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A History of 20th-Century Boron Neutron-Capture Therapy

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Abstract

Several important aspects, advances as well as setbacks, of 20th-century American BNCT research are clarified. The potential usefulness of BSSB for BNCT of malignant brain tumors, which was suspected in the1960s and demonstrated experimentally during the1980s and early 1990s but never tested clinically, are recalled.

Keywords: Boron; Neutron; capture; therapy; BNCT; History; Clinical studies; Sweet

Abbreviations: AEC- Atomic Energy Commission, USA; BGRR-Brookhaven Graphite Research Reactor; BMRR- Brookhaven Medical Research Reactor; BNCT -Boron Neutron-Capture Therapy; BNL-Brookhaven National Laboratory; BPA-Boronophenylalanine; BSH-Sodium Thioundecahydrododecaborate; BSSB-Sodium Dithioundecahydrododecaborate, the disulfhydryl dimer of BSH; CNS-Central Nervous System; CU-Cambridge University; DBM-Division of Biology and Medicine of the AEC; ^{4}He-Helium-4 (i.e., an alpha particle); HU-Harvard University; ICRR-International Congress of Radiation Research; L-BPA-Laevo enantiomer of BPA; LET-Linear Energy Transfer; MGH-Massachusetts General Hospital; MIT-Massachusetts Institute of Technology; MITR-MIT Research Reactor; NAS-National Academy of Sciences, USA; NCT-Neutron-Capture Therapy; RIH-Rockefeller Institute Hospital

Introduction

In late 1895, soon after the German physicist Wilhelm Conrad Röntgen discovered unknown radiation emitted from the anode of an evacuated glass tube carrying an electrical current, he used it to photograph his wife's hand, clearly distinguishing soft tissues, bones and wedding ring. Hitherto unknown radiations (X-rays) could image otherwise opaque objects if collimated to be rectilinear from their source at the electrically positive end of the tube. A potential of several thousand volts applied to the electrodes ionized the residual gas in the tube and caused it to emit colored light. The photographic film was positioned behind the subject of interest. Tragically, scientists who made use of Röntgen's discovery ("roentgenologists") were the first to discover that X-rays were invisibly and insensibly toxic to normal living tissues. Many roentgenologists became victims of their art, either disfigured or killed by X-ray-induced lesions. In the early 1900s, roentgenologists world-wide also discovered that, by judiciously shielding normal tissues, the growth of superficial neoplasms could be suppressed or cured by X-rays, marking the beginnings of radiotherapy.

It was opined in 1974 at the 5th ICRR that "Radiation therapy as currently practiced involves the subtle, largely empirical art of "balancing the recurrence of cancer due to under-treatment against severe damage to local tissues due to overtreatment". That situation has improved since then. BNCT, one of several binary form of radiation therapy, was designed in 1950 explicitly by the MGH neurosurgeon William Herbert Sweet, the pioneer of clinical BNCT, to spare normal brain tissues during radiotherapy of brain tumors [1,2]. BNCT is based on the release of micrometers-range, high-LET ionizing particles from the reaction of slow neutrons with ^{10}B, a minor stable isotope of boron artificially accumulated in the targeted tumor. BNCT was begun at BNL on February 15th, 1951. Sweet's initiative was widely publicized during the 1950s, but fell precipitously into disrepute soon after the over-irradiation of one of his patients in 1961.

The neurosurgeon Hiroshi Hatanaka, after being mentored in BNCT research at the MGH by Sweet and Sweet's chemist Albert Herman Soloway [3] for several years, pioneered clinical BNCT for brain tumors in Japan in 1967 [4-7]. About fifteen months after Hatanaka's sudden death in 1994, it was announced at the10th ICRR that 85 patients with glioblastoma (including grade 4 astrocytomas and anaplastic astrocytomas) had been treated in Japan, mainly by Hatanaka, using BSH-mediated BNCT since1968: about 25% of them so treated between1986 and 1991 survived at least five years after diagnosis. No such extraordinary statistics about survivals from high-grade gliomas has ever been reported, to our knowledge, before or since that announcement at any major medical congress or symposium whatsoever: naturally, it engendered optimism in the world's BNCT research community and considerable interest among neurosurgeons in the USA.

