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Central nervous system radiation syndrome in mice from preferential $^{10}B(n,\alpha)^{7}Li$ irradiation of brain vasculature

(lethality/endothelium/x-ray/enhancement)

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ABSTRACT **Ionizing radiations were directed at the heads of anesthetized mice in doses that evoked the acute central nervous system (CNS) radiation syndrome. Irradiations were done using either a predominantly thermal neutron field at a nuclear reactor after intraperitoneal injection of ^{10}B-enriched boric acid or 250-kilovolt-peak x-rays with and without previous intraperitoneal injection of equivalent unenriched boric acid. Since ^{10}B concentrations were ≈3-fold higher in blood than in cerebral parenchyma during the reactor irradiations, more radiation from α and ^{7}Li particles was absorbed by brain endothelial cells than by brain parenchymal cells. Comparison of the LD_{50} dose for CNS radiation lethality from the reactor experiments with the LD_{50} dose from the x-ray experiments gives results compatible with morphologic evidence that endothelial cell damage is a major determinant of acute lethality from the CNS radiation syndrome. It was also observed that boric acid is a low linear energy transfer radiation-enhancement agent *in vivo*.**

Irradiation of the head of a mouse by more than 120 Gy of x-rays usually causes death from the acute central nervous system (CNS) radiation syndrome within 3.5 days after irradiation (1). Blood vessels are damaged in the acute CNS syndrome (2). If a ^{10}B-enriched substance is injected rapidly into a mouse and then penetrates the blood–brain barrier slowly, endothelial cells and parenchymal cells of the brain will be irradiated unequally by heavy charged particles (HCP) from the $^{10}B(n,\alpha)^{7}Li$ nuclear reaction (3) when the head is exposed to thermal neutrons before concentrations of borate in the vascular and extravascular fluid compartments of the brain equilibrate. Thus, slow penetration of the blood–brain barrier by borate anions facilitates boron-neutron capture irradiation of the brain to induce the CNS radiation syndrome in the mouse under conditions of preferential irradiation of brain endothelial cells. The lethality of such microscopically anisotropic irradiation of mouse brains is compared quantitatively with comparable lethality from exposure of mouse brains to 250-kilovolt-peak (kV_P) x-rays to provide dosimetric evidence for an "endothelial" pathogenesis of the acute CNS radiation syndrome.§

METHODS

Irradiations. Anesthetized mice (8- to 16-week-old, female Swiss albino mice of the Brookhaven National Laboratory Hale–Stoner strain) were confined to plastic tubes for placement into body-shielding holders (Fig. 1) for boron-neutron capture irradiation or x-irradiation of their heads (5, ¶). Neutron exposures were carried out at the Brookhaven National Laboratory Medical Research Reactor (6), operated at 3 MW power. X-ray exposures were carried out with a Maxitron 250 (General Electric) at 250 kV_P through copper (0.5 mm) and aluminum (1.0 mm) filters (first half-value layer, 1.77 mm Cu; homogeneity coefficient, 0.49).‖ Boric acid [95.0 ± 0.5 atom % ^{10}B-enriched H_3BO_3 (Eagle-Picher, Miami, OK)** in reactor experiments or normal unenriched H_3BO_3 in some (see Table 3) x-ray experiments] was injected intraperitoneally 15–35 min before the start of irradiation in an aqueous solution that provided 12.5 μmol of boron and 0.02 ml of H_2O per g of body weight.

