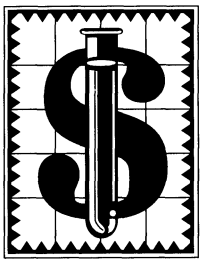
When Commerce and Academe Collide

Scientists with one foot in academe and another in commerce are being asked to disclose more about their personal investments and to avoid potential conflicts of interest in their research



CONSIDER A SCIENTIST about to embark on a clinical trial of what promises to be a blockbuster drug. He happens to have shares in the company that manufactures the drug. Should he decline to participate? Conduct the tests but declare his potential conflict of interest when he reports the results? Sell the shares? Or assume that his objectivity will overcome any possible bias and carry on regardless?

Or take a university researcher who has developed a new biological technique. He sets up a company with funding from a major corporation to exploit his discovery. But the corporation also funds research in the scientist's university lab. How can he respond to a charge that university resources are being used for private gain? And what about the students? How can they be sure that a professor's advice—on such things as choosing a thesis topic—is inspired by academic and not business interests?

Questions like these confront and often haunt faculty members and deans these days—a product of the boom in university-industry partnerships. And one reason they haunt academe is that they have also caught the attention of Congress. Last year, two congressional committees put the spotlight on academic conflicts of interest, focusing on cases in which commercial agreements went sour or violated ethical standards.

Goaded into action by these hearings, the National Institutes of Health (NIH) drafted a set of rules designed to steer its grantees toward a common approach to the problem. The guidelines would have required faculty to disclose their investments, along with those of their children and spouses, to college administrators. In addition, they would have prohibited faculty from having an interest in any company whose products they were testing. The rules sparked a storm of protest, and they were withdrawn last December (*Science*, 12 January, p. 154).

But the federal government hasn't entirely quit the field. There are rumblings that Representative Ted Weiss (D–NY) may attempt to add conflict-of-interest standards to the NIH authorization bill this year. And the Department of Health and Human Services may yet come back with a revised set of rules. Meanwhile, a few schools have taken the moral high ground by voluntarily adopting tighter standards. Their responses are diverse, however, making for a confusing array of requirements that vary from one university to another, even from one department to another. Some codes are quite explicit, like those approved by the Harvard Medical School in March, but others treat the subject almost in hypothetical terms.

The problem is anything but hypothetical, however. The two situations sketched at the beginning of this article, for example, have real-life counterparts. In 1988 and 1989, it was revealed that investigators at several clinical centers reviewing the heart-attack drug TPA were also stockholders in the company that makes TPA. Several of them later signed a pledge agreeing that in the future they would not hold stock in a company whose product they were studying. And in the early 1980s a controversy broke out among the faculty of the University of California at Davis when it became known that Allied Chemical Company was funding research on nitrogen fixation in plant geneticist Ray Valentine's lab and at Calgene, a company Valentine had founded. Valentine resolved the conflict by dropping out of the university-based research program sponsored by Allied. The university also adopted more stringent rules asking faculty to disclose outside commercial activities and established a standing committee to review potential research conflicts.

A similar conflict now confronts George Levy, a chemist at Syracuse University. Levy described his own predicament during a public meeting earlier this year in an attempt to show how the proposed NIH rules would punish innovators. A decade ago, Levy had an idea for improving the software for the nuclear magnetic resonance machines he uses in his research. He advanced the state of the art, and in 1983 founded a small company called New Methods Research, Inc. In 1986, NMRI moved off campus, and by 1988 it had $2.1 million in sales. The following year, NMRI was sold to new owners. Levy returned to his university lab to resume academic research full time. Meanwhile, the university lab got caught in the funding pinch at the National Institutes of Health and discovered this year that it may lose its grant.

In desperation, Levy says he may ask NMRI (in which he still has an interest) to spend discretionary funds on research at Syracuse. This would generate new ideas for the company and keep his lab at Syracuse

BIOMEDICAL FACULTY WITH BUSINESS TIES

Program	Biomedical Faculty	Number with Ties	Percentage
MIT	74	23	31.1
Stanford	82	16	19.5
Harvard	156	30	19.2
UC Davis	38	6	15.8
UC San Francisco	61	9	14.8
UC Berkeley	103	14	13.5
U. Washington	79	10	12.7
UCLA	115	14	12.2
UC San Diego	77	9	11.7
Yale	126	14	11.1

The Krimsky index. *This measure of commercial "penetration" of biology departments was disclosed at the AAAS meeting on 19 February. It comes from a partial survey of biology faculty and genetic engineering companies put together in 1985 to 1988 by Sheldon Krimsky, professor of urban and environmental policy at Tufts University. After serving on NIH's genetic engineering advisory committee, Krimsky became curious about the number of links between biology professors and such companies, and he asked students to assemble data on "dual-affiliated biomedical scientists." This is the result.*

The Florida Case: Appearances Matter

As University of Florida chemist Kenneth Sloan tells the story, the conflict-of-interest case that plagues his university began 5 years ago when he raised a question about the toxicity of a chemical invented by his department chairman, Nicholas Bodor.

