92.8	44.3	21.2	10.3	5.4
(% ^{10}B)	(85)	(77)	(69)	(61)	(50)
(% gamma)	(7)	(14)	(20)	(26)	(35)

The contributions to total doses from neutron-induced proton radiation (mainly from ^{14}N), from neutron-induced intrinsic gamma radiation (mainly from hydrogen), and from extrinsic radiations (mainly reactor-generated fast neutrons and gamma radiations) are listed. Numerical values of doses are given to the nearest 0.1 Gy-Eq.

TABLE 5. BNL-10-583-89. COMPONENTS OF THE MIXED-FIELD RADIATION DOSES TO CAPILLARY ENDOTHELIAL CELLS IN NORMAL BRAIN TISSUES AT VARIOUS DEPTHS IN CM (D) ASSOCIATED WITH BNCT OF 17 CEREBRAL TUMOURS TREATED BY BNCT AT THE BMRR DURING 1959–1961

	Proportion of total Gy-Eq dose (% ± SD)	
Source of radiation (D cm)	*^{10}B (RBE = 2.0)*	*Gamma (RBE = 1.0)*
0	85.0 ± 2.0	5.6 ± 1.0
2	76.2 ± 2.9	12.2 ± 1.5
4	65.7 ± 4.6	19.8 ± 1.8
6	54.3 ± 6.9	28.3 ± 3.0
8	40.3 ± 8.9	40.7 ± 5.0

later, not only had the paresis largely disappeared but remarkable improvements in speech, ability to read, and vision were observed in comparison with the serious deficits in these functions (right hemiparesis, complete expressive aphasia, complete right homonymous hemianopia) that developed before BNCT. The patient did not deteriorate neurologically thereafter, but he died at BNL, severely jaundiced, 5 months after BNCT with widespread extracranial metastases, probably from a primary anaplastic carcinoma originating in the head of the pancreas (autopsy no. A-151-61; BNL). At necropsy, there was no evidence of viable brain tumour tissue or of brain oedema.

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Patients treated at the BMRR, many of whom had radiation therapy previously, were provided with meticulous care by the neurosurgeon Y. L. Yamamoto. Temporary skin flaps were reflected and shielded by sheets of ^{6}Li before irradiation. Although this precaution avoided nonhealing ulceration of the skin, it did not prevent radiation dermatitis altogether. Moreover, it was not always possible to prevent postoperative infections within the irradiation field. These responded favourably to drainage and antibiotic therapy. Postirradiation rises of intracranial pressure were treated by continuous drainage of CSF from the brain and by intravenous urea. Nevertheless, 4 of the 17 patients died within 2 weeks after irradiation (Table 2) with cerebral oedema and intractable shock, the explanation for which was not immediately apparent.

It was stated by the Amerian radiation oncologist Philip Rubin (1989, unpublished) that large-field photon irradiation of the human brain with a single dose of 16 gray or 20 gray carries with it a 5% or 95% risk, respectively, of clinically unacceptable injury to the brain. Doses equivalent to these were apparently reached or exceeded in one hemisphere of the cerebrum during BNCT in Cases 6–13 to a depth of about 2 cm and in Cases 12 and 13 to a depth of about 4 cm (Tables 2 and 3) with no dire consequences within 2 weeks after BNCT. Progressive deeper coma, cardiovascular collapse (shock) and death ensued within 2 weeks after BNCT only in Cases 14–17, who also received the highest neutron doses in the series (Table 2). Dosimetric calculations for these patients, when contrasted with similar calculations for Cases 1–13, suggest that the acute (single fraction) BNCT tolerance dose for endothelial cells in basal ganglia at depths of ~6 cm is unlikely to be much greater than 10 Gy-Eq. Perhaps neuronal centres in the basal ganglia that were involved in cardiovascular homeostasis were secondarily compromised by doses to the endothelium of more than 10 Gy-Eq from BNCT and BNCT-associated reactor radiations in Cases 14–17. It is postulated that Case 13, who responded well to BNCT after a difficult postirradiation syndrome of acute cerebral oedema and mild hypotension, received nearly the maximum acutely tolerable dose of radiation to the capillary endothelium of his left cerebral hemisphere, especially in his left basal ganglia.