Dosimetry. The minor, naturally occurring stable isotope of boron, ^{10}B, has an exceptionally high effective capture cross-section for thermal neutrons, 3.40×10^{-25} m^2 at 2482 m·s^{-1}, the average neutron speed at 20°C (8, 9). In 6% of such captures, the $^{10}B(n,\alpha)^{7}Li$ reaction leads to the lower ^{7}Li energy state (E_α = 1.777 MeV; E_{Li} = 1.014 MeV; 1 eV = 1.602×10^{-19} J), whereas in 94% of captures, the reaction leads to the first excited state of ^{7}Li, from which a 478-keV photon is emitted (E_α = 1.471 MeV; E_{Li} = 0.839 MeV). For uniform distribution of boron, the kinetic energy released in matter (kerma) rate due to these HCP is, therefore, $7.68 \times 10^{-12}\ F_B\phi$ Gy·s^{-1}, where F_B is the ^{10}B mass fraction in the tissue and ϕ is the thermal neutron fluence rate (s^{-1}·m^{-2}).†† For endothelial cells, the usual assumption of equivalence between the kerma rate and the absorbed dose rate is inapplicable. Since endothelial cells demarcate the physiological blood–brain barrier anatomically (10, 11), and since blood ^{10}B concentrations were about 3 times greater than parenchymal ^{10}B concentrations during exposure to neutrons (Fig. 2, Table 1), there was then a significant difference between the average ^{10}B mass fractions in the blood, $F_{b,B}$, and in the parenchyma on the extraluminal side of endothelial cells, $F_{p,B}$. Almost all kinetic energy is imparted to small cylindrical volumes of tissue [≈14 μm long ($\alpha \approx 9$ μm, $^{7}Li \approx 5$ μm; ref. 13) and ≈0.1 μm in diameter] that envelop the colinear paths of the two mutually recoiling HCP. The radial gradi-

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Abbreviations: CNS, central nervous system; GyE, Gy equivalent; HCP, heavy charged particle; kerma, kinetic energy released in matter; kV_p, kilovolt peak; RBE, relative biological effectiveness.

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§Preliminary results of this study were presented at the 1986 Winter Meeting of the American Nuclear Society (4).

¶The upper surface of the plastic mouse holder (Fig. 1 *c* and *d*), not the upper surface of its Pb shield (5), was in a horizontal plane 9.5 cm below the focal point of the anode of the x-ray generator. Thermoluminescent dosimetry shows that mouse heads were irradiated within the penumbra of a cone of radiation from the x-ray generator and that backscattered radiation was less than estimated previously (5).

‖The homogeneity coefficient is the ratio of the first to the second half-value layer after penetration of the beam into a target.

**In some experiments, 95.0 ± 0.5 atom % ^{10}B-enriched boric acid prepared by P. C. Tompkins and A. D. Conger was used (7).

††The kerma rates (Gy·s^{-1}) due to α and ^{7}Li HCP are $4.89 \times 10^{-12}\ F_B\phi$ and $2.79 \times 10^{-12}\ F_B\phi$, respectively.

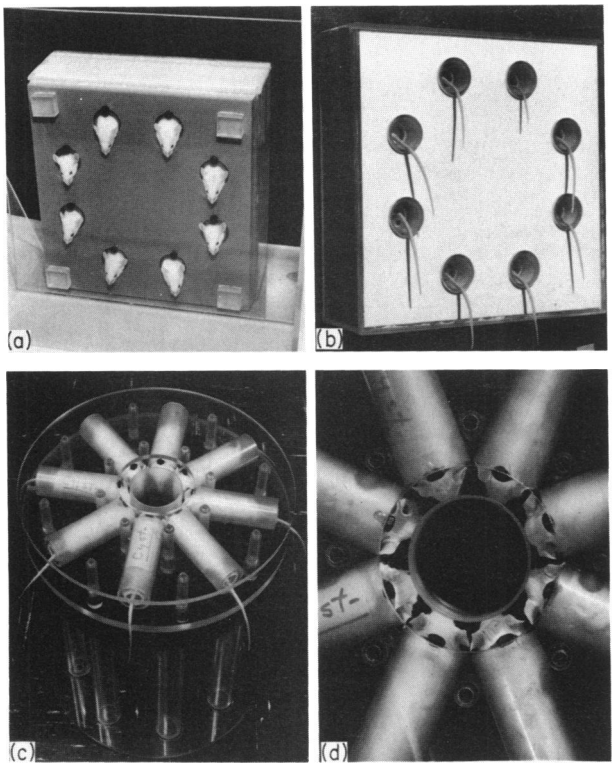

FIG. 1. (*a* and *b*) Reactor irradiation mouse holder; front (*a*) and rear (*b*) views. There is a 12-mm-wide air gap between the front face of the holder and the Bi metal face plate of the reactor port, into which mouse heads project downward. A plastic plate is used here as a transparent phantom for the Bi face plate. (*c* and *d*) Rotating x-irradiation mouse holder without its 1/4-inch Pb shield; general (*c*) and close-up (*d*) views. Mouse heads are irradiated in an unshielded 12-mm-wide air gap. Scale is indicated by the 1-inch diameter mouse tubes.

