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NEUTRON CAPTURE THERAPY FOR MELANOMA

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INTRODUCTION

The dose-limiting factor in cancer radiation therapy is the
tolerance level of normal tissues within the radiation field. In
boron neutron capture therapy (BNCT), thermal neutrons interact
with boron via the $^{10}B(n,\alpha)^7Li$ reaction (Taylor, 1935) to produce
short-range ($\sim$ 5-9 μm), high-linear energy transfer radiations
which have a large relative biological effectiveness (RBE) (Gabel,
1984; Fukuda, 1987). In theory, selective localization of ^{10}B
within the tumor should allow most of the dose to be restricted to
the tumor (Locher, 1936). The failure of the initial clinical
trials of BNCT, carried out between 1953 and 1961 at Brookhaven
National Laboratory and the Massachusetts General Hospital (Farr,
1954; Goodwin, 1955; Asbury, 1972) was attributed to two major
factors: (i) the use of boron-containing compounds which showed
no selective accumulation in tumor and (ii) the rapid attenuation
in tissue of the incident thermal neutron beam. The high neutron
doses employed resulted in excessive surface tissue exposure; via-
ble tumor was found at depth following the neutron irradiations.
The substantial levels of boron in blood during irradiation con-
tributed to the damage to normal brain vasculature (tumor/blood
ratio <1).

The development of boron-containing compounds which localize
selectively in tumor may require a tumor-by-tumor type of approach
that exploits any metabolic pathways unique to the particular type
of tumor. Melanin-producing melanomas actively transport and
metabolize aromatic amino acids for use as precursors in the syn-
thesis of the pigment melanin. It has been shown that the boron-

containing amino acid analog p-borono-phenylalanine (BPA) is
selectively accumulated in melanoma tissue, producing boron con-
centrations in tumor that are within the range estimated to be
necessary for successful BNCT (Mishima, 1983; Coderre, 1987). We
report here the results of therapy experiments carried out at the
Brookhaven Medical Research Reactor (BMRR).

METHODS

Murine Melanoma

Adult female BALB/c mice ($\sim$ 15-20 g) in which the Harding-
Passey melanoma had been implanted subcutaneously on either the
abdomen or the thigh were used. This tumor has been maintained in
our laboratory by serial transplantation for over 10 years and is
reproducible with respect to melanin content and uptake of mela-
nin affinic agents. Melanin content (0.68% melanin by weight) is
analogous to that found in human melanotic melanoma (0.1 to 0.8%;
average value, 0.35%) (Watts, 1981). The Harding-Passey melanoma
does not metastasize but grows at the original subcutaneous im-
plantation site with a volume doubling time of about 3 days. The
subcutaneous location of this heavily pigmented tumor facilitates
volume measurements. For therapy experiments, tumors between 30
and 100 mg in size were chosen; this size corresponds to 14-18
days of growth. Tumors which have grown to this size do not
undergo spontaneous remission. Mice with untreated tumors or mice
with tumors which eventually resumed growth following the irradia-
tion procedures were sacrificed when the tumors became unneces-
sarily large (approximately 2-3 cm^3). Mice whose tumors did not
regrow after therapy were monitored until they became incapaci-
tated by old age near the end of a normal lifespan ($\sim$ 18 months).

BMRR Dosimetry

The BMRR is a 5-MW modified, pool-type nuclear reactor
designed for biomedical research (Godel, 1960). The BMRR has been
the site of numerous BNCT experiments; the irradiations described
here were done at the BMRR patient port. Fast neutron and gamma
doses were measured directly using standard tissue equivalent and
graphite-CO_2 chambers as well as TLD-700 dosimeters (Robertson,
1972; Fairchild, 1966). Contributions from the $^{14}N(n,p)^{14}C$ and
$^{10}B(n,\alpha)^7Li$ reactions were calculated from gold foil measurements
of thermal neutron flux density and corrected for resonance re-
sponse by the cadmium difference technique (Beckurts, 1964).