Sloan claims that normal academic standards were distorted by the financial stake that many officials in the College of Pharmacy had in a company established to promote Bodor's invention. For this reason, says Sloan, they were unwilling to discuss the chemical's potential toxic side effects openly, and he claims he was ridiculed and harassed for raising concerns.

University officials have investigated Sloan's charges and judged them groundless. Nevertheless, they concede that the pervasive financial links between the college and Bodor's company could give the appearance of conflicts of interest, and they are changing the university's rules to limit certain financial relationships in the future.

Bodor's invention is a potentially lucrative system for delivering drugs directly into the brain. Bodor, a creative researcher who has published many articles on his idea (for example, *Science*, 1 July 1983, p. 65), founded a profit-making company, Pharmatec, Inc., of Alachua, Florida, to exploit it.

Pharmatec was for a time a pet project at the College of Pharmacy. Stockholders included two deans of the college—both of whom are responsible for overseeing conflict-of-interest policy—three other department chairmen, and Sloan himself. The university had licensed Bodor's invention to Pharmatec for commercialization, and Pharmatec supported research in Bodor's lab at the university.

The trouble began in 1984, according to Sloan, when *Nature* published an article by Sanford Markey, a researcher at the National Cancer Institute, describing the risks of a compound called MPTP, which has superficial similarities to Bodor's chemical system. But MPTP, Markey found, causes delayed Parkinson-like symptoms in humans.

Sloan says that the significance hit home suddenly when someone showed him a popular account of MPTP's "insidious nature." He read that "it could be inhaled, absorbed through the skin—just working with it in the lab you could get enough in through system circulation to cause Parkinson's syndrome." He worried that grad students and technicians working with the Pharmatec compound might face similar risks. As a Pharmatec adviser and stockholder he felt responsible.

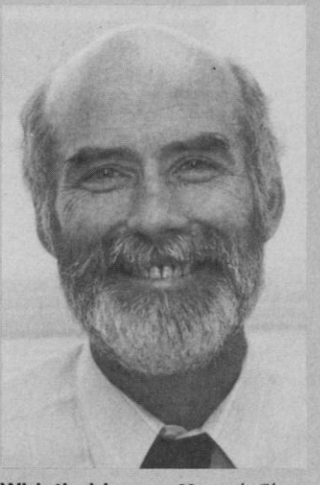
Rather than going directly to Bodor, Sloan turned, in December 1984, to the dean of the college, Michael Schwartz. Sloan says he did this because, "I was trying to avoid a direct confrontation with Nick." He asked Schwartz (who also had Pharmatec shares and served on the company's advisory panel) to take up the safety issue discreetly with Bodor, not mentioning Sloan's name.

Schwartz did this, but Bodor recognized Sloan's handwriting on a paper Schwartz gave him. He became angry with Sloan for violating "scientific principles" in going behind his back. He gave the dean a written response, followed by two long memos from Pharmatec scientists stating in blistering language that Sloan's query was based on ignorance. New toxicity studies were also begun. Schwartz, after receiving Bodor's reassurances, decided not to alert lab workers to the toxicity issue.

Markey himself says that there is no reason today to think that Pharmatec's chemical could produce the Parkinson-like effects. But back in 1984 and 1985, when the question first arose, there was not enough data to judge the risks.

The controversy went underground for a time, but Sloan complained to outside authorities, including the Securities and Exchange Commission, about the relationship between Pharmatec and officials at the College of Pharmacy. He pointed out that a company prospectus had Bodor spending 40% of his time on Pharmatec business, while the university said he was only spending 20% of his time on it. A congressional committee chaired by Representative Ted Weiss (D–NY) investigated, and news stories critical of the university appeared in the national press.

Says the university's vice president for research, Donald Price: "Dr. Bodor has really suffered because of some inappropriate accusations that escalated into a vindictive and bitter struggle that caused all kinds of problems for the company. The company's stock has dropped because of the bad publicity, and they were not able to go out and issue a new offering to continue the studies." David Challoner, vice president of the university's health center, said that Sloan's allegations have been thoroughly reviewed.



