THE POSSIBLE USE OF NEUTRON-CAPTURING ISOTOPES SUCH AS BORON^{10} IN THE TREATMENT OF NEOPLASMS. II. COMPUTATION OF THE RADIATION ENERGIES AND ESTIMATES OF EFFECTS IN NORMAL AND NEOPLASTIC BRAIN [1]

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The nuclei of the principal atoms found in normal living tissue have but little tendency to capture very slow (thermal) neutrons, whereas the nuclei of a certain few isotopes have a remarkable propensity for capture of thermal neutrons. Among the isotopes in the latter group, boron^{10} (B^{10}) attracted the attention of Kruger (1) and of Zahl, Cooper, and Dunning (2) as early as 1940 because the capture reaction yields a high energy alpha particle which dissipates all its energy in tissue within *circa* 14 μ. The reaction may be written:

$$B^{10} + n \rightarrow [B^{11}] \rightarrow Li^{7} + \alpha^{++} \text{ (2.4 mev.)}.$$

These writers pointed out that if B^{10} were concentrated in a neoplasm which was then irradiated with slow neutrons, the tumor might be destroyed. Since the destructive effect of the α particle will be limited either to the cell containing the parent atom of B^{10} or to cells in its immediate neighborhood, normal cells are likely to survive.

If this idea is to bear fruit in treatment of tumors in man, we need: *1*) a powerful source of slow neutrons, *2*) a method for achieving a high differential concentration of boron in tumor as compared with normal tissue, and *3*) information as to the absolute concentration of the boron in various tissues which would be essential for destruction of only the neoplastic cells by the energies consequent upon the neutron beam. Of these requirements No. *1* is now supplied by the intense beam of slow neutrons emerging from the nuclear reactor at the Brookhaven National Laboratories. Sweet and Javid (3) have recently described steps toward meeting the second requirement insofar as intracranial tumors are concerned. Briefly, it was found that if borax is injected intravenously it will appear in many rapidly growing brain tumors in ratios of $> 3:1$ as compared with normal brain. A maximal differential of 48:1 was recorded in one case. The peak ratios are usually present only during the first 15–30 minutes after injection. Clinical analyses indicate that the actual concentration attained in the brain tumors after the nontoxic dose of 15 g. borax/70 Kg. body weight is > 50 μg. B/g. of tumor, whereas the normal gray matter contains only about 15 μg. B/g. of tissue. The normal white matter contains even less. The amounts found in blood are insufficient to account for the larger concentration in tumor. The scalp contains less than the blood, tumor, or muscle. Figure 1 shows the variations in concentrations in boron in six types of tissue taken in a series of biopsies during operative removal of a glioblastoma multiforme. (The colorimetric method of Ellis, Zook and Baudisch [4] was used for the boron determinations.[3])

We also present here our moves toward requirement No. *3*, an estimate of the energies released and of their effects, but before we do so a summary of the pertinent background facts of nuclear physics in relation to biology may be helpful.

Most of the nuclear radiations, *i.e.*, gamma rays, beta particles, alpha particles (helium atoms with a double positive charge), protons and fast neutrons, are usually produced at radioactive decay with large energies ranging up into a few millions of electron volts (mev.). When rays

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or particles at these high energies react with matter dissipating their energies, the net result is the displacement of orbital electrons ionizing the remaining atom, with a potentially lethal effect on neighboring living tissue. These reactions are relatively nonspecific and most of the atoms of matter participate in them.

However, thermal neutrons, those whose speed has been cut down to about 2,200 meters/sec., leaving them with an energy of only .025 electron volts (ev.), interact with matter in an entirely different and much more specific fashion. Their energy, and that of the so-called epithermal neutrons moving somewhat faster, is insufficient to produce ionization, since approximately 10 electron volts is required to displace an orbital electron. Neutrons at these lower energies react with the atoms in living tissues largely by undergoing capture by the nuclei of certain of the atoms they meet.