An ongoing clinical trial of BNCT for malignant gliomas and other brain tumours has been led by the neurosurgeon Hiroshi Hatanaka in Japan since 1968. The age distribution of patients treated for malignant glioma in Japan, the median age of incidence of whom was approximately 40 y (Sano, 1981), seems to be quite different from the age distribution of patients with supratentorial malignant gliomas treated in Boston, where the median age at first operation was 59 y between 1952 and 1981 (Slatkin *et al.*, 1986*a*). Thus differences in age might contribute to differences in the survivals of groups of patients with malignant glioma treated similarly in Japan and in the West since age is an important prognostic of postoperative survival among glioma patients. Moreover, it is conceivable that some preparations of $Na_2B_{12}H_{11}SH$ (monomer) may have developed variable amounts of the spontaneous oxidation products $Na_4B_{24}H_{22}S_2$ (dimer) and $Na_4B_{24}H_{22}S_2O$ (dimer monoxide) by the time they were infused into patients (Hatanaka *et al.*, 1986*b*; Sweet *et al.*, 1986; Soloway, 1988). Consequently, inferences from the results of the Japanese trial of BNCT to date may not be unreservedly applicable elsewhere.

There have been reports of excellent clinical results in some malignant glioma patients treated with BNCT in Japan. For example, a man with glioblastoma multiforme so treated

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in 1972 at age 50 y was alive and neurologically stable in the spring of 1990 with no radiographic evidence of a brain neoplasm (Hatanaka, 1990, unpublished). Nine days after ~20 g of tumour was removed from a large glioblastoma in the posterior-inferior region of the left frontal lobe, 40 mg ^{10}B/kg body weight of monomer was infused into the left carotid artery over 2 h. A 7 h irradiation that delivered a thermal neutron fluence of $5.3-9.6\times10^{12}/cm^2$ to the residual tumour began 14 h after the end of the infusion. Half an hour before irradiation, a 3.5 cm diameter sterile ping-pong ball was inserted into the bed of the residual tumour, in a sample of which the ^{10}B concentration was 15.3 μg/g. Half an hour after the beginning of irradiation, the blood-^{10}B concentration was 27.5 μg/g (Hatanaka *et al.*, 1986*a*). Post-BNCT instillation of 25 mg of methotrexate into the patient's tumour cavity over a 5-day period (Hatanaka *et al.*, 1986*a*), conceivably may have contributed to the long-term control of this tumour. Despite Hatanaka's successes with some patients, American and European oncologists are reluctant to endorse the Japanese BNCT technique in preference to alternative methods of postoperative brain tumour therapy. However, the astonishing energy and bold initiatives of the Japanese BNCT team are followed in the West with great interest because that team demonstrated for the first time that BNCT and BNCT-associated reactor radiations can be useful for some patients with brain tumours.

The microscopic distribution of boron in the brains of 2 $Na_2B_{12}H_{11}SH$-infused patients with malignant glioma has been studied in joint BNL-MGH investigations (Finkel *et al.*, 1989; Slatkin *et al.*, 1989*a*, *b*). One of these patients, who had a right temporal malignant glioma, demonstrated a continuum of concentrations of ^{10}B in tumour and in peritumour brain tissue by neutron-induced ^{10}B radiography (fig. 1, right) of an air-dried, unfixed, unstained cryomicrotome section of a surgical specimen from the right temporal lobe (fig. 1, left). The specimen was snap-frozen in isopentane cooled