Whistle-blower. *Kenneth Sloan says concerns were brushed aside.*

Bodor recently wrote a negative review of Sloan's academic performance, resulting, according to Sloan, in his getting "the lowest salary increase [4.3%] in the whole college."

Schwartz, Price, and Challoner say that they find no basis for Sloan's complaint that Bodor's extra-academic interests rendered him unfit to review Sloan's performance. Bodor adds, "The evaluation I gave him had nothing to do with what he had done on the issue of toxicity, on which he has no knowledge or competence to make a judgment." "So far as I know," says Price, "nothing that Dr. Bodor put in [the evaluation] has been refuted." The matter is still under review within the university.

Meanwhile, Price says the experience has taught him an important lesson: the appearance of a conflict of interest can be just as damaging as the real thing. For this reason, he has established a couple of new policies. One is the "recommendation" that administrators like himself should not hold equity in a company with which the university has a sponsored research agreement. Another is a rule that the university itself should not become involved with a company that intends to raise funds for its first round of capitalization through a public stock offering. The reason, says Price, is to avoid the university's name being used to promote questionable ventures. In addition, Price strongly advocates full disclosure of all faculty-industry relationships. ■ **E.M.**

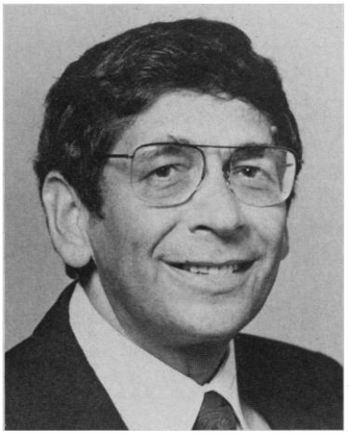
going. The profits would be shared between the school and NMRI.

This rescue may succeed, but it makes Levy uncomfortable because, "Here am I, sitting in the middle," trying to negotiate between NMRI and the university. Levy's position is troublesome because he has a direct personal financial stake in the outcome. "I don't like it," he says.

Syracuse has been kept informed at every stage of NMRI's creation and development, says Levy, and he is very much in favor of disclosing the necessary details of academic-industry deals like this.

The university has no formal conflict-of-interest guidelines to cover such situations, according to spokesperson Sandi Mulchonry. "The departments handle it on a case-by-case basis," she says. But Levy says that neither the rescue of his lab nor the creation of NMRI in the first place would have been permissible under NIH's aborted conflict rules. Nor is it likely that the rescue would be allowed under stringent rules being adopted voluntarily today by Harvard and several other universities.

Indeed, even a brief survey of major schools reveals, as Carol Scheman of the Association of American Universities says, that "there are a huge number of ways in which institutions approach these issues." Some institutions are taking a laissez faire approach. Caltech, for example, relies on its strong honor code to keep the faculty out of conflict situations, according to vice provost David Goodstein. "There are no requirements for disclosure as far as I know," he says. The only "really explicit rule" is that faculty may not take operational responsibilities outside the school. "We have not had any problems," Goodstein says. In contrast, the Massachusetts Institute of Technology requires everyone, staff and faculty alike, to file full outside interest reports every year.



Uniform rules. *Representative Weiss argues for "strong minimum standards for all research institutions."*

The latest to adopt strong measures is Harvard University, and many observers believe its rules could be a model for others. Harvard was stung last year by news coverage of a researcher named Scheffer C. G. Tseng at a Harvard-affiliated eye clinic who had a financial stake in an experimental eye medicine he was testing on patients. Before releasing data showing that the medication was ineffective, Tseng cashed in most of his 530,000 shares in a company established to promote the drug. Two other scientists who advised Tseng, one at Harvard and another at Johns Hopkins, also had a financial stake in the company.

Medical school dean Daniel C. Tosteson appointed a committee in 1989 to review conflict-of-interest policies and suggest changes. Tosteson did this, he says, not because of any scandal but because Harvard has encouraged its faculty to spread new ideas to the world through commercial agreements, and many gray areas that were vaguely discussed in the old (1983) rules have now become important.