An atomic nucleus that has captured a neutron becomes a new compound nucleus with an excess of energy which it immediately gives up in one of two major ways by:

(*1*) Emission of a capture radiation (gamma ray or heavy particle) forming a stable isotope.

$$\text{hydrogen}^1 + \text{neutron} \rightarrow [\text{hydrogen}^2] \rightarrow \text{hydrogen}^2 + \text{gamma ray}$$

$$H^1 + n \rightarrow [H^2] \rightarrow H^2 + \gamma \ (2.23 \text{ mev.})$$

$$\text{boron}^{10} + \text{neutron} \rightarrow [\text{boron}^{11}] \rightarrow \text{lithium}^7 + \text{alpha particle}$$

$$B^{10} + n \rightarrow [B^{11}] \rightarrow Li^7 + \alpha^{++} \ (2.4 \text{ mev.})$$

(*2*) Emission of a capture radiation (gamma ray or heavy particle—in the example below, a proton), forming a radioactive daughter which then continues to emit a further radiation at its characteristic rate.

$$\text{nitrogen}^{14} + n \rightarrow [\text{nitrogen}^{15}] \rightarrow \text{proton} + \text{carbon}^{14} \xrightarrow{\frac{\text{half life}}{5{,}700 \text{ years}}} \text{nitrogen}^{14} + \text{electron}$$

$$N^{14} + n \rightarrow [N^{15}] \rightarrow p^+ + C^{14} \rightarrow N^{14} + \beta^-$$

Both the immediate "capture" radiations and the "decay" radiations from any radioactive daughter are ionizing and capable of producing a biologic effect which must be estimated for every type of atom within any tissue to be irradiated with slow neutrons. Although the neutrons arising in the nuclear reactor as the consequence of the fission of uranium are given off at high speeds, their velocity can be reduced by collisions within graphite or heavy water until the thermal neutron range is reached. Furthermore since the neutron carries no electrical charge it wanders more freely in matter than do the charged particles.

The potential usefulness of such radiations depends upon the remarkable eagerness of a few unusual isotopes to capture slow neutrons while all of the common naturally occurring elements in living tissue tend relatively to ignore them. The avidity of an isotope for absorption of slow neutrons is expressed as its capture cross section σ_a, the apparent area in cm.^{2} presented by a single nucleus of the element to an incident beam of neutrons, = "barns"

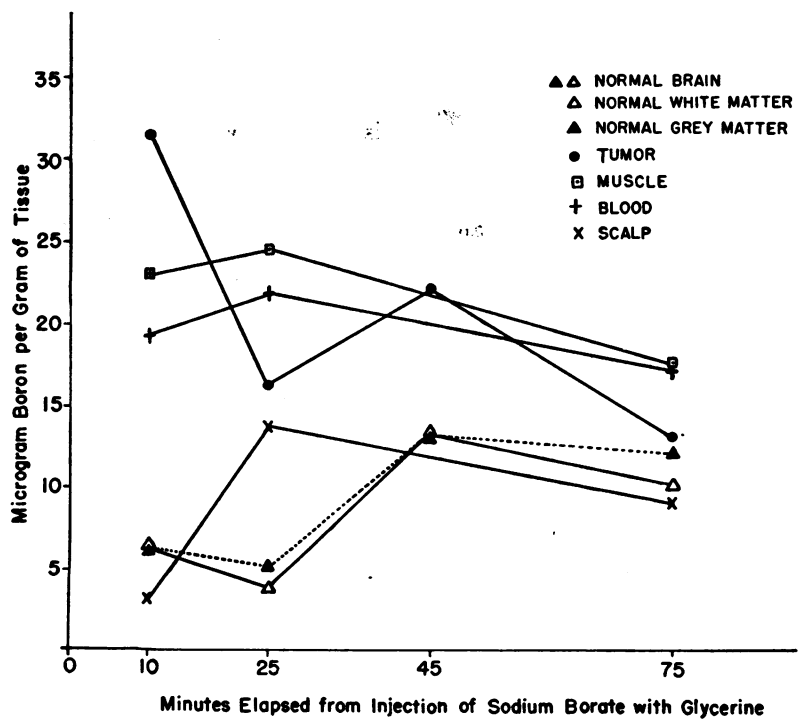

FIG. 1. VARIATIONS IN BORON CONCENTRATION IN TISSUES AFTER I.V. INJECTION IN PATIENT A. M.

Five g. sodium borate, containing 0.57 g. boron, injected.

$\times 10^{-24}$ cm^2. The σ_a for the main elements in normal tissue is as follows: H = .32, N = 1.7, O = <.001, P = .15, Cl = 32.5, Na = .45, C = .0045, Mg = .07, S = .5, K = 2.05, Ca = .42. In contrast with these low values are those for a limited number of isotopes among all the others to be found in matter. Thus Li^6 = 870; B^{10} = 3,900; Cd^{113} = 24,000; Sa^{149} = 46,000; Eu^{155} = 14,000; Gd^{157} = 200,000; Dy^{164} = 2,620; Hg^{199} = 2,500.