ents of absorbed dose in these slender cylinders are very steep (14, 15) and therefore are neglected because most

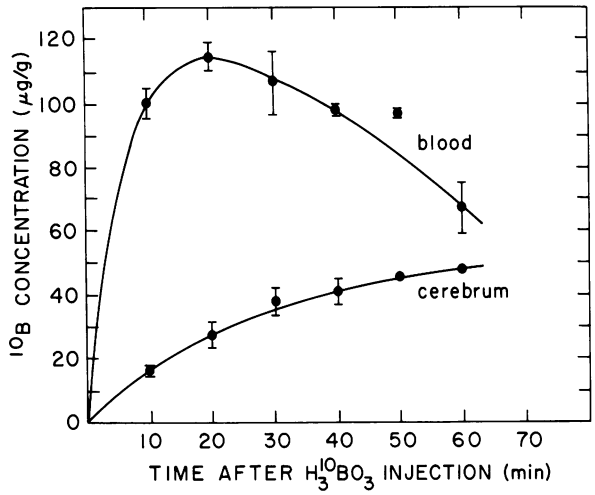

FIG. 2. Concentrations of ^{10}B in blood and cerebrum after a single intraperitoneal injection of boric acid [12.5 μmol of boron (12.0 μmol of ^{10}B) per g of body weight]. Each point in a vertical bar represents mean and range of ^{10}B concentrations in two to four mice. At 50 and 60 min after injection, cerebral concentrations are from one mouse each.

blood vessels have dimensions >0.5 μm.

Using either bare or Cd-shielded Au foils and wires with a polymethylmethacrylate mouse dosimetry phantom, it was determined that the thermal neutron fluence rate at the Bi metal face plate of the reactor port, against which mouse heads were buttressed (Fig. 1), was 6.9×10^{14} s^{-1}·m^{-2} (Cd ratio, ≈13), and that the fluence rate decreased almost exponentially by the factor e^{-107d} with distance d (in meters) from the vertical plane of the face plate to a parallel plane in the mouse phantom. This result was verified by inserting Au wires transversely at several positions in the brains of recently killed mice through a hypodermic needle and then irradiating the dead mice at the reactor as the experimental mice and the mouse dosimetry phantom were irradiated. Thus, the absorbed dose rate, $\dot{D}_{HCP,B}$ (Gy·s^{-1}), to endotheli-

Table 1. Reactor irradiations of ^{10}B-enriched boric acid-injected mice

Mouse group	Duration of irradiation, s	Average H_3BO_3 injection to midirradiation interval (±SD), min	Average ^{10}B concentration during irradiation, μg/g		Mortality <4 days after irradiation, fraction
			Blood	Cerebrum	
R1B	903.7	40 ± 6	98	41	9/24
R1C	1053.7	42 ± 4	95	42	9/24
R2B	903.7	29 ± 4	109	35	22/24
R2C	1053.7	34 ± 5	104	38	24/24
R3C	1053.7	30 ± 3	108	35	27/27
R3B	903.7	24 ± 3	113	31	24/28
R4A	753.7	26 ± 4	112	33	10/20
R4B	903.7	29 ± 5	109	35	22/24
R4C	1053.7	29 ± 3	109	35	19/22
R5A	753.7	25 ± 2	112	32	39/56
R5B	903.7	25 ± 2	112	32	45/48
A (normalized)	[804]	—	[105]	—	49/76
B (normalized)	[937]	—	[105]	—	122/148
C (normalized)	[1044]	—	[105]	—	79/97
	[649]	—	Extrapolated [105]	[37]	[LD_{50}]

Summary of acute (<4 days postirradiation) mortality data from 321 anesthetized, $H_3{}^{10}BO_3$-injected (see text) mice exposed to a shutter-controlled irradiation port of the Brookhaven National Laboratory Medical Research Reactor (operated at 3 MW) with their heads unshielded and their bodies substantially shielded from thermal neutrons. The duration of irradiation that corresponds to LD_{50} was extrapolated from these data by normalizing the average concentration of ^{10}B in the blood during reactor irradiations (column 3) to a standard ^{10}B concentration (105 μg/g). The corresponding ^{10}B concentration in the cerebrum is 37 μg/g (see Fig. 2), a value that differs only slightly from the weighted average of observed values (35 μg/g). The extrapolation to LD_{50} was performed by probit analysis using Bliss's weighting coefficients (12).