Barbara J. McNeil, chair of the department of health care policy, headed the rule-drafting group. Their recommended changes were unveiled before a full faculty meeting in February, where they met a noisy and hostile reception. Opponents, who had bused in scores of doctors from the Massachusetts General Hospital, dominated the podium. Many felt, as one professor said, that Harvard was "using a cannon to kill a fly." But a month later, McNeil and the reformers won a quiet victory in the select faculty council, which backed the dean with a lop-sided vote of more than 30 to 1. Says council member Leon Eisenberg, "We sensed the world was watching."

The new rules require all faculty members to make a full disclosure of their potential conflicts of interest to university administrators at least once a year, and they require researchers to get explicit approval before embarking on studies funded by companies in which they or their families have a financial interest. They also put strictures on faculty involvement in the operations of profit-making companies (see box). The rules will go into effect in May and faculty members will be allowed 6 months to adjust, either by divesting financial holdings or bringing their research into compliance.

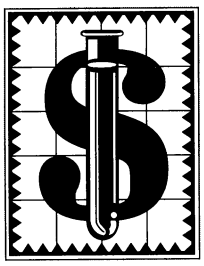
Tosteson notes that Harvard's approach is "more explicit" than most. Other institutions that are revising their own conflict-of-

Harvard's Tough New Rules

Over the objections of some faculty members enraged by invasion of their privacy, Harvard Medical School adopted new conflict-of-interest guidelines last month. They are among the toughest yet adopted by a U.S. university. Among the provisions:

- The rules define two problem areas: conflict of commitment and conflict of interest. Commitment issues are simpler, requiring faculty to give "their primary professional loyalty" to the university and to devote no more than 20% (one working day per week) to outside activities.
- Faculty members must now disclose all potential conflicts at least once a year on a new form, which must be updated whenever a new conflict arises. The forms will be collected by the appropriate hospital or dean's office and be kept "strictly confidential." Questionable cases are to be reviewed and settled by a standing committee of the faculty.
- Unless they receive explicit approval, faculty members and their families may not hold stock in or receive consulting fees from a company whose technology they are investigating in clinical trials.
- Without prior approval, faculty members may not do sponsored research at a university facility for a business in which they or their families have an interest.
- Without approval, faculty members may not sit on a review committee (such as a Food and Drug Administration panel) judging a technology in which they or their families have an interest.
- Without approval, faculty members may not serve as a managing executive for a profit-making biomedical company, nor may they have a financial interest in a business that competes with services provided by the university or its hospitals.
- Without approval, faculty may not make clinical referrals to a business in which they or their families have an interest.
- Faculty members must disclose to the public (not just to an administrator) their financial interest in a subject which they discuss in a research publication, a formal presentation, or an expert commentary, and they must do so "simultaneously" as they speak or publish. ■ **E.M.**

Should Science Journals Play Cop?



Should science journals help guard against potential conflicts of interest in the reporting of research findings by asking authors to disclose relevant financial information when they submit an article? Absolutely, says Barbara Mishkin, a Washington, D.C., attorney and member of the Committee on Scientific Freedom and Responsibility of the American Association for the Advancement of Science, "Part of submitting a manuscript could include signing a form that says something like, 'I have no financial interest in any company or entity that would be marketing a product of this research.' " In cases when an author does have an interest, that interest should be disclosed. Then "readers could weigh for themselves how much that affiliation may bias the interpretation of results."

One journal already does this: the *Journal of the American Medical Association*. Beginning last fall, *JAMA* asked every author to include the following signed statement with a submission: "I certify that I have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g. employment, consultancies, stock ownership, honoraria) except as disclosed in an attachment." Authors must include the relevant financial information, which is kept confidential. Later, if the editor (George D. Lundberg) thinks it necessary, he negotiates the text of a footnote to be included with the article.

Other journals have less explicit rules, although they believe they manage conflicts just as well:

The *New England Journal of Medicine*, according to editorial office manager Marlene Sayers, "doesn't ask for a balance sheet," but puts the responsibility on authors to reveal all significant financial interests to the editors. If necessary, an informational addendum is published.

The *Lancet* has "no formal declaration" of policy, says deputy editor David Sharp. "We expect people to declare in a covering letter or in an acknowledgement any financial support they've received."

Cell has no explicit policy on conflict of interest, according to managing editor Dan Lipow.

At *Science*, potential conflicts are handled on a "case by case basis," says managing editor Patricia Morgan. "Our editors know the field well enough to be attuned to possible problems."

Nature's editor John Maddox says, "authors should declare their source of funding, and if they fail to do so, it's reprehensible. We try to police it."