We now give our computation of the roentgen equivalent physical/min. (rep/min.) evolved in brain tumor and in normal gray and white matter containing the previously mentioned amounts of boron when such tissues are subjected to a specified flux of thermal neutrons. In this calculation we follow the lead of Conger and Giles (5), who studied the effect on buds of the plant *Tradescantia* of the neutron beam at Oak Ridge, Tennessee. If the fast neutrons and gamma rays arising in the nuclear reactor are excluded from the patient by shielding, then atomic ionization and its associated tissue destruction occur only when the thermal neutrons are captured. Radiations arise from every atom at the time of capture, and in addition a few capture reactions result in the formation of a radioactive daughter isotope, the continuing energy from which may be computed.

The energy of ionization per unit time per unit volume of tissue for each element therein =

$$F \times N \times \sigma_a \times E \times A$$

in which F = flux, number of thermal neutrons crossing a cm.^{2} per second, N = number of atoms of an element per unit volume; σ_a = the capture or absorption cross section, the tendency to capture expressed as the apparent area in cm.^{2} presented by a single nucleus of the element to the beam of slow neutrons; E = energy in million electron volts of radiations emitted after the capture of the neutron; A = the fraction of this emitted energy absorbed in the tissue.

To convert electron volts into roentgen equivalent physical per minute (rep/min.), the factor $r = 5.22 \times 10^{13}$ ev. was used, so that when all values are expressed in the proper units, we have:

Equation I: rep/min.

$$= \frac{(F \times 60)N\sigma_a(E \times 10^6)A}{5.22 \times 10^{13}}.$$

Our source for each of the values was as follows:

F: to facilitate comparison of our data for the brain with those of Conger and Giles in plants, we have used their figure for flux of thermal neutrons $- 1.25 \times 10^9$ n_{th}/cm.^{2}/sec.; N = the number of atoms/cc.; the concentration of each of the elements in normal and neoplastic brain was given to us by Dr. J. Folch-pi largely from his personal analysis of both types of tissue (6).

σ_a: the isotopic capture cross sections, with the exception of that for B^{10} taken from the later compilation of Sullivan, are from Nuclear Data by Way, Fano, Scott, and Thew (7).

A: all of the energy from electrons, protons and alpha particles is absorbed in the brain, so that in these cases A = 1. This is not true, however, for gamma rays.

In order to arrive at a first approximation of the fraction of gamma ray energy absorbed in the radiated material, an assumption as to the geometry of the neutron distribution is required. Because of the fairly rapid absorption of thermal neutrons in tissue or water, the flux will drop rapidly as neutrons diffuse into the brain. This tendency is measured in terms of the diffusion length of neutrons, defined as that distance required to reduce the flux of a plane infinite beam of neutrons to 1/e of its original value. This figure for thermal neutrons in water is 2.85 cm. The absorption is somewhat greater in tissue, especially in tissue containing B^{10}. We have not attempted to calculate a corrected diffusion length for slow neutrons in brain, but experimental measurements of this datum in phantoms are being undertaken. This correction is probably not important for the computation here because, as will be seen in the table and further discussion, the total gamma ray energy is of small significance in comparison with that from the heavy particles.

The percentage of the energy absorbed from the gamma radiation may be calculated on the basis of the following model. A sphere of radius equal to the diffusion length of thermal neutrons in water (2.85 cm.) is assumed to be uniformly irradiated with the production of N gamma rays/cc./min. Let dD represent the contribution to the radiation dosage at the center of the sphere resulting from the gamma rays originating in the volume element enclosed between the radial shells at r and r + dr of Figure 2.

TABLE I

Neutron radiation of brain and glioma

rep/minute of ionization absorbed in normal brain and tumor due to capture reactions of each of the elements present plus boron given i.v.