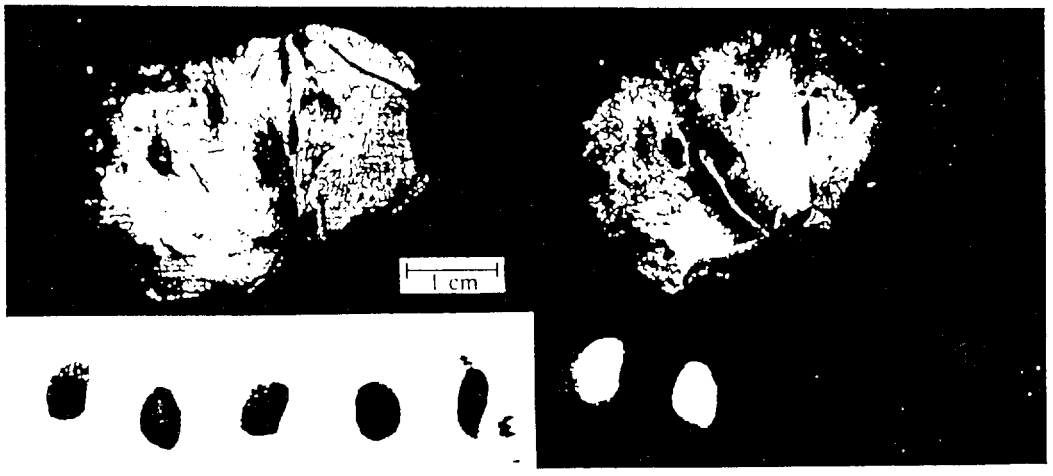

FIG. 1. BNL-1-140-88. Reflected-light (left upper frame) and alpha-track (right upper frame) images (Slatkin *et al.*, 1989*a*, *b*) of unfixed, unstained, 50 μm thick cryostat microtome sections from a right temporal lobe specimen removed during operation on a patient with a malignant glioma. The small left and right lower frames are the corresponding reflected light and alpha track images of cross-sections of frozen brain homogenates to which have been added 30, 9, 3, 0.3 and 0 μg ^{10}B/g, respectively, as non-^{10}B-enriched sodium tetraphenylborate.

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with liquid nitrogen within 1 min after its excision by the MGH neurosurgeon Charles Poletti to preserve the microarchitecture of fluid-filled spaces in tumour and peritumour tissues in microscopic sections and to minimize loss of ^{10}B from the specimen. Fig. 2 shows intermediate-power views by light microscopy of haematoxylin and eosin-stained, 8 μm cryomicrotome sections from several areas of the temporal lobe specimen shown in fig. 1. Fig. 2A is from a 2–3 μg ^{10}B/g zone, heavily infiltrated by glioma cells, that is contiguous with the intermediate alpha track density zone near the left margin of the specimen (fig. 1, right). Fig. 2B is from a 1–2 μg ^{10}B/g, apparently tumour-free, slightly oedematous, low alpha track density zone just to the right of centre of the specimen. Fig. 2C, shown at the same magnification as figs. 2A and B, is from a highly oedematous, high alpha track density zone further to the right of centre of the specimen. Only two isolated tumour cells are noted in this field, but alpha track densities in the alpha radiograph of that zone correspond to 4–6 μg ^{10}B/g of tissue, the highest seen in the specimen. It is surmised that the relatively high extravascular ^{10}B concentration was due mainly to diffusion of protein-bound sulphydryl borane from the blood plasma through leaky capillary endothelium (Slatkin *et al.*, 1989*b*). The patient had received an intravenous infusion of 95% ^{10}B-enriched $Na_2B_{12}H_{11}SH$ to a total dose of 15 μg ^{10}B/g of body weight over a 20 h period. The specimen was removed about 26 h after the end of infusion during a neurosurgical debulking. The total dose of $Na_2B_{12}H_{11}SH$ infused into this patient was 2- to 5-fold less than the doses administered to BNCT patients in Japan (Hatanaka *et al.*, 1986*a*). The uniform distribution of boron tracks in the peritumour oedema zone suggests that BNCT has the potential to deliver therapeutic doses of radiation to oedematous brain tissues that harbour tumour cells beyond the macroscopic limits of malignant gliomas.

It was shown that $Na_4B_{24}H_{22}S_2$, one of the spontaneous oxidation products of $Na_2B_{12}H_{11}SH$, has more favourable properties as a carrier of boron to a transplantable mouse melanoma than does the parent monomer (Slatkin *et al.*, 1986*b*). Other favourable aspects of the dimer were recognized earlier (Hatanaka and Sano, 1973) and concurrently (Slatkin *et al.*, 1986*c*; Sweet *et al.*, 1986). There is striking improvement in boron uptake and in tumour boron retention in rat gliosarcomas after delivery of boron as dimer as compared with delivery of boron as monomer (Joel *et al.*, 1989). Indeed, recent studies have shown a prolonged amelioration of neurological symptoms and a greatly increased median duration of survival in rats with otherwise rapidly lethal transplanted intracranial gliosarcomas treated with BNCT using ^{10}B-enriched dimer as the boron transport agent (Joel *et al.*, 1990). The estimated radiation dose to these tumours was 25.6 Gy-Eq, whereas the estimated dose to capillary endothelial cells of the normal cerebral parenchyma of these rats was 15.2 Gy-Eq, which is somewhat higher than the postulated tolerance dose limit ($\sim$10 Gy-Eq) to such cells in the human basal ganglia. The estimated dose to the normal rat brain parenchyma was only 6.9 Gy-Eq, which corresponds to a tumour-to-brain radiation dose ratio of nearly 4:1 (Joel *et al.*, 1990). As in the 1972 BNCT of one of Hatanaka's long-term surviving patients (cited above), ^{10}B concentrations in the rats' blood were higher than in the gliosarcomas during irradiation.