Frances Zwanzig, managing editor of the *Proceedings of the National Academy of Sciences*, says the staff has "never considered" financial interests of the authors to be a problem. "We publish very few clinical studies," she explains. ■ **E.M.**

With reporting by Sarah Williams.

interest standards have been looking carefully at Harvard's new rules, but many schools will find some of the specific provisions too Draconian. That, at least, is the view of the Association of American Universities' Carol Scheman, who says that Harvard, with its network of 14 affiliated clinics and hospitals, has a "unique and difficult problem" in trying to keep tabs on its diverse faculty.

Johns Hopkins University went part way toward a stringent code of ethics in November. According to associate dean David Blake, "We didn't get that many disclosures under the old system," so it was revised. "Our assumption is that the problem is mostly one of perceptions, so disclosure is the key." Faculty must report all written agreements involving privately sponsored research and disclose consulting deals that demand more than 26 days a year. Blake himself does not think that clinical research needs special attention because it is already heavily regulated by the federal government. But the medical school does have one "absolute prohibition": you may not own even one share of a corporation that is sponsoring your research at the university.

The Stanford University School of Medicine, according to its dean, David Korn, has begun doing some "spot auditing" of the disclosure forms it requires faculty members to submit each year. In addition, Korn says, the review protocol for human subjects has been rewritten to include an extensive series of questions about the financial involvement of the investigators and their students. This information must be cleared by the human subjects review committee, and the patients must see it, too.

Because of the diversity among individual schools, Korn argues that it makes no sense to issue blanket prohibitions for the entire country, as the NIH guidelines attempted to do. Korn himself advocates using the system of Institutional Review Boards that watch over research on human subjects to do a similar job for conflicts of interest. In this approach, each institution would have to assure the government that it had put an effective system into place, subject to spot auditing by some federal supervisor like the NIH. He thinks this would allow for the greatest local autonomy while maintaining high standards. Stanford works under "the philosophy that people are generally decent and behave well," says Korn. "You don't have to tie them up in a bunch of minutiae." Although employees at state universities must work under very strict prohibitions, "rules like those would be anathema on this campus." In general, Korn thinks national policy should avoid detail and give broad, philosophic direction.

This is precisely the aim of two major reports issued this spring by university leaders—one drafted by a panel Korn chaired for the Association of Academic Health Centers (AAHC), and the other by a group at the Association of American Medical Colleges (AAMC), headed by Michael Jackson of the George Washington University School of Medicine.

Korn's AAHC report, issued on 22 February, traces the boom in academic-industrial collaborations since the 1970s, now encouraged by federal law, and it notes that there are several areas of growing concern. For example, it says the possibilities for conflicts are "legion" in spin-off companies started by faculty members, because the founders live in both the academic and profit-making worlds and control resources and young people's careers in both (see story, page 153).

An academic's chief loyalty, both reports say, must always be to the university, but they remain a bit vague in the measures they would use to reinforce that loyalty.

One point on which all experts seem to agree is the need to disclose potential conflicts in advance. A set of guidelines issued recently by the AAMC says universities ought to develop procedures for full disclosure of financial and professional interests not only for use by the school but to inform "the interested public." In addition, the AAMC paper says, institutions should review researchers' personal holdings, including those of the immediate family, at least

once a year. Questionable cases should be passed up the chain of command to the university president or, better, to a standing committee. Those at odds with the rules "must be handled expeditiously and conclusively," the AAMC panel believes, and "all decisions must be documented."

The AAHC goes further, saying that "significant" financial or other relationships, if they raise a potential conflict of interest, should be "fully and accurately disclosed in all speeches, writing, advertising, public communications, or collegial discussions" of sponsored research.

These guidelines are new, but others like them have been in existence at major universities for some time—and "honored in the breach," according to C. Kristina Gunsalus, associate vice chancellor for research at the University of Illinois at Champaign. The way to make principles work, Gunsalus says, is to develop a reporting system that will win faculty cooperation and actually do the tedious job of screening and reading the disclosure forms. You must look for trouble, as she does, because "it is extremely difficult for the most honest and upright of scholars to acknowledge their own conflicts for what they are."

Representative Weiss says that while he "applauds" the AAMC and AAHC for developing conflict-of-interest guidelines, they do not go far enough. He favors "strong minimum standards for all research institutions." Unless everyone plays by the same rules, Weiss says, "universities that make serious efforts to minimize conflicts of interest could be at a disadvantage in recruiting scientists who enjoy lucrative financial relationships with the private sector."

