Will History Repeat for Boron Capture Therapy?

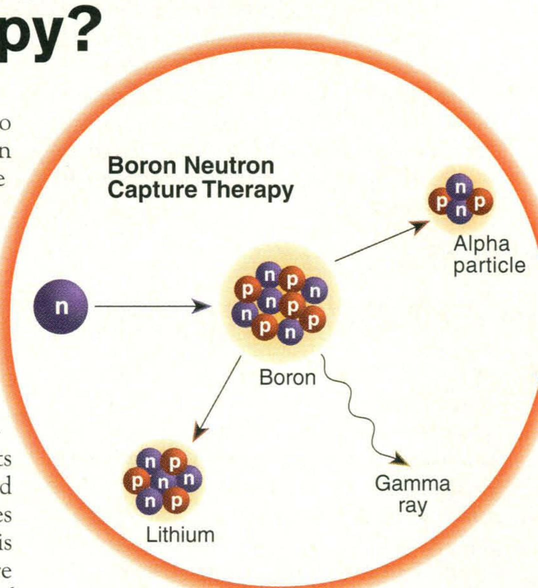


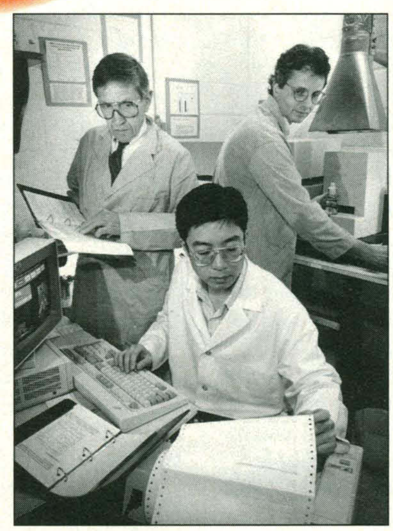
ILLUSTRATION: C. FABER SMITH SOURCE: BROOKHAVEN

Between 1951 and 1960, 70 people who were dying of brain cancer submitted to an experimental radiation treatment at the Massachusetts Institute of Technology (MIT) and the Brookhaven National Laboratory. Neurosurgeons injected the patients with boron compounds, cut openings in their skulls, placed them up against nuclear reactors, and sent beams of neutrons into their exposed brains. Publicity before the treatment had raised hopes, but the results were considered disappointing or even disastrous: The patients irradiated with low doses of neutrons died from their tumors; those who got high doses died from the radiation. But in spite of this unpromising history, U.S. researchers are about to try again. And both the advocates of boron neutron capture therapy (BNCT) and its critics fear that history may repeat itself.

Skeptics like Princeton University physicist William Happer, who directed Department of Energy (DOE) research during the 1980s, say the procedure remains dangerous. In the original trials, the nuclear reactions triggered by the neutron bombardment harmed patients, Happer points out, "and now they are going to do it again." Neurosurgeon Victor Levin of the University of Texas Anderson Cancer Center contends that BNCT is diverting money from more promising avenues of brain-cancer research. "The likelihood that it [BNCT] will have a significant impact on the disease is infinitesimal."

Not so, says a team of researchers at Brookhaven, which is staking its hopes on an improved boron compound, better neutron sources, and anecdotal reports of success from Japan. Like the critics, however, they are uneasy about the move to human trials because it is taking place in a blaze of publicity, kindled by groups of researchers and patients trying to persuade Congress to provide funds to resurrect mothballed reactors for BNCT. Because Brookhaven is one of the only places in the United States currently able to carry out the therapy, researchers there worry that they may be pressured into starting treatments before they've completed safety studies of the new boron compound. "We will be rushed by politics to start treatments too soon," says Brookhaven biochemist Jeffrey Coderre, who is leading the new round of BNCT studies there. The results could be disastrous for patients, Coderre and his colleagues fear, and they could blacken the reputation of BNCT for good.

Over the years, this form of treatment has retained a seductive appeal, says researcher Francis Mahoney of the National Cancer Institute (NCI). The concept is relatively simple: First, inject a boron-containing compound into the bloodstream. The boron concentrates in the cancer cells because the blood-brain barrier, which keeps foreign substances out of the normal brain, sometimes breaks down in the tumor. The second step is to shower the tumor with neutrons from a nuclear reactor. The neutrons should pass harmlessly through normal, boron-free brain cells. But the boron atoms in cancer cells will capture neutrons, become unstable, and fission into two cell-destroying fragments. In theory, it looks great, says Mahoney. "I've seen two or three generations of researchers come in and get enchanted with it," he says.