BNCT's Inception and Nuclear Physics

Moritz Goldhaber was an undergraduate student of theoretical physics at Berlin University in January, 1933, when the Nazis seized power in Germany. Goldhaber asked for and received recommendations from his renowned professors Max von Laue and Erwin Schroedinger for study at some foreign university. Their recommendations immediately elicited a favorable response from Ernest Rutherford, discoverer of the atomic nucleus; Goldhaber was welcomed at CU in 1933 to study theoretical nuclear physics under Ralph Howard Fowler, Rutherford's son-in-law. On December 10, 1934, Goldhaber helped James Chadwick (assistant chief under Rutherford of CU's Cavendish Laboratory and a 1935 Nobel-Prize winner for identifying the neutron) in discovering the capture of slow neutrons by lithium and boron nuclei [8]. That the slow-neutron-boron reaction yielded nearly straight, microscopically short tracks in borax-impregnated photographic emulsions was discovered under Goldhaber's supervision in 1935. In 1936 Goldhaber was awarded a PhD and a two-year fellowship at CU's Magdalene College. In December 1936, Goldhaber co-authored the discovery that slow-neutron disintegration of nitrogen yields an energetic proton, a crucial aspect of BNCT dosimetry [9,10]. Concomitantly, in 1936, the Pennsylvanian astrophysicist Gordon Lee Locher published several ingenious concepts of NCT for superficial cancers. He intended to test them at a nearby cancer hospital using its four-gram radium source to generate fast neutrons from beryllium. Although fast neutrons can be slowed through hydrogen-rich paraffin, Locher never implemented a slow-neutron-capture experiment [11].

The physical basis of NCT is straightforward: slow neutrons ionize matter via the nuclear-reaction products formed following their capture by stable nuclei. ^{1}H and ^{14}N, abundant in living tissues, are among the most slow-neutron-avid stable light nuclei. ^{10}B and ^{6}Li, present only in minuscule concentrations in living tissues, are thousands of times more slow-neutron-avid than are ^{1}H and ^{14}N.^{10}B nuclei number only about 20% of boron nuclei in borax, the source of virtually all boron. ^{10}B captures slow neutrons, with immediate emission of two oppositely directed positively-charged particles, a ^{7}Li nucleus and an oppositely-directed ^{4}He nucleus. These impart ionizations to soft tissues along the narrow paths of their ranges in soft tissue: about 5 μm and 9 μm, respectively. Thus, radiation energy is imparted preferentially and intensely to cancerous tissues artificially enriched in ^{10}B. The only modality of NCT deployed clinically to date is mediated by ^{10}B [12].

BNCT's clinical inception in 1951 was serendipitous, resulting from the geopolitical challenges of the Cold War after World War II. The AEC undertook costly activities of designing and fabricating uranium, plutonium and hydrogen bombs, competing with the USSR. AEC Chairman David E. Lilienthal, under USA's President Harry S Truman, authorized the DBM to use BNL and its new BMRR, under prolonged construction during the late 1940s, to put a peaceful facade on them [13,14].

At the University of Illinois in Urbana, during September 1938, Goldhaber, recently immigrated from Cambridge and evidently unaware of Locher's publications, suggested to his new physics research advisor Peter Gerald Kruger that they initiate BNCT experiments using Kruger's cyclotron, the world's second cyclotron that furnished an external ion beam. The experiment failed on account of its feeble power. Kruger pursued the experiment vigorously during his autumn sabbatical, using Ernest Orlando Lawrence's far more powerful cyclotron in Berkeley, California. In early 1940, Kruger described his results in the PNAS, generously mentioning Goldhaber and their incomplete experiment at Urbana [15].

Sweet was mentored during his HU medical school and postgraduate years, 1930-1940, by the senior MGH neurosurgeon James Clarke White. After voluntary wartime service in the English Midlands (mentored by Geoffrey Jefferson, the doyen of British neurosurgeons) Sweet returned to the MGH. Fortuitously, Sweet was befriended by his suburban neighbour, HU's chief of biological chemistry and DBM's principal advisor Albert Baird Hastings, an NAS member, as was Hastings' mentor, the RIH's pioneer clinical chemist Donald Dexter Van Slyke. Hastings was an éminence grise within the Roosevelt, Truman, and Eisenhower administrations [16]. In 1947, Hastings invited HU's distinguished radiopathologist Shields Warren to lead the AEC's newly formed DBM [17,18]. In 1948, he persuaded Van Slyke, then retired from the RIH, to reshape BNL's biology and medical departments. Van Slyke's former RIH subordinate Lee Edward Farr, a research pediatrician, was invited to direct BNL's medical department [19].