The consensus among those who actively manage faculty conflicts is that one must begin with written forms. They are "the only thing that everybody agrees is absolutely essential," says John Lombardi, the former provost at Johns Hopkins, now president of the University of Florida at Gainesville. "If you actually disclose and write down the relationships you have, the conflict of interest is much easier to discern."

Lombardi finds that 95% of the cases turn out to be fine. But "5% are very difficult because they skirt the borders of a conflict of interest. Then you have to do what rule-makers don't like to do: you have to exercise judgment."

Both Gunsalus and Lombardi say that when the system works well, it encourages the faculty to venture out into the commercial world, because the responsibility for error—if something goes wrong—falls squarely on the official who gave approval and not on the individual researcher.

■ ELIOT MARSHALL

Pork in a Medical Wrapping

It seems like the kind of bargain Congress would find irresistible: For a mere $20 to $30 million, a defunct government research reactor in Idaho could be turned into a state-of-the-art facility to pioneer a technique for treating deadly brain cancer and melanoma. But when Senator James McClure (R) and Representative Richard Stallings (D)—both not so coincidentally from Idaho—recently tried to persuade the appropriations committees to stuff some money into the Department of Energy's (DOE) budget to convert the reactor, researchers around the country cried foul.

The reason: three other institutions—Brookhaven National Laboratory, the Massachusetts Institute of Technology, and Georgia Institute of Technology—have similar facilities that could provide the same kind of treatment at little or no additional expense to the government. Worse, researchers affiliated with some of these facilities fear that their federal R&D support could be cut if the Idaho center is shoehorned into the fiscal 1991 budget. Moreover, 2 years ago, a panel convened by the National Cancer Institute recommended against converting the Idaho reactor until a peer-reviewed research program had been developed for the facility.

In other words, the McClure-Stallings move is being viewed as another grade A example of congressional pork-barreling. "They are doing something highly unethical" in attempting to bypass peer review, charges Robert G. A. Zamenhof, the head of medical imaging physics at the New England Medical Center.

McClure and Stallings want to convert the reactor to a facility for a treatment known as boron neutron capture therapy, which entails injecting boron compounds into the blood stream and bombarding the tumor with low-energy neutrons. When a boron atom captures a neutron, it emits a burst of radiation that kills surrounding cells. While the technique holds potential for treating tumors that have been resistant to conventional radiation therapy, the efficacy of several candidate boron compounds is still being studied in animal tests.

Because the therapy has not yet been tested in humans, Ralph G. Fairchild of Brookhaven argues that it is premature to convert the reactor to a medical facility. But Ronald V. Dorn, principal investigator for Idaho Nuclear Engineering Laboratory's boron neutron capture research program, says that results from tests on dogs and reports of clinical results from Japan demonstrate that the technology is very promising. He argues that conversion of the Idaho reactor, which is known as the Power Burst Facility, is warranted now in light of these results.

McClure makes an even stronger claim: because the reactor, located at the DOE's Idaho laboratory, is more powerful than the other machines, he says it would be better for treating "typical, deep-seated human [brain] tumors."

Not so, says Zamenhof. Both the Brookhaven and MIT reactors are capable of delivering neutrons to the required depth of approximately 7 centimeters, he says. The only apparent advantage that the Idaho reactor has is its ability to deliver therapy more quickly and in a single dose. But Zamenhof and Fairchild say this is not important. Neutron treatments, they point out, most likely will be broken down into four to six sessions to limit damage to healthy tissues. Each treatment would take 6 to 15 minutes on the MIT and Brookhaven reactors and a few minutes at Idaho.

Officials in DOE's Office of Health and Environmental Research have deferred making a decision to convert the reactor in large part because of a 1988 National Cancer Institute assessment of the neutron therapy capture research program. The reviewers advised DOE then to keep the reactor in a "standby condition for a period not to exceed 5 years pending the development of a peer-reviewed, highly meritorious [boron neutron capture therapy] research program" at the Idaho facility. The NCI group also expressed strong doubts about the suitability of using Idaho as a site for clinical trials because of its remote location. As *Science* was going to press, DOE's Health and Environmental Research Advisory Committee was expected to make a similar recommendation against converting the Idaho reactor at this time.

Unless Congress overrides these recommendations and forces DOE to convert the reactor, the machine will probably remain in limbo. The department had wanted to shut the reactor down and decontaminate the site in 1985 when it finished an R&D program on nuclear fuel rods. But Congress forced the Administration to keep the facility on standby—at a cost of about $3 million a year.

■ MARK CRAWFORD