Table 2. Significant sources of reactor-induced radiations in the brains of ^{10}B-injected mice

Source no., j	Type of radiation	RBE, R_j	Tissue dose rate, Gy·s^{-1} (SI units)
1	585-keV protons and 42-keV ^{14}C particles from ^{14}N(n,p)^{14}C	2.0 [R_N]	$7.06 \times 10^{-16}\ F_N\phi_o e^{-107d}$
2	478-keV γ photons from ^{10}B(n,α)^{7}Li	1.0	$1.0 \times 10^{-14}\ F_B\phi_o$
3	2.22-MeV γ photons from ^{1}H(n,γ)^{2}H due to the hydrogen content of the mouse head	1.0	$4 \times 10^{-18}\ \phi_o$
4	β particles from decay of radionuclides created by slow neutrons in tissue	1.0	$1 \times 10^{-18}\ \phi_o$
5	γ photons from the mouse holder and from the reactor	1.0	0.84×10^{-2}
6	Fast and epithermal neutrons from the reactor	2.0	1.17×10^{-2}
7	^{7}Li and α particles from ^{10}B(n,α)^{7}Li	— [R_B]	$7.68 \times 10^{-12}\ F_B\phi_o e^{-107d}$

Significant sources of radiation to brain cells of ^{10}B-treated mice, the heads of which were exposed to a port of the Brookhaven Medical Research Reactor operated at 3 MW. Indices j = 1–6 correspond to the most important radiations that accompany the radiations from the ^{10}B(n,α)^{7}Li reaction. R_B denotes the RBE of the HCP from the ^{10}B(n,α)^{7}Li reaction (relative to a standard RBE of 1.0 for 250-kV$_P$ x-rays) with respect to lethality from the acute CNS syndrome before 4 days after irradiation.

al cells from HCP due to ^{10}B in blood and parenchyma can be expressed as

$$\dot{D}_{HCP,B} = (7.68 \times 10^{-12})[f_B F_{b,B} + (1 - f_B)F_{p,B}]\phi_o e^{-107d}, \quad [1]$$

where: f_B is the fraction of the HCP dose to endothelial cells that would be due to ^{10}B in the adjacent blood if the endothelial cells were surrounded completely by a tissue with the same concentration of ^{10}B and the same HCP stopping power as the blood; $F_{b,B}$ and $F_{p,B}$ are the ^{10}B mass fractions in blood and parenchyma, respectively; ϕ_o is the thermal neutron fluence rate (s^{-1}·m^{-2}) at the face plate of the reactor port. Although the dose from ^{10}B within endothelial cells is neglected in these calculations because of our ignorance of the gradients of borate concentrations across these cells during irradiations, it is assumed that borate diffuses in aqueous tissue compartments and that ^{10}B concentrations in endothelial cells were intermediate between blood and parenchymal concentrations. The neglect introduces some error into these calculations (16), but if endothelium does not accumulate borate selectively this source of error must be small because of the thinness of endothelial cells relative to the range of alpha particles.

Other nuclides in brain tissue, most importantly ^{1}H, ^{14}N, ^{23}Na, ^{31}P, ^{38}Cl, and ^{41}K, also capture thermal neutrons and irradiate the brain by liberating HCP and photons and by forming β-emitting radionuclides. The non-^{10}B-related radiation dose rates to the brain (Table 2) are based on average concentrations of elements in the brain (17) and on generally accepted relative biological effectiveness (RBE) values (Table 2). As in the case of ^{10}B, the nitrogen mass fraction in mammalian blood is higher than that in brain: $F_{b,N} = 0.029$; $F_{p,N} = 0.019$ (17). Thus, the absorbed dose rate (Gy·s^{-1}) in endothelial cells due to 0.585 MeV protons and 0.042 MeV ^{14}C particles from the ^{14}N(n,p)^{14}C reaction (effective thermal neutron capture cross-section, 1.64×10^{-28} m^2) is‡‡

$$\dot{D}_{HCP,N} = (7.06 \times 10^{-16}) \times [f_N F_{b,N} + (1 - f_N)F_{p,N}]\phi_o e^{-107d}. \quad [2]$$

To a first approximation, $f_N = f_B = f$ because α particles from the ^{10}B(n,α)^{7}Li reaction and protons from the ^{14}N(n,p)-^{14}C reaction have similar ranges in tissue ($\approx$9 μm) and acquire a major portion of the energy liberated by their respective reactions of origin and because, in this study, the absorbed dose of HCP radiation to endothelial cells from ^{14}N disintegrations was <4% of that from ^{10}B disintegrations.