Arthur Kaskel Solomon, HU's leading radiophysical chemist, mentored Sweet in radioisotope technologies. The English polymath Douglas Edward Lea had mentioned the potential applicability of NCT to cancer therapy favorably in his groundbreaking 1944 monograph on physical radiobiology [20,21]. In 1949, Sweet, evidently unaware of the studies of Goldhaber, Locher and Lea, happened to peruse an AEC/Oak Ridge National Laboratory report showing that approximately 1/3rd of chromosomal damage from slow–neutron irradiation of Tradescantia stamens could be attributed to their minuscule content of natural borates. Knowing that the AEC had recently released gram quantities of 95 atom% boron-10-enriched borax for civilian use, Sweet independently surmised that a borax–mediated clinical BNCT program for glioblastomas could be initiated at the AEC's nearly completed BGRR. Expeditiously, Sweet sought and quickly received generous funding from the DBM to prepare for a trial of clinical BNCT at the BGRR, the first reactor built for use by civilians. In 1950, Sweet was able to enlist the MGH neurosurgical resident Manucher Jeffrey Javid to help evaluate the pharmacokinetics of intravenous borax with or without glycerol in dozens of volunteer brain-tumour patients [22]. He also enlisted the MIT postdoctoral physicist Gordon Lee Brownell to quantify clinical BNCT's radiation dosimetry. Late in 1950, Hastings informed Farr of Sweet's plan to implement borax-mediated clinical BNCT at the recently commissioned BGRR for newly debulked MGH glioblastoma patients transported from Boston to BNL. His BNCT group being far short of identifying any boron compound suitable for clinical BNCT of brain tumors, Farr gladly joined Sweet: a two-year MGH-BNL collaboration on clinical BNCT was begun [19,23]. To Farr's fury, confidentiality of the world's first clinical BNCT irradiation was broken by the unauthorized intrusion of John Lear, a popular science reporter [24].

To our knowledge, NCT was not cited in the biomedical literature after Locher's 1936 report until the post-World War II publication of Lea's pioneering monograph in 1947 on quantitative radiobiology [23]. The weakness of the slow neutron sources available for civilian uses also had precluded clinical BNCT experiments before the 1950s.

After a sojourn in South America during 1951, Brownell rejoined Sweet's research team. Sweet referred nine more glioblastoma patients to the BGRR for borax-and-glycerol-mediated BNCT during 1951–1952. BNL's BNCT program was superseded by Farr's in 1953: sodium pentaborate, an analogue of borax (sodium tetraborate), was employed almost exclusively from 1953 until 1961 in BNL's BNCT research [23]. In 1961, Goldhaber, distinguished at BNL as a group leader since 1950, was recommended to become BNL's director by Isidor Isaac Rabi who, with his student Norman Foster Ramsey, each a Nobel prize winner, founded BNL in 1946 [14]; Goldhaber served as BNL's director from 1961 until 1972. In 1961, several early post-BNCT fatalities, for which Farr was held mainly responsible, had severely tarnished BNCT's original luster. In 1962, Goldhaber replaced Farr as BNL's Medical Department Director by Victor Potter Bond, a US Navy and BNL physician and radiobiologist.

Bond was also a steadfast champion of BNCT. In 1958, Sweet was appointed Harvard's scientific representative on BNL's board of trustees. During1961-1972 Sweet also directed MGH's neurosurgical service and some neurosurgical research activities.

In 1962 the physicist Ralph Grandison Fairchild, a BNL technician, launched BNL's ambitious program with Bond's support to develop an epithermal–energy-neutron source for BNCT at the BMRR [25,26].

Vulnerability to BNCT of the CNS Vasculature

It was emphasized in Hine and Brownell's influential 1956 textbook "Radiation Dosimetry" that, apart from its technical complexity, the main intrinsic disadvantage of clinical BNCT mediated by thermal-energy neutrons was the rapid reduction of the thermal neutron flux with depth, unfavorable for treatment of most brain tumors. That disadvantage could be ameliorated, to some extent, by the use of "epithermal-energy" neutrons, to be thermalized by water in the patient's tissues proximal to the targeted neoplasm. Another technique, tested and used much later in Japan, was to partially deuterate the water of the patient bearing the targeted neoplasm, thereby increasing the penetration of slow neutrons toward their deep target while reducing the toxicity of associated radiations. Although neuropathological studies by Shields Warren [27] and rabbit experiments by Dorothy Stuart Russell [28] revealed the early post-irradiation vulnerability to X-rays of the brain vasculature, nobody realized before the calamity of 1961 that one had to pay attention to the concentration of ^{10}B in the circulating blood, especially in its plasma moiety and pericapillary tissues, during neutron irradiation for clinical BNCT.