Element	Atomic number	Atomic weight	Per cent of net weight			N No. of atoms/cc. × 10^{24}			σ_a Capture cross section $\times 10^{-24}$ cm^2	E Capture radiation emitted and energy		A Fraction of energy absorbed in tissue	Rep/min. absorbed in tissue		
			Gray matter	White matter	Tumor	Gray matter	White matter	Tumor		Type	Energy (mev.)		Gray matter	White matter	Tumor
H	1	1.0078	10.8	11.1	10.8	.0645	0.0663	.0645	.32	γ	2.23	.071	4.72	4.86	4.72
C	6	12.00	10.0	20.0	10.0	.00502	.0104	.00502	.0047	γ	5.0	.051	.0087	.0180	.0087
N	7	14.008	1.74	1.70	2.20 (maximum)	.000748	.000731	.000945	1.7	p^+	.6	1.0	1.10	1.08	1.39
O	8	16.00	76.5	65.9	76.0	.0288	.0248	.0286	.0009	γ	>2	.076	.0057	.0049	.0057
Na	11	22.997	.116	.107	.116	.0000304	.0000280	.0000304	.45	γ	>1	.091	.0018	.0017	.0018
Mg	12	24.32	.013	.013	.013	.0000032	.0000032	.0000032	.07	γ	>1	.091	.00003	.00003	.00003
P	15	31.02	.210	.390	.248	.0000407	.0000737	.0000482	.15	γ	~1.25	.086	.00076	.00141	.00090
S	16	32.06	.050	.200	.040	.0000094	.0000376	.0000075	.5	γ	>1	.091	.00062	.00247	.00049
Cl	17	35.457	.128	.128	.128	.0000217	.0000217	.0000217	32.5	γ	~2.85	.066	0.191	0.191	0.191
K	19	39.10	.374	.374	.374	.0000576	.0000576	.0000576	2.05	γ	>1	.091	.0155	.0155	.0155
Ca	20	40.08	.004	.004	.004	.0000006	.0000006	.0000006	.42	γ	>1	.091	.00003	.00003	.00003
B^{10}	5	10.00	.0015	.0010	.0050	.00000090	.00000060	.00000301	3900.	α^{++}	2.40	1.0	12.20	8.11	40.73
Rep/min. from radioactive daughters															
Na^{23}			.116	.107	.116	.000304	.0000280	.0000304	.45	β	.47 average	1.0	.0093	.0085	.0093
										γ	4.13	.057	.0047	.0043	.0047
P^{31}			.210	.390	.248	.0000407	.0000757	.0000482	.15	β	.57 average	1.0	.0050	.0094	.0060
Cl^{37}			.0315	.0315	.0315	.0000051	.0000051	.0000051	.6	β	1.1 average	1.0	.0048	.0048	.0048
										γ	1.9 average	.077	.00013	.00012	.00012
F = Thermal neutron flux = $1.25 \times 10^9 n_{th}$/cm.^{2}/sec.										Total rep/min. absorbed			18.27	14.31	47.09
										Per cent of total rep/min. due to B^{10}			66.8%	56.7%	86.5%

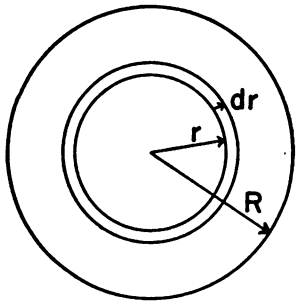

FIG. 2. PERCENTAGE ABSORPTION OF ENERGY OF GAMMA RADIATION

Then:

$$dD = (k)(N)\frac{(e^{-\mu r})}{r^2}(4\pi r^2\, dr)\ \text{rep/min.}$$

In this equation, k represents the radiation dosage rate in rep/min. at a distance of 1 cm. from a gamma ray source of 1 disintegration/min., and is a constant for a given gamma ray energy. N is the number of gamma rays/cc./min. in the source material, and $(e^{-\mu r}/r^2)$ is the attenuation of the gamma rays at a distance r in cm. from the point of their source. The absorption coefficient includes the photoelectric effect, the effect of Compton absorption, and pair production, and is a function only of the energy.

X-rays and gamma rays are absorbed by matter in three different ways: *1)* When the minute mass associated with an X-ray or gamma ray (quantum or photon) collides with an atom it may transfer its entire energy to an orbital electron, ejecting it from the atom. This process is known as the photoelectric effect. A wave strikes and an electron emerges. *2)* A gamma ray photon of shorter wave length, *i.e.*, with higher energies, is more likely to retain some of its energy and bounce off the orbital electron sending it off at one angle while the photon moves off at another angle—a billiard ball type of collision—in which the scattered photon, after the collision, has a longer wave length, less energy and a different direction from the incident photon. This is the Compton effect. *3)* A photon at a still shorter wave length and higher energy above 1.02 mev. may, when it passes near a nucleus, lose its wave characteristic and abruptly materialize into two particles—an electron and a positron. This is known as pair production.