A tissue-equivalent ionization chamber (IC-17A, Far West Technology) was used to determine doses from exogenous gamma photons and from fast and epithermal neutrons while the reactor port was shielded with 2-mm-thick ^{6}Li metal to absorb thermal neutrons. In separate exposures, ^{7}Li-enriched thermoluminescent dosimeters (TLD-700, Harshaw/Filtrol Partnership) were irradiated at the center of small vials containing ^{6}Li-enriched LiF powder. The shapes of glow curves (18) and the activation of Au wires confirmed adequate shielding from thermal neutrons by ^{6}Li metal. The extrinsic γ (j = 5) and nonthermal neutron (j = 6) dose rates were determined by combining the thermoluminescent dosimeter and ionization chamber measurements. The dose rate from induced β radioactivity (j = 4) in the head was calculated by assuming that the average β particle track length within the head was half the average chord length in a 1-cm-diameter sphere ($\approx$3 mm) (19). The dose rates to the mouse head from γ photons generated by neutron capture reactions in the mouse (j = 2, 3) were calculated (20).

The total biologically effective dose rate [Gy equivalent (GyE)·s^{-1}] to brain endothelial cells in a vertical plane d meters from the face plate of the reactor port is then

$$(7.68 \times 10^{-12})R_B[fF_{b,B} + (1 - f)F_{p,B}]\phi_o e^{-107d} + (7.06 \times 10^{-16})R_N[fF_{b,N} + (1 - f)F_{p,N}]\phi_o e^{-107d} + \sum_{j=2}^{6} R_j\dot{D}_j, \quad [3]$$

where $\dot{D}_j$ (j = 2, . . ., 6) are absorbed dose rates from the five minor radiations (Table 2) that are assumed to irradiate the brain uniformly and R_j are the corresponding RBE with respect to death from the CNS radiation syndrome before 4 days after irradiation. R_B and R_N are the RBE for HCP from neutron capture by ^{10}B and ^{14}N, respectively. It is assumed that the arithmetic sum of GyE measures of biologically effective radiation from the individual components of the mixed reactor radiation field is an appropriate measure of the effectiveness of the combined radiations for acute CNS lethality.

X-ray dosimetry was performed with LiF thermoluminescent dosimeters. The absorbed x-ray dose rate, $\dot{D}_x$, at the anterior, buttressed surfaces of mouse heads was 153 ± 10 mGy·s^{-1}. The absorbed dose of x-rays in mice decreased radially by the factor e^{-21d}, where d (in meters) is the distance from the plane that is tangent to the vertical, cylindrical plastic head buttress of the x-irradiation mouse holder to a parallel plane of interest in the mouse or in the mouse dosimetry phantom. Because the width of the gaps between the anterior rims of the cylindrical tubes in which mouse bodies were confined and the vertical buttresses to which mouse heads were apposed was the same (12 mm) for x-ray and reactor irradiations (Fig. 1), structures in mice that were in transverse, vertical planes at the same distance d from these

‡‡For uniform distribution of nitrogen in tissue (mass fraction F_N, 99.63 atom % ^{14}N) the total kerma rate, $7.06 \times 10^{-16} F_N\phi$ Gy·s^{-1}, comprises $6.59 \times 10^{-16} F_N\phi$ from proton and $0.47 \times 10^{-16} F_N\phi$ from ^{14}C HCP, respectively.

two buttresses were anatomically comparable targets of irradiation.