Of seventeen terminally ill brain–tumor patients similarly infused intravenously with sodium pentaborate and irradiated with increasing fluences of thermal neutrons by Farr's BNCT group at the new Brookhaven Medical Research Reactor during 1959–1961, four died soon after BNCT from intractable cerebral edema. Years later, those seventeen patients were re-ranked according to a measure of total ionization energy imparted to the endothelial and perithelial cell nuclei of their cerebral capillary vessels: the incident neutron fluence multiplied by the area of unshielded skull exposed to the incident neutrons. Twenty-eight years after the events, it was realized that only those glioblastoma patients with the four greatest of those measures had died within two weeks after pentaborate-mediated clinical BNCT at the BMRR in 1961 [29].

During 1960-1961, Sweet's Boston group treated sixteen glioblastoma patients with BNCT at the MITR using paracarboxyphenylboronic acid (rather than pentaborate) delivered intravenously. Clinical outcomes were also unsatisfactory, as were those following most therapies of glioblastomas in that era. An experimentally superior agent, sodium decahydrodecaborate, was then tested in the seventeenth glioblastoma patient: it was delivered *via* the ipsilateral internal carotid artery rather than intravenously, also with an unexceptionally unsatisfactory effect. The outcome for the eighteenth glioblastoma patient, who was treated as was the seventeenth, was disastrous. She lapsed into coma during BNCT and died ten days later without recovering - in hindsight because transcarotid decahydrodecaborate infusion had caused excessive endothelial and perivascular boron levels in her tumor-debulked edematous brain during the irradiation. Complete postmortem examinations were eventually implemented on fourteen patients of that trial [30]. Those fourteen, fortuitously, included the only two (Asbury's #9 and#11) who had received the boron compound directly into their carotid artery. Before fixation, those two brains were more swollen, more edematous and more friable than were the other twelve: only in those two brains were erythrocytes judged by neuropathologists to have been extravasated diffusely *in vivo*. That experience led Sweet to promulgate a universally accepted principle of clinical BNCT: allow an interval of at least several weeks after neurosurgical debulking (to allow restoration of the blood-brain barrier) before implementing clinical BNCT for a brain tumor. Especially after Soloway published those considerations in 1964, BNCT researchers worldwide have paid close attention to blood-boron levels in their preclinical and clinical studies of BNCT [3].

Boron Chemistry

Soloway's group, which included Sweet's protégé, the young neurosurgeon Hiroshi Hatanaka, who became the doyen of Japanese BNCT research [4-6] was the first to screen BSH in tumor–bearing animals as a potential BNCT agent [3]. By 1973, it was thought that higher tumour boron concentrations obtained by Hatanaka in Japan than by Soloway in Boston were attributable to BSH's spontaneous slow oxidation to the yellowish dimer BSSB, which splits spontaneously into a pair of identical, exceptionally stable, highly reactive free radicals $B_{12}H_{11}S\bullet$ that bind to proteins in tissues [31], in particular to albumin in blood plasma, where their concentration could be reduced by plasmapheresis, advantageously for clinical BNCT [26]. BSSB was the first boron-containing agent used with BNCT to control experimental malignant gliomas [32]. It has never been tested for clinical BNCT. As exposure of purified BSH infusates to air reportedly discoloured it, we presume improving the efficacy of Hatanaka's clinical BNCT.

About 30 months before his death, Hatanaka and several American colleagues opined at a meeting of British and American neurosurgeons in London, England, that BNCT would be best mediated, at least in part, by BPA and/or BSSB [7]. Oddly, no preclinical test or use of BSSB has been revealed to the clinical BNCT community, to our knowledge, since Hatanaka died in 1994. A strange aspect of BNCT research was that a special publication in1987 commemorating the accomplishments of BNL omitted all mention of BNCT, favorable or otherwise, although BNCT was a major AEC-sponsored program at BNL from 1948 through 1999 [14].

BPA, too, was first screened for BNCT by Soloway at the MGH. At first, racemic BPA was used for clinical BNCT of human skin melanomas in Japan by the dermatologist Yutaka Mishima. Afterwards, BPA's pharmacologically effective enantiomer L–BPA was synthesized enzymatically by the American chemist John David Glass, Jr.; L-BPA was employed henceforth for clinical BNCT in Japan and elsewhere.

