San Francisco, put a warning on the network: "We are currently under attack from an Internet virus. It has hit Berkeley, UC San Diego, Lawrence Livermore, Stanford, and NASA Ames. . . . " He gave a preliminary description of its modus operandi, suggesting that "the only help" for the moment was to turn off the vulnerable services.

At Berkeley, "We felt guilty," says Bostic, because the worm was feeding on a couple of 5-year-old weaknesses in Berkeley's version of UNIX. The Berkeley team consulted with the visiting UNIX experts and summoned a computer whiz from the South Bay area for special help in decompiling the worm. As distributor of the UNIX software, Berkeley posted the official remedies, but Bostic says help came in from all over the country. He gives special credit to Jeffrey Schiller and Mark Eichin at MIT, who also decompiled the worm, and to Eugene Spafford at Purdue, who served as the central post office during the crisis.

On Thursday, Berkeley researchers discovered that deep in the worm's logic was a mysterious code linking it to a Berkeley computer called "Ernie," a popular hub in the network. Every time a worm child broke into a new computer, its code required it to send a message back to Ernie, as though Ernie was keeping track. "When we saw that," Bostic says, "We got very nervous. . . . We staked out Ernie like no tomorrow"—unobtrusively monitoring the machine's every move.

The same day, MIT researchers trapped a worm in an isolated network in Boston and dissected it. "We all had pet worms after a while," Bostic says. When the people at MIT saw Ernie's address, they delicately questioned their colleagues at Berkeley. For a time there were rumors that either a Berkeley or an MIT grad student was responsible. Everyone was relieved when the *Times* on Saturday blamed a Cornell student.

The Ernie puzzle remains unsolved, however. The surveillance at Berkeley was of no use, as it turned out, because the instructions in the worm may have been badly written. Ernie never received a message.

James Bruce, vice president for information systems at MIT, says that 200 out of the 2000 machines at his university were infected. So were machines at nearly every big university in the East. Using the MIT ratio, he figures that perhaps 6000 computers worldwide got the worm. The problem is well under control now, although 4 days after the attack Bostic said, "I just stomped on another one this morning."

Postmortems have just begun. One of the questions security experts will be asking is: How bad might it have been if the worm had not been benign? ■ ELIOT MARSHALL

# NIH Delays Gene Transfer Experiment

*NIH director James Wyngaarden postpones approval pending review of withheld data but asks committee to act quickly*

BY A VOTE of 16 to 5, the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health said yes to a proposal for a precedent-setting experiment in gene transfer in human beings.

However, for reasons of politics and process, NIH director James B. Wyngaarden has decided to reject the RAC's advice in the hope that further review of the experimental protocol and the data that back it up will enable at least some of the five who voted no to change their minds.

Just last week the gene transfer proposal got a unanimous endorsement vote when the NIH's own Institutional Biosafety Committee met to review the data. Wyngaarden made it a point to be there himself.

No one seriously argues that the proposed experiment is particularly risky, genetically speaking. In fact, it is important to note that the experiment has little to do with gene *therapy*; rather it involves adding a marker gene to anticancer cells. As one scientific observer noted, "We add markers all the time." Initially there was a debate about whether it was appropriate to refer the proposed experiment to the RAC at all.

But the political sensitivity surrounding any human research that has to do with transferring genes is high. A full-dress review was judged the responsible thing to do. And for this reason, Wyngaarden wants the approval process to be impeccable.

Several months ago, Steven A. Rosenberg and R. Michael Blaese of the cancer institute, and W. French Anderson of the heart institute, began the lengthy process of seeking approval for a gene transfer study in people dying of cancer. First, their proposal was reviewed by the institutional review boards of the cancer and heart institutes. Then, this summer, the researchers submitted their data (most of it, anyway) to the RAC's human gene therapy subcommittee for its review prior to review by the entire RAC. That is where trouble began.

Two important pieces of data were withheld from the subcommittee during its pre-RAC review. Then, when the full RAC met, those data were presented with slides, but no hard copy was released for the committee's examination. Anderson said the critical data were withheld, in part, because of apprehension that their release at a public meeting would jeopardize subsequent publication in *Science* and *The New England Journal of Medicine* (see box). The committee was outraged. When Wyngaarden heard about the incident, he was furious. The journal editors, when later asked about their policies, declared that they would never interfere with the workings of a duly constituted government advisory body. And Anderson called the incident a regrettable case of misunderstanding. But the damage was done.

The experiment is this:

Ten desperately ill cancer patients would be the volunteer subjects in a test designed to track the course of tumor-killing white blood cells to see where they lodge in the body and how long they stay there. The plan is to use recombinant DNA technology to insert a marker gene into specially "activated" tumor infiltrating lymphocytes or TIL cells and then monitor their ability to attack and shrink massive tumors in patients who are expected to otherwise die within weeks.

Rosenberg, a pioneer in efforts to manipulate immune system cells in cancer therapy, has unpublished data (currently under review at the *New England Journal*) on 15 patients with advanced melanoma who had

Ken Heinen

**James Wyngaarden:** *Rejected the RAC's advice for reasons of politics and process.*

had no therapy prior to receiving infusions of TIL cells in one of his cancer studies. Nine of the patients responded with a 50% reduction in tumor size. One of the nine had a complete remission. As Rosenberg reported, these are terminal patients whose tumors were, in some cases, the size of a tennis ball in the chest.