This "endothelial" model of the pathogenesis of acute CNS radiation deaths implies the following equality for biologically equivalent doses of radiation (GyE) to endothelial cells in anatomically comparable planes of the brain from reactor irradiations (left side of equation) and from 250-kV_P x-rays (right side of equation):

$$t_r[(7.68 \times 10^{-12})\phi_o e^{-107d} R_B[F_{p,B} + f(F_{b,B} - F_{p,B})] + (7.06 \times 10^{-16})\phi_o e^{-107d} R_N[F_{p,N} + f(F_{b,N} - F_{p,N})] + \sum_{j=2}^{6} R_j \dot{D}_j] = t_x \dot{D}_x e^{-21d}, \quad [4]$$

where t_r and t_x are the extrapolated LD_{50} irradiation times for the reactor exposures (649 s; Table 1) and for the x-ray exposures (890 s; Table 3), respectively. The RBE of x-rays was assumed to be 1.0. Solving Eq. 4 for R_B, one derives an equality of the form

$$R_B = (K_1 e^{86d} - K_2(1 + K_3 f) - K_4 e^{107d})/(1 + K_5 f), \quad [5]$$

where K_1, K_2 . . . K_5 are constants calculated from the data of Tables 1, 2, and 3. These constants are 1.070, 0.0943, 0.526, 0.181, and 1.838, respectively. The relationships of Table 4 are computed from Eq. 5.

Boron Concentrations. Mice were exsanguinated under deep ether anesthesia before removing cerebra for ^{10}B analysis. Concentrations of ^{10}B in whole blood and cerebra were measured by prompt neutron activation analysis (21). The ^{10}B uptake in blood and cerebrum is shown in Fig. 2. Supplementary experiments (data not shown) indicate that the rate of transport of borate into brain parenchyma was not altered by approximate LD_{50} doses of reactor radiations or of x-radiation to the heads of mice during the first hour after injection of similar doses of boric acid.

RESULTS

The physical conditions of irradiations and the fractions of mice that died before 4 days after irradiation (day of irradiation = day 0) are summarized in Tables 1, 3, and 5. Characteristic signs of the acute CNS syndrome without diarrhea (1, 5) were observed during the first 3 days after irradiation. Those mice that lived 4 days or more after head irradiation died within 10 days after irradiation, apparently from combined gastrointestinal (2, 22, 23) and CNS radiation damage. Thus, the fraction of mice that died before 4 days after head irradiation was a convenient measure of the lethality of radiation damage to the brain (1). The brains of mice killed 2 days after an approximate LD_{50} dose of predominantly $^{10}B(n,\alpha)^7Li$ irradiation of the head show dilatation of capillaries and of pericapillary spaces with swelling of endothelial cell cytoplasm. The extravascular structures of the cerebrum (but not of the cerebellum) appear to be histologically normal 2 days after such reactor irradiation (J.A.L., unpublished data).

Table 3. X-ray irradiations of non-^{10}B-enriched boric acid-injected mice

Mouse group	Duration of irradiation, s	X-ray dose at head buttress, Gy	Average H_3BO_3 injection to midirradiation interval (± SD), min	Mortality <4 days after irradiation, fraction
X1D	1201.8	184	31 ± 3	28/32
X2B	901.8	138	36 ± 6	7/24
X2C	1051.8	161	33 ± 3	16/24
X2A	751.8	115	32 ± 2	4/24
X2D	1201.8	184	36 ± 3	24/24
X3B	901.8	138	37 ± 4	24/40
X3C	1051.8	161	39 ± 6	36/40
X4B	901.8	138	33 ± 5	33/56
X4C	1051.8	161	33 ± 2	45/56
B (cum.)	901.8	138	—	64/120
C (cum.)	1051.8	161	—	97/120
D (cum.)	1201.8	184	—	52/56
	[890]	[136]	Extrapolated —	[LD_{50}]

Summary of acute (<4 days postirradiation) mortality data from 320 anesthetized mice exposed to 250-kV_P x-rays. The heads were unshielded and the bodies were substantially shielded in a slowly rotating holder (Fig. 1) during exposure. Extrapolation to LD_{50} was by probit analysis using Bliss's weighting coefficients (12). Mice were injected with boric acid before irradiation (see text). cum, Cumulative.

DISCUSSION

Calculations of HCP doses to endothelial cells (24–26) show that f is within the range 0.1–0.5 for radiation targets that are <2 μm from a blood vessel lumen. Since vital structures of the CNS occupied the zone 8 mm < d < 16 mm in the cranial cavity and vertebral canal, it seems likely from the data of Table 4 that $R_B \leq 2.6$. The compatibility of this result with *in vivo* measurements of R_B (27–29) lends credence to an endothelial pathogenesis of the CNS radiation lethality syndrome and thereby underlines the significance of ^{10}B in the blood during boron neutron capture therapy of brain tumors (30, 31).