The spatial distributions of slow neutrons in BNCT patients at MIT during 1959–1961 were different from those at BNL. At MIT, Sweet used an air-filled balloon to facilitate the transport of thermal neutrons to the deep margins of the tumour bed. This idea was adopted by Hatanaka for certain cases, including his outstanding case of 1972. Although

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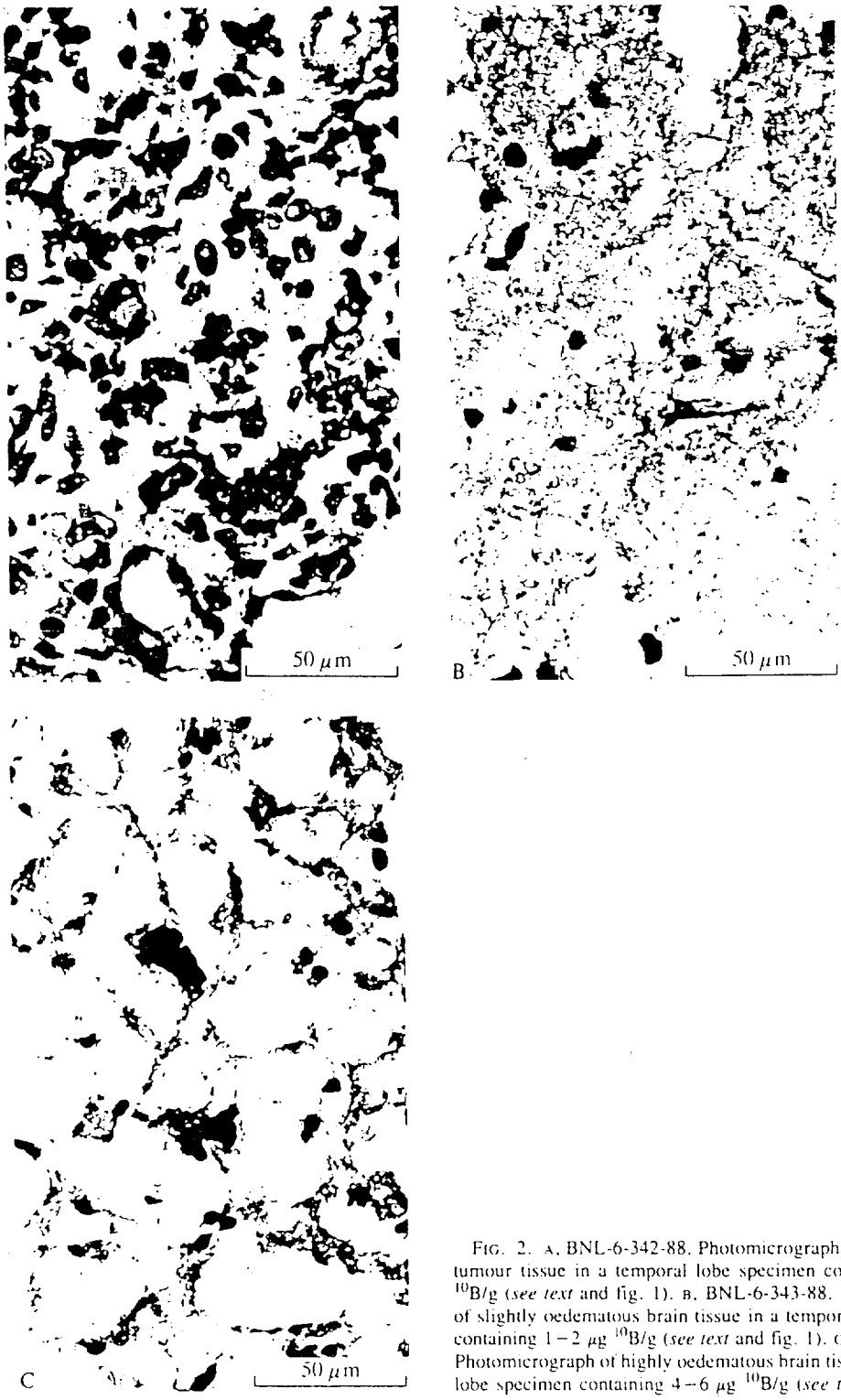