Irradiation Procedures

During irradiations, mice were anesthetized with sodium pen-
tabarbital (65 µg/g body weight via i.p. injection). To evaluate

the radiosensitivity of the Harding-Passey melanoma to conven-
tional x rays, mice bearing thigh tumors were irradiated with a
Phillips RT-100 superficial x-ray machine using 100 kVp x rays
(1.7 mm Al added filtration) at a dose rate of 1000 rad per min.
The tumor-bearing region of the thigh was exposed directly, the
body and foot were shielded with lead.

For neutron irradiations, the BMRR patient port thermal beam
(25 x 25 cm) was restricted to 1.5-cm diameter using an insert of
1:1 ^{6}LiF mixed with epoxy resin molded to collimate the beam at
the port center. Additional body shielding was provided by sheets
of lithium metal in oil-filled plastic bags. The tumor-bearing
leg was extended over the 1.5-cm beam port during irradiation.
Neutron exposures ranged from 2.5 to 6.7 x 10^{12} n/cm^2.

Therapeutic Endpoint

The endpoint used to assess the effectiveness of the tumor
irradiations was a determination of tumor growth delay or tumor
control. Tumor size was measured daily following irradiation.
Tumor volumes were estimated by the formula $v \approx 0.5\ ab^2$, where a
and b are the longest and shortest diameters, respectively
(Rofstad, 1985). Tumor volumes were normalized to the volume on
the day of irradiation, then averaged for each group. Irradiated
tumors exhibited a longer volume doubling time and, at higher
doses, a lag period of no growth followed by a resumption of
growth at a slower rate than unirradiated controls. Tumors show-
ing apparent growth control, following irradiation, were monitored
for subsequent regrowth during the residual lifespan of the
mouse. Tumor growth control was considered complete only if the
mouse lived out its residual lifespan (over 1 year) with no evi-
dence of tumor regrowth.

RESULTS AND DISCUSSION

Distribution Studies

We have recently described the results of our tumor uptake
and distribution studies (Coderre, 1987). Using the Harding-
Passey melanoma carrying s.c. in BALB/c mice, we have demonstrated
that BPA is taken up by melanoma tissue to a much greater extent
than by normal tissues. Following a single i.p. injection or a
series of injections given over 1 h, the accumulation of boron in
melanoma was found to be transient, reaching a maximum approxi-
mately 6 h post-injection. The concentrations of boron achieved
in tumor ranged from 9-33 μg/g and are within the range estimated
to be necessary for successful application of the nuclear reaction
^{10}B(n,α)^{7}Li for neutron capture therapy. Boron concentrations in
tumor and tissues were determined using either a prompt-gamma

spectroscopic technique or by quantitative neutron capture radio-
graphy using whole-body sections. Distribution studies with the
resolved stereoisomers of BPA indicated that the L isomer is pre-
ferentially accumulated in the melanoma compared to the D isomer
(see Figure 1). The L isomer of BPA was shown to be targeted to
actively dividing tumor cells by simultaneously comparing the
boron and [^{3}H]thymidine ([^{3}H]Thd) distribution in tumor (see
Figure 2).