BROOKHAVEN NATIONAL LABORATORY

Test of concentration. Brookhaven researchers Darrel Joel, Ben Liu, and Jeffrey Coderre *(left to right)* analyze a tissue sample for boron, which can fission and destroy a cancer cell when it captures a neutron *(above)*.

Because it promised to concentrate the cancer-fighting radiation in the tumor cells, BNCT seemed ideally suited to treating glioblastoma—a cancer that infiltrates the brain, making it virtually impossible to treat by surgery or conventional radiation. William Sweet, a neurosurgeon at Massachusetts General Hospital, recalls the enthusiasm of the pioneering BNCT researchers at MIT 40 years ago. "We thought we had it—we were going to cure glioblastoma, one of the most malignant tumors anywhere in the body."

But as it turned out, BNCT damaged more than the cancer cells. "We began a series of patients after some animal studies and were horrified to discover that the reason the patients died was that the blood circulating in the normal brain also had a substantial amount of boron in it," Sweet says. The fissioning boron had catastrophic effects on the blood vessels. "It didn't kill the cells lining the blood vessels, but it irritated them enough that it caused a connective-tissue blockade of the blood supply to the brain." That unpredicted side effect killed four of the 70 patients; the remainder died of their cancers.

A second wind. The treatment did get a second chance—in Japan. In the 1970s, chemists at Ohio State University found a boron compound, borocaptate sodium (BSH), that seemed to bind more selectively to cancer cells. The memory of the original trials was too fresh for anyone in the United States to try it on human subjects, but a Japanese neurosurgeon named Hiro Hatanaka, who had worked on the initial trials, returned to Japan and did a larger study at a reactor there.

The results were inconclusive, say U.S. BNCT researchers. Of the 120 or so patients Hatanaka treated using BSH, six or seven survived for dramatically longer than average. Brookhaven neurosurgeon Daniel Slatkin points out, however, that a small number of glioblastoma patients do survive without treatment, and the Japanese record does not significantly beat the background rate. What's more, researchers say that Hatanaka, who died recently, gave his patients many different combinations of treatments, making it impossible to evaluate the effects of BNCT alone. "It [was] not science," says NCI's Mahoney.

Still, some of Hatanaka's disciples continue to give the treatment in Japan. And BNCT enthusiasts in the United States think the Japanese results offer a glimmer of hope. "The evidence is largely anecdotal, but there's something there," says Coderre. "Patients with high-grade tumors have been treated and are alive, and there are a few patients who've lived 10, 15 years." And now there's another factor contributing to the optimism of Coderre and his colleagues: a promising new boron compound.

Known as boronophenylalanine (BPA), the compound was developed in the late 1980s by Yutaka Mishima and his colleagues at Kobe University School of Medicine in Japan. When Coderre and other experimenters at Brookhaven transplanted aggressive cancers into rats, then injected them with BPA, they say the compound concentrated in the tumors better than did any of its predecessors. And when they bombarded the animals with neutrons, the tumors—which should have killed the rats within 14 days—often regressed. "The animal data are very, very convincing," says Coderre. "In small rodents we've seen 80% cured completely."

Last December, Coderre and his colleagues at Brookhaven moved on to studying the compound in humans. Five people with glioblastoma were given BPA before they had surgery to remove as much of their tumors as possible. During the operation, surgeons removed tissue samples and afterwards measured boron concentrations in tumor tissue, normal brain, and capillaries. So far, the results support BPA's promise, says Coderre. If the pattern holds up through studies of another five patients, Coderre and his colleagues think a new trial of the full regimen of boron plus neutrons will be warranted. They point out that besides the improved compound, Brookhaven has a more powerful neutron source than was used in any of the earlier trials. As a result, the treatments could be done without removing the skull and be completed in 45 minutes instead of hours.

The group has already applied for FDA approval to start safety trials of the full treatment, although they say as much as a year's work remains before they will be ready. Besides the BPA studies, says Richard Setlow, a biophysicist at Brookhaven, "we need a lot of work to figure out what doses to give and where to aim the beam and just how much radiation to give and so on."