FIG. 2. A, BNL-6-342-88. Photomicrograph of human glioma tumour tissue in a temporal lobe specimen containing 2–3 μg ^{10}B/g (*see text* and fig. 1). B, BNL-6-343-88. Photomicrograph of slightly oedematous brain tissue in a temporal lobe specimen containing 1–2 μg ^{10}B/g (*see text* and fig. 1). C, BNL-6-341-88. Photomicrograph of highly oedematous brain tissue in a temporal lobe specimen containing 4–6 μg ^{10}B/g (*see text* and fig. 1).

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the MIT BNCT trial failed, it is not clear that the usefulness of a gas-filled space in the tumour cavity during BNCT can be discounted. Not only might it aid penetration of slow neutrons into the brain, but it could also be used to mitigate postirradiation brain swelling and to apply postirradiation hyperthermia to the residual tumour. Conceivably, a semipermeable balloon could provide a steep concentration gradient of oxygen in tissue at the margin of the tumour cavity to enhance the radiotherapeutic efficacy of the concomitant gamma radiation. The catheter leading to the balloon might also serve as a conduit for delivery of chemotherapeutic agents directly to the residual tumour bed.

Current research on BNCT focuses on the pharmacological and radiobiological evaluation of new boron-transport agents (Barth *et al.*, 1990). Besides that, a major accomplishment has been the design, construction and physical evaluation of an intermediate energy or 'epithermal' neutron beam at the BMRR suitable for clinical BNCT (Fairchild, 1965; Fairchild *et al.*, 1990). An epithermal beam produced by a different neutron-moderation technique (G. Constantine, unpublished) is near completion at a nuclear reactor in The Netherlands under the sponsorship of the Commission of the European Communities (Gabel, 1990). Epithermal beams for clinical BNCT can be constructed at several nuclear reactors that are not far from centres of population in the USA (Fairchild *et al.*, 1990; Brugger and Herleth, 1990), probably at modest cost. Whether the monomer $Na_2B_{12}H_{11}SH$, its dimer $Na_{24}B_{24}H_{22}S_2$, a boronated porphyrin (Kahl *et al.*, 1990), a boronated amino acid (Coderre *et al.*, 1990), or some other boron carrier will be tested clinically for BNCT of malignant gliomas in the USA has not been determined. It is likely that the distributions of trace amounts of several boron carriers will be studied in volunteers before trials of BNCT of human gliomas will resume in the USA, and that the new trials will use epithermal neutron beams. The use of ^{10}B-microlocalization techniques such as neutron-induced alpha track registration in etchable plastic films (Becker and Johnson, 1970; Amano and Sweet, 1973; Abe, 1982; Fairchild *et al.*, 1986; Gabel *et al.*, 1987; Finkel *et al.*, 1989), as in fig. 1, should facilitate such distribution studies.

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Many interesting contributions to neutron capture therapy research have not been cited here either because of space limitations or because of my assessment of their relevance to this restricted review. This research was supported by the US Department of Energy under Contract DE-AC02-76CH00016. Accordingly, the US Government retains a nonexclusive, royalty-free licence to publish or reproduce the published form of this contribution, or allow others to do so, for US Government purposes.

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APPENDIX

Dosimetry for normal human brain capillary endothelial cells

The normal brain capillary endothelium received radiation doses during BNCT of brain tumours at the BMRR, 1959–1961, that were estimated indirectly as follows. Fig. 3 shows the average time course of ^{10}B concentrations in whole blood and in brain after prompt i.v. injection into mice of 100 μg ^{10}B/g body weight as 96 atom% ^{10}B-enriched sodium pentaborate with D-glucose in the molar ratio 2:1. The crosses and large dots represent measurements of boron