Toxicity of BPA

BPA is not toxic. We have been unable to deliver a lethal
dose of BPA to mice by normal means. The solubility of BPA at pH
values which are tolerated physiologically is about 6 mg/ml.
Volume limits the amount that can be administered. At this con-
centration, i.v. injections are limited to roughly 3 mg (150 mg/kg
body weight). Using i.p. injections, we have been able to admin-
ister 6 mg (1-ml i.p. injection) or up to 12 mg (four 0.5-ml i.p.
injections over the course of 1 h). Even at the highest i.p. dose
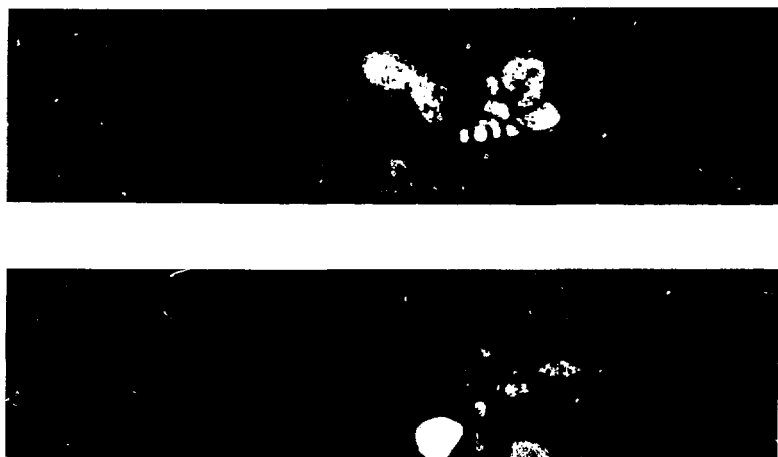of 12 mg (600 mg/kg), no toxic effects were observed.

Fig. 1.   Distribution of L-BPA vs. D-BPA. Tumor-bearing mice
           given injections of D-BPA or L-BPA, sacrificed 6 h post-
           injection; whole-body sections prepared; neutron capture
           radiograms shown. Top, D-BPA containing natural abun-
           dance boron; neutron fluence - 6.0×10^{12} n/cm^2. Bottom,
           ^{10}B-L-BPA; neutron fluence - 1.2×10^{12} n/cm^2. Note
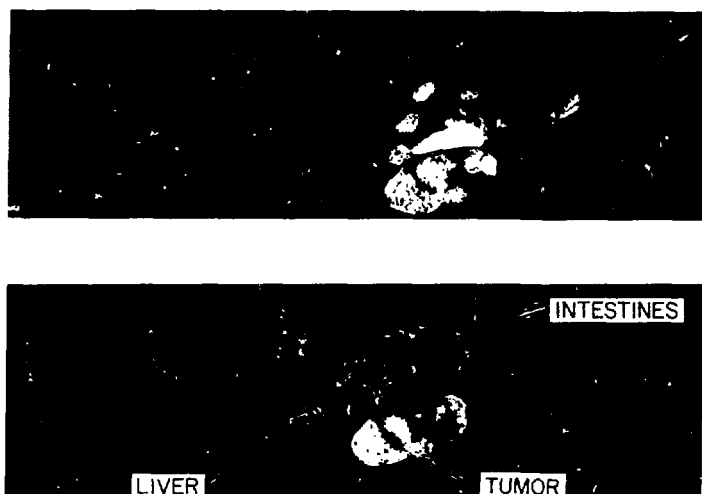   preferential accumulation of L-BPA in melanoma.

Fig. 2. Double labeling with boron and [^{3}H]Thd. Tumor-bearing
mouse given injections of both ^{10}B-L-BPA and [^{3}H]Thd;
whole-body sections prepared. Top, neutron capture
radiogram prepared from whole-body section. Neutron
fluence used to generate this image - 2.4 x 10^{12} n/cm^2.
Bottom, [^{3}H]Thd autoradiogram prepared from same whole-
body section used for neutron capture radiogram. Note
highest concentrations of boron in tumor correspond
closely with areas of rapid cell division identified by
[^{3}H]Thd incorporation.

Oral Dose

Since our distribution data indicated that bolus injections
were most effective, we have recently begun using oral administra-
tion of BPA as a slurry in water to deliver as much as possible in
a single dose. The time course for tumor uptake was similar to
i.p. injections; at 6 h post- (oral) injection, the tumor values
were maximal. The amount of BPA that can be delivered orally is
now increased to a maximum of 40 mg (2000 mg/kg). Even at this
high oral dose of 40 mg, BPA was not toxic. This is in contradic-
tion to previously published reports for the LD$_{50}$ of BPA of 1600
mg/kg (Soloway, 1961) and 840 mg/kg (Mishima, 1980) administered
i.p. These values were obtained using aqueous solutions of BPA at
a pH of 10 and 3, respectively, in order to increase the solubil-
ity. The observed toxicities were probably due to the extremes of
pH utilized.