Brookhaven Trials: 1994–1999

New BNL trials of BNCT mediated by L–BPA using epithermal-energy neutrons were begun amidst controversy on September 13, 1994 [33,34]. Over 48 glioblastoma patients were treated at the BMRR before mid-1999: Intervals to tumour recurrence were generally unexceptional, but exceptionally vigorous qualities of life during the months prior to brain tumor recurrence gratified some patients and their families [35,36]. In the 1990s at the MITR, epithermal-energy neutrons were used to treat several kinds of malignancies including gliomas: clinical trials of BNCT were also started in Europe, notably in Sweden [37] and Finland [38]. Early accounts of those trials, with which the authors are not personally acquainted, were published in the proceedings of the 11th International Congress on Neutron Capture Therapy, Boston, Massachusetts [39]. During the 1990s also, the American public was bombarded with press reports of some patients' relatives' allegations of radiotoxic injuries to their deceased kin by Sweet's allegedly ill-conceived, supposedly unethical BNCT, focusing on injuries allegedly sustained by several glioblastoma patients who had volunteered to undergo BNCT 3- to 4-decades previously, i.e., during the 1951–1961 clinical trials [34]. Sweet was convicted *in absentia* of medical malpractice by a jury, and then heavily fined just as a progressive neurological disease tragically prevented him from attending the courtroom proceedings, from understanding the allegations, and from confronting his denigrators. Nineteen months after Sweet's death from his disease, three Massachusetts appeals court judges reversed Sweet's conviction unanimously: in summary, they ruled that the

plaintiffs' evidence rested on nothing other than information reported publicly by Sweet and his research collaborators after those therapies and that Sweet conformed to contemporary American guidelines for clinical research during the mid-20th century on experimental therapies for rapidly progressive lethal malignancies such as glioblastoma.

A slow leak of tritiated water from a holding tank at another BNL research reactor was discovered by BNL scientists in December 1996, but was not reported to the DOE until February 1997. Citizens, some remote from BNL, raised alarms among their legislators and the press about their imagined tritium-induced cancers. Harassed by the DOE because of his two-month delay in responding to its concerns, BNL's director resigned, although the small plume of tritium in BNL's ground water had already been confined and remediated. The public's radiophobic backlashes shut down both nuclear reactors at BNL, which was then declared "neutron-free" by its new director. BNCT research at BNL supported by the DOE was terminated by the end of the 20th century, but was carried on nevertheless at BNL and elsewhere in the USA [40].

Conclusion

Ten international symposia during 2000-2016, one each in Argentina, Finland, Germany and Italy, three in the USA and three in Japan, attest to the vigor of modern NCT research. Further investigations of lipophilic carboranylporphyrins and other new boron compounds in combination with each other, using novel clinical BNCT-enhancing techniques seem possible [41,42]. At least one porphyrin combines the advantages of biodistribution favourable to BNCT: tumour-preferential enhancement of photon therapy and negligible toxicity [43-45]. An analogue of L-BPA reportedly is superior in those respects to L-BPA itself [46,47]. Boron in a tumour-cell nucleus is about threefold more effective for BNCT than in the cytoplasm. Although the challenges of synthesizing and testing minimally and reversibly toxic boron agents for BNCT that accumulate preferentially in tumour nuclei while clearing from the blood have not been surmounted, tags to allow entry of certain substances into the nucleus, at least transiently, might be developed for boron compounds to address that issue. An important advance, described fifteen years ago, has been the adaptation of secondary-ion mass-spectrometric microscopy to delineate ^{23}Na, ^{39}K, ^{40}Ca, and ^{11}B in thin sections of tissues, which should greatly promote the experimental evaluation of candidate boron-transport agents for clinical BNCT [48]. A major factor in the slow development of clinical BNCT during the 20th century was its reliance on a dedicated low-power nuclear reactor such as the BMRR to generate an intense, forward-collimated source of epithermal-energy neutrons. Research on designing such a source using a compact ion-accelerator that can be built near a tertiary-care hospital has proceeded apace during the past thirty years [49,50]. It was announced in 2014 at the 16th International Congress on Neutron Capture Therapy that a successful clinical trial using a proton accelerator near a major Japanese hospital was well underway [51]. It is now evident that replacing reactors by proton accelerators for BNCT is feasible, relatively economical, and environmentally safe.

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