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concentrations in tissues by a modified quinalizarin method (Konikowski and Farr, 1965). The time curves for ^{10}B concentrations in blood, B(t), and brain C(t), are related by a first-order differential equation:

$$dC(t)/dt = 0.012[B(t) - C(t)] \quad [1]$$

where concentrations are expressed in $\mu g/g$ tissue or blood, and time (t) is expressed in min. The same equation describes, with less precision, the mouse blood-brain boron concentration relationship when the i.v. dose was reduced to 35 μg $^{10}B/g$ body weight, the dose which was given in the 17-patient series at the BMRR. Blood and brain boron concentrations (measured by the prompt-gamma technique) after a single i.p. injection into mice of boric acid at a dose of 125 μg boron/g body weight (Slatkin *et al.*, 1988) can be correlated by the same kind of equation with a slightly greater rate constant:

$$dC(t)/dt = 0.015[B(t) - C(t)] \quad [2]$$

These equations are analogous to the expression of Fick's first law of diffusion, whereby the rate of diffusion of a substance across a boundary between two compartments is proportional to the concentration gradient between the compartments. Since tissue constituents and their microscopic dimensions in human and mouse brains are similar, Equation [1], which contains no term that is an explicit measure of a macroscopic brain dimension or of a macroscopic brain boron concentration, can be used to estimate the average concentration of boron in nonoedematous zones of the human cerebrum after i.v. injection of pentaborate. The net rate of entry of pentaborate into oedematous zones of the radiation-damaged human brain most probably exceeds the rate of entry into the nonoedematous brain, so that concentrations so derived for brain tumour patients from Equation [1] are low estimates. Upper estimates are reasonably equated with blood concentrations. The upper curve of fig. 4 follows ^{10}B concentrations in 4 of the series of 17 patients with cerebral tumours (Tables 1–5) treated at the BMRR who had the lowest measured blood concentrations after a standard 5-min i.v. infusion of 35.1 ± 0.9 (SD) μg $^{10}B/g$ body weight (range: 32.4–36.9 μg $^{10}B/g$) as sodium pentaborate decahydrate:D-glucose in the molar ratio 2:1 (Hospital of the Medical Research Center, BNL, unpublished medical records, 1959–1961). This standard infusion ended about 30 min before the start of irradiation at the BMRR. Blood concentrations measured in other patients of the same series were about one-fifth to one-third greater than those of the 4 patients indicated in fig. 4. The doses, timing and other conditions of administration of pentaborate, as well as the infusion-irradiation time intervals (~30–35 min), were almost identical in the 17 patients. Thus for the purpose of these comparative dosimetric calculations, the blood and normal brain concentrations of ^{10}B during irradiations are estimated to be 60 ± 10 $\mu g/g$ and 35 ± 5 $\mu g/g$, respectively.

Radiation doses from the ^{10}B-neutron capture therapy reaction to capillary endothelial cells in the brain are derived

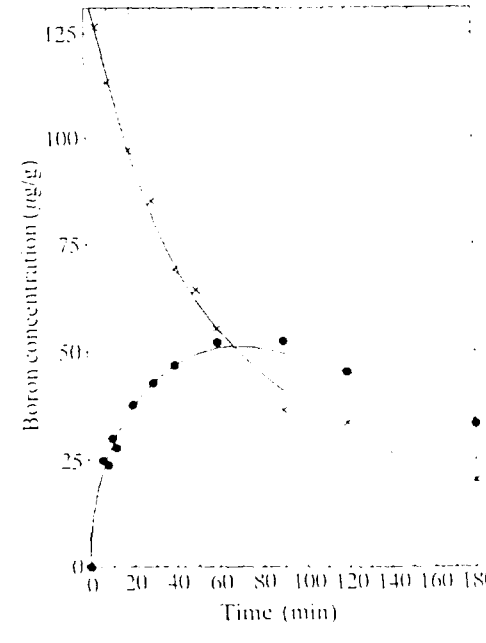

FIG. 3. BNL-9-109-89. Concentrations of ^{10}B in mouse blood (crosses) and brain (circles) after prompt i.v. injection of 100 μg $^{10}B/g$ body weight as 96 atom % ^{10}B-enriched sodium pentaborate with D-glucose, molar ratio 2:1 (T. Konikowski and D. N. Slatkin, unpublished data).