Table 1.   Boron content of tissues (μg/g) following an oral
            dose of BPA

No. of Mice	Blood	Tumor	Muscle	T/B	T/M
n = 2	3.1 + 0.8	23.8 + 3.2	5.1 + 0.7	7.7	4.7
n = 5	7.6 + 2.3	41.1 + 2.1	8.7 + 2.1	5.4	4.7

Using a standard dose of 15 mg ^{10}B-L-BPA in 0.5 ml water, sacrifice at 6 h, we have been able to increase the boron concentration in the tumor considerably. Table 1 summarizes these results.

Therapy Experiments

Table 2 summarizes the dosimetry calculations for the mouse leg irradiations at the BMRR. The total dose to the tumor during BNCT depends on the ^{10}B concentrations in the tumor. The contribution to the dose from the ^{10}B(n,α)^{7}Li reaction was calculated by assuming 15 μg ^{10}B/g tumor; actual boron concentrations in tumor varied from 15-30 μg/g (Coderre, 1987). Using the dose estimates given in Table 2, exposure times at the BMRR were chosen to give total doses in the therapeutic range. The BMRR operating power was 1 megawatt (MW); exposure times were 3, 6, and 8 minutes (the corresponding fluences were 2.0, 5.0, and 6.7 x 10^{12} n/cm^2, respectively). The doses to normal tissue within the neutron field at these exposure times were 234, 468, and 624 (rad x RBE), respectively. (Absorbed dose in a mixed radiation field is expressed as effective dose (rad x RBE), due to the different relative biological effectiveness (RBE) of the component radiations). The corresponding doses to tumor, assuming a ^{10}B concentration of 15 μg/g, are 1020, 2040, and 2720 (rad x RBE). The whole-body doses were 144, 288 and 384 (rad x RBE).

Preliminary BNCT experiments using BPA and the conditions outlined above indicated that irradiation for 3 MW-minutes produced only transient growth delays, whereas, 6 and 8 MW-minute exposures resulted in significant tumor growth delays (>4 weeks), as compared to irradiated controls, while still holding the whole-body dose within tolerable limits.

Figures 3 and 4 show the results of BNCT experiments carried out at the BMRR with exposure times of 6 and 8 MW-minutes, respec-

Table 2. Dosimetry for mouse irradiations at the BMRR.
Irradiations and dosimetry measurements using
a ^{6}LiF/epoxy (1:1) collimator with a 1.5-cm
cone aperture; reactor power, 1 MW.

Component	Dose Rate (rad/min)	RBE	Effective Dose Rate (radxRBE/min)
Gamma	8	1	8
Fast neutrons	20	2	40
Thermal neutrons	15	2	30
Total	43		78
^{10}B(n,α)^{7}Li (assuming 15 µg ^{10}B/g)	105	2.5	262
Total + ^{10}B	148		340

Flux density, bare port face   = 1.93×10^{10} n/cm^2.sec
Flux density, center of aperture = 1.15×10^{10} n/cm^2.sec
Flux density w/mouse leg
 (i.e., 20% backscatter)   = 1.38×10^{10} n/cm^2.sec
Fluence (Φ) (1 minute)   = 8.4×10^{11} n/cm^2
^{14}N(n,p)^{14}C dose* (rad)   = $(1.84 \times 10^{-11})(\Phi)$ = 15 rad/min

^{10}B(n,α)^{7}Li dose* (assuming 15 µg ^{10}B/g tissue)   = $(1.26 \times 10^{-10})(\Phi)$ = 105 rad/min