When the CNS radiation syndrome was evoked with x-

Table 4. Values of RBE that satisfy Eq. 5

f	R_B								
0.0	1.6	1.9	2.3	2.7	3.1	3.7	4.3	5.1	6.0
0.1	1.4	1.6	1.9	2.2	2.6	3.1	3.7	4.3	5.0
0.2	1.2	1.4	1.6	1.9	2.3	2.7	3.2	3.7	4.4
0.3	1.0	1.2	1.4	1.7	2.1	2.4	2.8	3.3	3.8
0.4	0.9	1.1	1.3	1.5	1.8	2.1	2.5	2.9	3.4
0.5	0.8	1.0	1.2	1.4	1.6	1.9	2.3	2.6	3.1
0.6	0.8	0.9	1.1	1.3	1.5	1.7	2.1	2.4	2.8
					d				
	0.008	0.010	0.012	0.014	0.016	0.018	0.020	0.022	0.024

R_B is the *in vivo* RBE of particle radiation from the $^{10}B(n,\alpha)^7Li$ reaction, distances d (meters) are measured horizontally from the mouse head buttress to radiation targets in the mouse (see text), and f is the average fraction of heavy charged particle radiation to endothelial cells that would be derived from disintegration of ^{10}B in the lumens of blood vessels if ^{10}B were distributed uniformly around those cells at the same concentration as in the blood (see text).

Table 5. X-ray irradiations of non-boric acid-injected mice

Mouse group	Duration of irradiation, s	X-ray dose at head buttress, Gy	Mortality <4 days after irradiation, fraction
X1D′	1201.8	184	8/30
X1E′	1351.8	207	17/28
X2D′	1201.8	184	6/28
X2E′	1351.8	207	7/31
X3D′	1201.8	184	4/36
X3E′	1351.8	207	12/36
X4D′	1201.8	184	7/32
D′ (cum.)	1201.8	184	25/126
E′ (cum.)	1351.8	207	36/95
		Extrapolated	
	[1445]	[221]	[LD_{50}]

Summary of acute (<4 days postirradiation) mortality data from 221 anesthetized mice, the heads of which were exposed to 250-kV_P x-rays (Fig. 1). Extrapolation to LD_{50} was by probit analysis using Bliss's weighting coefficients (12). Boric acid was not administered to these mice. cum., Cumulative.

rays after injection of boric acid (Table 3), the LD_{50} was 136 Gy. Without preinjection of boric acid (Table 5), the LD_{50} was 221 Gy. Thus, boric acid is a low linear energy transfer radiation-enhancement agent with a radiation-enhancement factor of ≈1.6. Whether this enhancement is primarily biochemical or primarily radiochemical (32), is unknown. Nevertheless, it should be considered appropriate for any prospective boron neutron capture therapy boron carrier substance to be tested for its radiation-enhancement or radiation-protective characteristics.

A RBE value of 2.3 for ^{10}B-neutron capture radiation, determined from an *in vitro* V79 Chinese hamster cell radiation lethality experiment (33), is within the RBE ≤2.6 limit indicated by this *in vivo* study.§§ Whether this *in vitro–in vivo* correspondence reflects radiation damage to similar structures in V79 cells and in brain endothelial cells may be doubted because of the 34-fold difference between the radiation doses (≈4 Gy and ≈136 Gy, respectively, from 250-kVp x-rays) required to observe 50% death in the two disparate experimental systems. A RBE of 3.7 reported for the lethality of $^{10}B(n,\alpha)^7Li$ radiation *in vitro* (34) is apparently inapplicable to acute CNS lethality *in vivo* because such a large RBE would place the most vital targets of brain irradiation outside the cranial cavity, at least 18 mm (Table 4) from the head buttress.

§§Atypical mortality fractions were observed from only 72 of the 617 mice used to estimate the range of RBE for HCP from the $^{10}B(n,\alpha)^7Li$ reaction *in vivo* [in groups R1B and R1C (Table 1) and X2B (Table 2)]. Since the number of mice in each group is a multiplicative factor for statistical weight of the group in this probit analysis (12), elimination of the atypical data would not appreciably affect the results of the study.

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