$(4\pi r^2\, dr)$ is the volume of the differential element enclosed in the radial shells at r and r + dr. If the equation is integrated from 0 to R, the total dose rate at the center of the sphere of radius R will be found.

$$D_R = \frac{4\pi kN}{\mu}(1 - e^{-\mu R}).$$

The dosage rate of a sphere of infinite radius, *i.e.*, one in which all of the liberated energy would be absorbed, would be:

$$D_\infty = \frac{4\pi kN}{\mu}$$

and the ratio is:

$$\textit{Equation II:}\ \frac{D_R}{D_\infty} = (1 - e^{-\mu R}) = A.$$

This ratio is important because it gives an approximation to the ratio of the energy absorbed per cc. of medium, D_R, to the energy liberated per cc., D_∞. This is identical to the constant A in Equation I.

μ is determined primarily by the Compton absorption coefficient as calculated from the Klein-Nishina (8) equations. A convenient graph from which values of μ in water can be read off directly has been published by Marinelli, Quimby, and Hine (9) (R = 2.85 cm.). In the present case where μR is much less than 1, A can be simply written as $A = \mu R$. It is obvious that these calculations give only a rough estimate of the contribution of the gamma ray to the total dose.

Using the foregoing data and method, we have computed the roentgen equivalent physical/min. arising in normal brain and in neoplasm as a consequence of slow neutron capture for the naturally occurring elements H, C, N, O, Na, Mg, P, S, Cl, K, and Ca and for boron.[10] The results are recorded in Table I.[4]

We have injected only 5 g. of sodium borate into patients during operations on their gliomas, obtaining data of the order of magnitude recorded in Figure 1. However, when the patient is irradiated at the nuclear reactor for therapy, Dr. Farr and his collaborators give intravenously about 15 g. of sodium borate/70 Kg. of body weight so that levels about 3 × those recorded in Figure 1, or 50 γ of B^{10}/g. of tumor and 15 γ of B^{10}/g. of normal gray matter during the first 30 minutes af-

[4] If the conversion factor 5.9×10^{13} instead of 5.22×10^{13} is used to convert electron volts into roentgen equivalent physical per minute (rep/min.) we arrive at values of total rep/min. absorbed in gray matter as 16.17, in white matter as 12.66, and in tumor as 41.67.

ter injection, have been selected as the values on which to base the computation. It will be noted that the estimate is above .02 rep/min. only for H, N, and Cl. All of the remaining eight elements normally present add a total of only .05 rep/min. In addition, we give our computation for the ionization arising from the formation of radioactive Cl^{38} from the Cl^{37} constituting 24.67% of the normally occurring Cl, since we conclude that this gives rise to an inconsequential amount of radiation—a marked divergence from the opinion expressed by Conger and Giles, who estimate .1 — .52 rep/min. in their plants, which have only ¼ the Cl concentration of the human brain. Our result is based on these figures for Cl^{38} decay:

β^- 5.2 mev. 53%, 1.2 mev. 36%, 2.7 mev. 11%, giving an average maximum energy of 3.49 mev. resulting in an average energy formation of 1.16 mev. per disintegration. (A for β^- particles was taken as 1.)

γ 1.60 mev. 43%, 2.15 mev. 57%—average 1.91 mev.

We computed A from $\mu R = .023 \times 2.85 = .066$ for γ rays. Substituting these figures in Equation I, we calculate only .0049 rep/min. arising from Cl^{38} decay in our material, and even this small figure assumes that the biologic effect from this radiation at half life 37 min. would be the same as though it were all given off at once. In subsequent correspondence with Dr. Conger, we learn that the capture cross section of 40 for naturally occurring Cl was used by him instead of the value 0.6 for Cl^{37} which has since become available and which is, of course, the figure applicable to the formation of Cl^{38}. This accounts for much of the discrepancy between the two calculations. The results of similar calculations based on our same assumptions for Na^{24} and P^{32} are also charted in Table I and show that no significant quantities ensue from these sources. A further delayed radiation comes from the C^{14} yielded by the reaction $N^{14} + n = [N^{15}] = C^{14} + p^+$, but the 5,700 year half life of this weak (.155 mev.) β^- emitter precludes an observable biologic effect under these circumstances over a 50 year period in man.