*Fairchild, 1966

tively. Tumor volumes were normalized to the day of irradiation;
each line is the average of 6 mice. Irradiation in the absence of
^{10}B delivers a dose sufficient to delay tumor growth (5 and 6
weeks for 6 and 8 MW-minutes, respectively), but all "neutrons
only" controls eventually regrew. In the 6 MW-minute experiment
shown in Figure 3, neutron irradiation in the presence of BPA pro-
duced growth delays of from 5 to 7 weeks, yet all of these tumors
also eventually regrew. At 8 MW-minutes (Figure 4), however, of
the 6 BPA-containing tumors, 3 resumed growth after delays of from
7 to 10 weeks, but the remaining 3 showed complete tumor growth
control, surviving for over 1 year with no sign of tumor re-
growth. Figure 5 shows the individual growth data for the 6
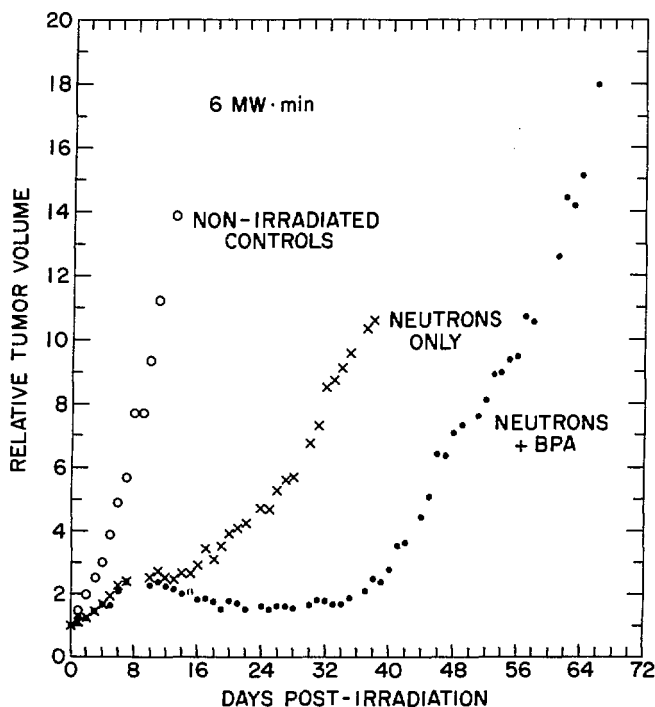tumors in the "neutrons + BPA" group in Figure 4.

Fig. 3.   BNCT at BMRR; neutron fluence - 5.0×10^{12} n/cm^{-2}.
BALB/c mice bearing Harding-Passey melanoma subcutane-
ously on thigh each received 12 mg BPA (four 0.5-ml in-
jections/1 h); irradiated 6 h after final injection.
Each line = average 6 mice. Tumor volumes normalized to
day of irradiation. Tumor dose, neutrons only = 468
(rad x RBE). Tumor dose, neutrons + BPA = 2040 (rad x
RBE). Whole-body dose = 288 (rad x RBE).

        The experiments described here show that the response of the
Harding-Passey melanoma to BNCT after a fixed course of BPA
injections was directly related to the neutron fluence; increasing
the exposure time resulted in longer tumor growth delays. At the
highest neutron fluence utilized, 6.7×10^{12} n/cm^2 (8 MW-minutes),
3 of 6 treated tumors regressed completely and did not regrow
during the remainder of the mouse's lifespan. The calculated
absorbed dose for the tumor at this exposure level was 2720 (rad x

Table 3.   BNCT using BPA and the Harding-Passey Melanoma in
           BALB/c Mice

No. of mice	Dose	Neutron Exposure[a]	Positive response[b]
6[c]	12 mg i.p.	6 MW-min	0/6
6[d]	12 mg i.p.	8 MW-min	3/6
8	15 mg oral	8 MW-min	7/8
6	15 mg oral	6 MW-min	5/6

[a]One megawatt minute (MW-min) corresponds to a neutron fluence
of 8.4×10^{11} n/cm^2

[b]To be counted as a positive response, the tumors must undergo
complete and permanent regression.