Even a year is too soon for BNCT critics like Happer and Levin. And Ohio State University chemist Albert Soloway, who developed the boron compound used in Japan, recommends delaying human trials until the promise of other compounds that might home in on tumors even better than does BPA has been explored. "What we need is an integrated study among the chemists, physicists, radiation biologists, and neurosurgeons," he says. "I think you need to do this scientifically and not emotionally." But Darrel Joel, chair of the medical department at Brookhaven, says he is "cautiously optimistic" that BPA will prove to be good enough.

Stage fright. Joel acknowledges, however, that "when we treat the first patients there will be some jitters." And a major reason for his jitters is the wave of publicity being generated by a separate effort to promote BNCT (*Science*, 15 October 1993, p. 329). A group of nuclear engineers and patient advocates has been pressing DOE to convert a mothballed research reactor at the Idaho National Engineering Laboratory into a BNCT research facility. Although independent panels from DOE, NCI, and the Institute of Medicine have all advised against the plan, advocates have turned to Congress. A separate group is now seeking funding for BNCT research at a reactor at Georgia Tech.

These advocates persuaded the Senate Energy and Natural Resources Committee to hold a hearing in May at which they presented BNCT as a promising therapy. Several scientists testified that the Japanese studies show that the treatment worked, and witnesses brought in a single patient allegedly "cured" of glioblastoma after treatment at a reactor in Japan. Stoking the publicity was an Associated Press article that appeared shortly afterward in newspapers around the country under headlines such as "U.S. Impeded Effort to Treat Brain Tumors."

As a result of the attention, says Coderre, Brookhaven has received "hundreds of calls from people with brain tumors who want to know if they can be treated now. These people are desperate." One patient, he adds, is both persistent enough and well enough connected to have pressed her case to Energy Secretary Hazel O'Leary and others at the highest levels of government. Officials at DOE say they've convened a panel, including doctors, researchers, and an ethicist, to decide what to do about her case. When *Science* went to press, DOE officials and Brookhaven researchers were still negotiating over this case.

Coderre and his colleagues worry that the DOE will force the Brookhaven group to start administering the untried therapy under "compassionate use" rules, which allow the usual FDA approval steps to be bypassed for some terminal conditions. If it does, they fear that BNCT could become a victim of overoptimism. The first patients probably won't be cured, says Mahoney, and if they die in a glare of publicity, future research on BNCT might be jeopardized. And once treatments start, hundreds of others may seek treatment and "there go our controlled studies," says Coderre.

But in spite of their fears, Coderre and his colleagues think it's time for BNCT to show it can live up to its promise. NCI's Mahoney, among others, agrees. "You reach a point where you have to try it in humans," he says. "We are sort of reaching that point."

–Faye Flam

1995 R&D SPENDING

Mikulski Boosts NSF Budget

What a difference a year makes. Last fall, scientists were hurling imprecations at Senator Barbara Mikulski (D–MD), chair of the appropriations subcommittee that funds the National Science Foundation (NSF), for ordering NSF to support more "strategic research" likely to benefit industry (*Science*, 17 September 1993, p. 1512). They worried that such a move would come at the expense of NSF's funding of basic academic science. But now lobbyists for research universities are singing her praises. Why the turnaround? Last week, Mikulski's subcommittee approved a bill that—if it survives running the rest of the congressional funding gauntlet—would give NSF its biggest budget increase in 11 years, and a report accompanying the bill contains none of the threats or harsh rhetoric Mikulski used last year. Indeed, the senator even thanked NSF for paying more attention to strategic research in its overall budget.

RICK KOZAK

Three big ones. Senator Mikulski has proposed a $300-million academic facilities program at NSF.

"It's just amazing what has happened to her relationship with NSF and the scientific community," enthuses Jack Crowley, special assistant to the president of the Massachusetts Institute of Technology and director of its Washington office. "She is a remarkably strong supporter of research, and I think everybody is pulling in the same direction now."

Crowley is particularly impressed that Mikulski has managed to find enough money to boost NSF's budget in a year when funding prospects seemed bleak at best. "She went the extra mile for science," he says. Indeed, the subcommittee that Mikulski chairs started in a deep hole, since it was allocated $729 million less than it needed to meet the President's request for all the agencies it oversees, which include the Department of Housing and Urban Development, NSF, the National Aeronautics and Space Administration (NASA), and the Environmental Protection Agency. Mikulski and her House counterpart, Representative Louis Stokes (D–OH), got around the funding limit by working out a deal with the White House