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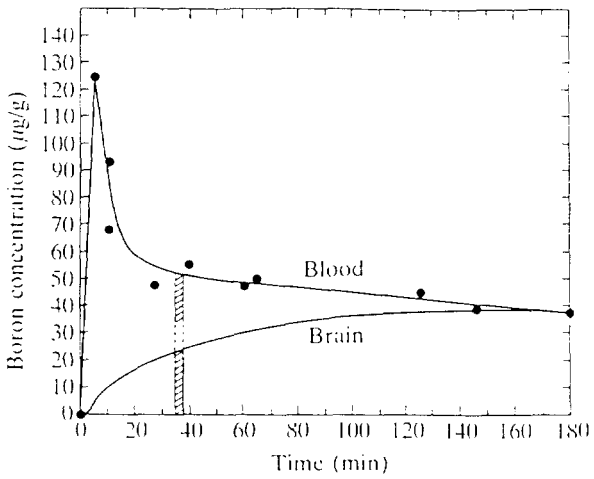

FIG. 4. BNL-9-111-89. Concentrations of ^{10}B in patients after a 5 min i.v. infusion of 35 μg ^{10}B/g body weight as 96 atom % ^{10}B-enriched sodium pentaborate with D-glucose, molar ratio 2:1, measured in the blood (circles) and calculated in the brain (lower curve) for the 1959–1961 BMRR BNCT study. Estimated minimum concentrations during the irradiations correspond to the intersections of the vertical bar with the two curves (T. Konikowski, unpublished data; D. N. Slatkin, Appendix).

in part from ^{10}B in blood and from ^{10}B in brain parenchyma in the relative proportion of approximately 1:2 (*see text*). That is, the effective ^{10}B concentration for irradiation of normal brain capillary endothelial cells in the 1959–1961 BMRR study was about 1/3 (60) + 2/3 (35), or 43.3 μg ^{10}B/g. Similarly, since the parenchymal brain ^{14}N concentration is about 19 mg/g and the blood ^{14}N concentration is about 28 mg/g, the effective ^{14}N concentration for brain endothelial irradiation from the neutron-^{14}N reaction was approximately 1/3 (28) + 2/3 (19), or 22 mg ^{14}N/g. Assuming that the effective thermal neutron capture cross-sections for the neutron-^{10}B and neutron-^{14}N reactions are 3.40×10^{-21} cm^2 and 1.64×10^{-24} cm^2, respectively (Slatkin *et al.*, 1988), the doses to endothelial cells from these reactions are 6.651×10^{-12} Φ Gy-Eq from ^{10}B and 0.311×10^{-12} Φ Gy-Eq from ^{14}N, where Φ is the thermal neutron fluence in neutrons per cm^2. These formulae are based on an assumed RBE of 2.0, which is appropriate for acute effects in normal mammalian brain capillary endothelium of the short-range ionizing particles produced by the neutron-^{10}B and neutron-^{14}N reactions (Slatkin *et al.*, 1988). It is calculated from published data (Matsumoto *et al.*, 1986) that the half-attenuation depth, $D_{1/2}$ cm, for thermal neutrons in the human head is approximately 0.32 ln A, where A is the surface area exposed to the thermal neutron beam, in cm^2.

It is surmised (Fairchild *et al.*, 1966) that during 1959–1961, fast neutrons (RBE = 2) from the BMRR delivered radiation doses to skull surfaces of 0.0030 Gy-Eq/s per MW reactor power. It is also surmised (Fairchild *et al.*, 1966) that the extrinsic gamma dose rate (RBE = 1) at skull surfaces was 0.0030 Gy/s per MW reactor power, and that the intrinsic gamma dose at skull surfaces was 0.0204 Gy/10^{13} neutron/cm^2 maximum surface fluence/cm^2 of surface exposed to the thermal neutron field. The relative attenuation as a function of depth of penetration in the head of each component type of radiation is given by the following chart, which was inferred from published studies of thermal neutron beams (Stickley and Farr, 1960; Fairchild *et al.*, 1966; Robertson *et al.*, 1967; Matsumoto *et al.*, 1986):

Depth D (cm)	*Extrinsic gamma*	*Intrinsic gamma*	*Fast neutrons*
0	1.00	1.00	1.00
2	0.87	1.07	0.67
4	0.77	0.66	0.43
6	0.67	0.33	0.27
8	0.60	0.18	0.17

The endothelial radiation dose estimates of Tables 3, 4 and 5 are based on these attenuation parameters. The justification for adding radiation doses and radiation dose-equivalents arithmetically from several different kinds of irradiation is, in part, inferred from other experiments (Zirkle, 1950). The sum of such doses is considered to be a conservative predictive measure of the effect of different, concurrent ionizing radiations on a living target, because superadditivity of the effects of biologically-defined doses of different kinds of ionizing radiation delivered concurrently has never been observed.

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