[c]Results illustrated in Figure 3.

[d]Results illustrated in Figures 4 and 5.

RBE). This apparently curative dose is in concordance with the
observed sensitivity of the Harding-Passey melanoma to 100 kVp x
rays. The x-ray dose required to cure 50% of treated tumors was
about 3000 rad. The absorbed dose to the tumor in control mice
that received no BPA was 624 (rad x RBE). The effect of the BPA
treatment was, therefore, to increase the effective radiation dose
to the tumor by about 4.4 relative to controls which received no
BPA prior to irradiation. The therapeutic gain or ratio of tumor
dose to normal tissue dose within the treatment volume was ~ 3.3,
assuming a tumor/normal tissue boron distribution of 10 to 1. It
should be noted that this radiation enhancement was achieved un-
evenly over the tumor with the highest effective radiation doses
concentrated in the most actively growing areas of the tumor. The
growth rates of unirradiated tumors were unaffected by administra-
tion of BPA.

Additional Therapy Experiments

Using the oral delivery method for BPA, higher boron concen-
trations can be achieved in the tumor (25-45 µg $^{10}B/g$). Therapy
experiments are summarized in Table 3 which illustrate the greater
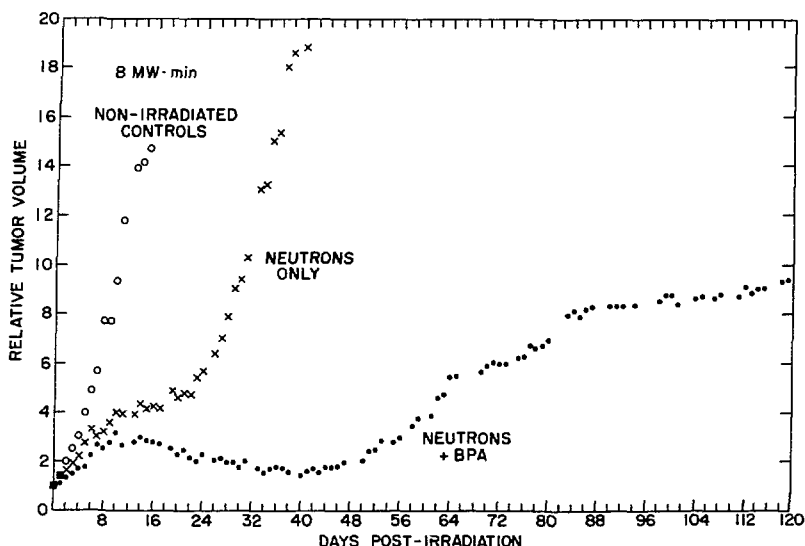effectiveness of BNCT following the oral doses of BPA.

Fig. 4. BNCT at BMRR; neutron fluence - 6.7×10^{12} n/cm^{-2}. Experimental details as in Fig. 3, except: tumor dose, neutrons only = 624 (rad x (RBE); tumor dose, neutrons + BPA = 2720 (rad x RBE). Whole-body dose = 384 (rad x RBE).

Dose Fractionation in BNCT

Conventional radiation therapy is given in multiple small doses in order that normal tissues within the treatment volume can repair sublethal damage. This assumes that normal tissues have a greater capacity for repair of such damage than malignant tissues.

Our demonstration of the ability to produce complete and permanent tumor regression of the murine melanoma implanted subcutaneously on the thigh with a single BPA/BNCT treatment enables us to utilize this model for testing the effects of dose fractionation on the effectiveness of BNCT. To date, one experiment has been carried out. All mice received 15 mg of ^{10}B-L-BPA orally 6 h prior to irradiation. Group 1 received BPA followed by 6 MW-min of neutron irradiation. Group 2 received BPA and 3 MW-min, then 2 days later, another full dose of BPA and another 3 MW-min. The results:

        Group 1 (6 HW-min)   0/6   complete regression
        Group 2 (3 + 3 MW-min) 4/6   complete regression
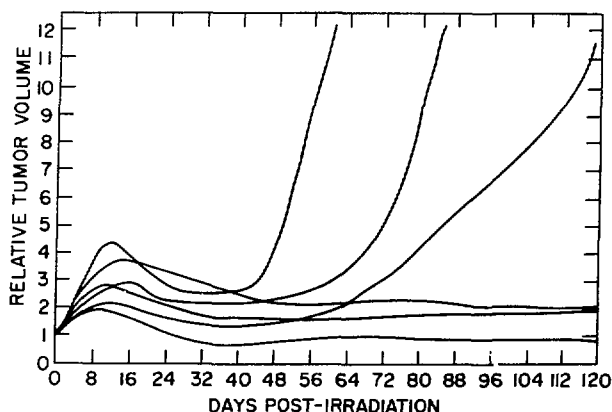
Fig. 5.   Individual tumor growth curves from neutrons + BPA group
         shown in Fig. 4.   Of 6 tumors treated, 3 eventually grew,
         3 were controlled.   Average of 6 lines shown produced
         neutrons + BPA line in Fig. 4.

These results are preliminary, but the greater effectiveness of
the fractionated therapy may be due to the killing of cells in the
second irradiation that were somehow missed during the first irra-
diation.   This could be due to a non-uniform boron distribution
within the tumor or perhaps to the presence of a latent cell pool.

        Boron-containing compounds that show affinity for a wide
variety of tumors (such as boronated porphyrins or antibodies)
would be ideal for BNCT, but efforts to develop such compounds
have not yet been able to demonstrate biological efficacy.   It may
be that BNCT of a particular type of tumor will require the iden-
tification and development of boron-containing compounds with spe-
cific affinity for that tumor; such affinity may also provide for
favorable distribution within the tumor.   BPA is demonstrably the
first example of such a compound.   As an analog of a melanin pre-
cursor, BPA selectively delivers boron to murine melanoma, espe-
cially to rapidly growing areas of the tumor, making it possible
to obtain ratios of boron in tumor to that in normal tissues in
the range of 5 to 15.   To our knowledge, such selective accumula-
tion in tumor of a systemically applied boronated compound has not
been reported.   NCT with the sulfhydryl borane BSH is based pri-

marily on its exclusion from normal brain by the blood-brain bar-
rier, rather than by selective binding. However, high blood boron
concentrations from BSH present obvious problems, as it is be-
lieved that damage to normal tissue blood vessels is a limiting
factor in radiotherapy of brain tumors (Sweet, 1986; Moustafa,
1980).

Investigators in Japan have described the enhanced killing
effect of thermal neutrons on melanoma cells in vitro that had
been preincubated with BPA (Ichihashi, 1982; Itsumi, 1986).

Mishima (1983) has described the use of BPA to effect the
apparent cure of a spontaneously occuring melanoma in a Duroc pig
and to suppress the growth of the Green melanoma in hamsters, fol-
lowing a single thermal neutron treatment. In the pig experiment,
the BPA was administered via two peri-lesional injections at 19 h
and 20 min before the irradiation. Mishima has recently carried
out the first BNCT treatment of human melanoma using BPA (de-
scribed at this Workshop), initial results are encouraging.

We have shown that BPA has little or no affinity for either a
mammary adenocarcinoma (Coderre, 1987) or the KHJJ murine mammary
tumor carried in BALB/c mice (unpublished data). Interestingly,
preliminary results indicate that BPA does accumulate signifi-
cantly in a poorly pigmented B-16 melanoma carried in C57Bl mice
(unpublished data). This observation implies that BPA uptake is
dependent upon amino acid transport and not upon melanin synthe-
sis. Human melanoma metastases vary significantly in degree of
pigmentation (Watts, 1981). If BPA can accumulate in both pig-
mented and non-pigmented metastatic sites, the chances for suc-
cessful BNCT will be greatly enhanced.

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DISCLAIMER