The figures in Table I show that for the concentrations of B^{10} indicated in normal and neoplastic brain, the site of this isotope largely determines the site of the rep/min. Further factors contribute to the conclusion that the B^{10} will be the main cause of radiation damage, to wit, that heavy particles are much more efficient than γ rays in their biological effect on chromosomes. Kotval and Gray (1947), cited by Conger and Giles, found alpha particles 7.8 times as efficient as X-rays per unit dose measured physically in producing isochromatid deletions, and the same particles were 4.1 times as effective as X-rays in producing chromatid plus isochromatid deletions.[5]

Conger and Giles have demonstrated a further increase in efficiency when the alpha radiation arises from within the tissue of 14:1 for isochromatid deletions and 11:1 for chromatid plus isochromatid deletions. The chief disturbing factor in normal tissue, aside from the B^{10} there, is the gamma ray evolving when hydrogen captures a neutron, which has the same lesser efficiency as X-rays in causing cellular death.

If we multiply a factor of roughly 6 of Kotval and Gray for the increased efficiency of heavy particles over X- and gamma rays, by 12, the additional increase in efficiency noted by Conger and Giles for alpha radiation arising within tissue, we might conclude that the rep/min. arising from the disintegration of boron would be about 70 times as destructive as the γ ray from hydrogen. However, one of the major reasons suggested for the increased efficiency of the internal particulate radiation in the lily bulbs of Conger and Giles is the concentration of the boron in the nucleus and chromosomes as compared with the cytoplasm. Hence an increased number of chromosome "hits" per unit dose is more likely from the intracellular and intranuclear boron. Since within 30 minutes after intravenous injection of the borax in man it seems unlikely that much of it has penetrated into the cell, much less the nucleus, we have thought it appropriate to estimate conservatively the greater efficiency of particulate radiation in our material

[5] A "chromatid" is one of the two sister structures formed by the longitudinal splitting of a chromosome during mitosis. Irradiation at a stage in which the chromosomes are split may produce a break in only one of the members of a pair of chromatids. Removal of a portion of the chromatid at the breakage point will tend to prevent reunion of the broken ends and a chromatid deletion is said to have occurred. If both chromatids of the pair are broken at the same level and reunion does not occur, the aberration is termed an isochromatid deletion.

TABLE II

Element	Rep/min. absorbed in tissue × RBE		
	Gray matter	White matter	Glioma
N	5.5	5.4	7.0
B^{10}	61.0	40.6	203.7
All other elements in Table I	5.0	5.1	5.0
Totals	71.5	51.1	215.7
Per cent of radiation effect in tissue due to B^{10}	85%	79%	94%

It is apparent that at these concentrations the site of the boron largely determines the radiation effect, and that when the concentration in tumor is 3.3× that in gray matter (50γ:15γ), the destructive effect in tumor may perhaps be expected to be 3× that in the gray matter.

and to place it at about 5 × that of the gamma rays.

Accordingly we use a factor for relative biologic efficiency (RBE) of 5 for particulate radiation and our tentative estimate of the radiation effect in tissue is based on the factor rep/min. × RBE. This factor we may call roentgen equivalent biological/min.; we use this more general term in preference to Parker's roentgen equivalent mammal/min. (10) because most of the data on which the extrapolation is based are derived from plants. If then we multiply by 5 the rep/min. arising from N and B^{10} and substitute this for the values in the last three columns of Table I we emerge with the estimate of effect on tissue indicated in Table II.

SUMMARY AND CONCLUSIONS

Data are presented to show the degree to which intravenously injected borax concentrates in malignant brain tumors and in normal tissues including brain. On the basis of these data for boron and those from other sources for other elements we have computed to a first approximation the amount of biologic radiation damage (relative biologic efficiency × rep/min.) arising from each element consequent upon exposure to a beam of slow neutrons. The figures reveal that: *1*) for the expected concentrations in tissue following injection of borax, the locus of the boron atom would be the principal determinant of the site of damage; and *2*) at the readily achieved differential concentrations between glioma and brain of 3.3:1, the radiation damage in tumor would be about 3 × that in normal brain—if one assumes uniform distribution of the neutron flux.

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