The question is "Why did nine patients improve noticeably while six did not." Attempts to track the course of infused TIL cells using radioactive labels proved unsuccessful because the half-life of the markers was too short. Rosenberg and Anderson decided to collaborate in an attempt to mark the TIL killer cells with a bacterial gene for antibiotic resistance (the neomycin 2 gene). In vitro and limited animal data suggest that as a marker it will work. Thus, Rosenberg might be able to learn whether the TIL cells head preferentially for lymph nodes, for example, or for other sites.

The encouraging TIL cell data constitute a strong argument for approving the gene transfer experiment. But they were not sent out with other data sent to the committees in preparation for the RAC meeting.

The other critical piece of information withheld from the package of material pertains to safety. It is necessary to show that the retrovirus that will carry the neomycin gene into the TIL cells will not replicate or spread once it is infused into patients. The slide showing the results of the safety assay from animal tests was of great interest to the subcommittee members who are most familiar with the technical details of gene transfer work. They wanted to examine that slide, not just see it flashed on the screen.

Richard Mulligan, a gene worker at MIT's Whitehead Institute in Cambridge, expressed concern about the assay data and also suggested that a retrovirus vector designed in his own lab is preferable to the one Anderson and Rosenberg propose using. In an interview with *Science*, Anderson said that "in theory Mulligan's packaging system," which does not work in Anderson's hands, is probably "safer" in ways that would be important in a real gene therapy experiment in which the gene would be put into bone marrow cells rather than cells transformed in the lab into tumor killers. But says Anderson, it is not important to the present case. One high-ranking NIH official agrees. "Anderson shouldn't be penalized because Mulligan thinks he has a better vector," he told *Science*.

Then there is a question about the adequacy of the animal data. Animal data are available for tests in a half dozen mice and one monkey. One subcommittee member, William Kelley of the University of Michigan, himself a participant in the gene therapy enterprise, argues for more animal data. He was one of the five who voted no.

On the other hand, Charles Epstein of the University of California at San Francisco, a RAC member who describes himself as a man who makes animal models for a living, took the position that Anderson's animal data are quite sufficient. And RAC member Robert Murray of Howard University argued that medicine would not have made the progress it has in sickle cell anemia if researchers had been required to have "perfect" animal data before doing human testing.

But it was RAC veteran Bernard Davis of Harvard who finally stated a position that prevailed with the 16 to 5 majority of the committee. Davis referred to some of the arguments against approval as "nit-picking" and reminded the group of medicine's long-standing tradition of taking chances. "The sicker the patient, the higher the risk you're willing to take," said Davis who says this experiment poses no meaningful risk to the patients who would volunteer or to the health workers who would treat them. Besides, "It is virtually not possible to have more risk than certain death," he said.

It is probably safe to say that the risk in the proposed experiment lies in the infusion of toxic killer TIL cells, not in the addition of a marker gene. But the former risk is one commonly accepted by both physicians and the public when it comes to terminal cancer.

What happens now?

The human gene therapy subcommittee has all of the data and Wyngaarden has urged members to review it carefully and meet to discuss it. The subcommittee will assemble at NIH on 9 December. Then, to avoid further meetings, Wyngaarden proposes rapid approval from the full RAC if the subcommittee first gives its OK. He has said in an 18 October letter to the RAC chairman that RAC concurrence by telephone conference should do it if no additional issues arise. Regulations do not require a unanimous vote of the RAC in order for Wyngaarden to give his approval, but it is clear that on this sensitive issue he wants to cover all the bases.

■ BARBARA J. CULLITON

## Journals and Data Disclosure

For years, researchers have been apprehensive (and confused) about the prepublication policies of competitive journals, especially *The New England Journal of Medicine* and *Science*. Concern that public release of crucial data would jeopardize publication was one (but only one) of the elements in a decision by NIH scientists not to circulate some data prior to their oral presentation to an advisory committee that had authority to review a proposed human experiment in gene transfer (see story).

Withholding the data backfired. Committee approval was postponed. The incident also raised concern about the role of journals in "controlling" information. And it prompted NIH director James B. Wyngaarden to declare that NIH committees "would not be held hostage to *The New England Journal of Medicine*."

*New England Journal* editor Arnold S. Relman and *Science* editor Daniel E. Koshland, Jr., have taken the occasion to make their policies clear. Each journal wants to publish new data that has not previously been published in another journal. Each hopes that information accepted for publication will not be extensively discussed in the press prior to journal publication.

But neither the *New England Journal* nor *Science* would bar researchers from presenting their data to colleagues at a scientific meeting. And, most certainly, neither would ask a potential author to withhold data from a duly constituted federal committee, be it an NIH or National Science Foundation body, for instance, or Congress.

Says Koshland, "Our prepublication policy is designed to maximize the orderly and accurate presentation of scientific data to the public. It is designed to allow reporters to evaluate the data in a comprehensive manner and to prevent fragmented release of information. It was never intended, has not been and will not be used to prevent scientists from presenting needed data to fact-finding bodies, either in the executive branch or in Congress. If data presented in such a public inquiry were given widespread publicity it would not jeopardize subsequent publication of a proper scientific article in *Science*."

Relman is equally clear. "The first duty is to cooperate with the government when it is appropriate," he told this reporter. "If a scientist is asked to testify, we'd expect him to comply up to and including turning over the manuscript if it is requested," he said. "The *New England Journal* doesn't want to hold the NIH or any other government body hostage, and we don't." ■ B.J.C.