AIDS VACCINES

Army Investigates Researcher's Report of Clinical Trial Data

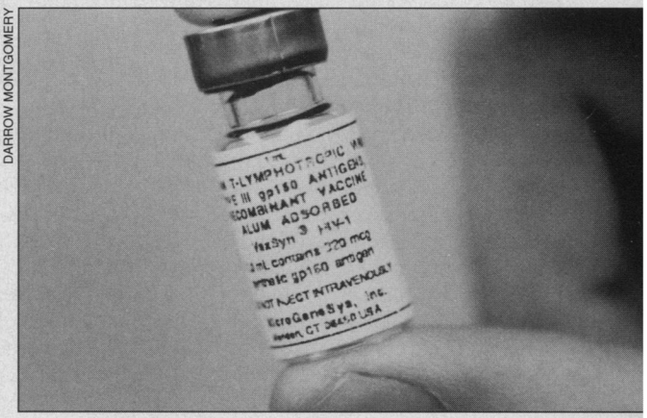
One of the Army's foremost AIDS researchers, Lt. Col. Robert Redfield of the Walter Reed Army Institute of Research, has become the target of an investigation by Army officials into concerns that he may have presented misleading research results at a public meeting. Redfield is well known in the scientific community as one of the first investigators to test vaccines as a form of therapy in HIV-infected people. At issue in the investigation is whether he overstated the significance of early results from a trial of an AIDS vaccine called gp160 in a presentation he gave at the international AIDS conference in Amsterdam last July.

Science has learned that on 30 October, the Army, in an "information paper," notified members of Congress of the "fact-finding" investigation, stating that the inquiry was focusing on allegations "that the effectiveness of the gp160 vaccine was overstated." In addition, it says, "fellow researchers" have disputed Redfield's statistical analysis and interpretation of the data. "We do not hold Dr. Redfield's data suspect in any way," the Army said in a statement to *Science*. "What is being questioned is only the interpretation of that data."

According to an Army spokesman, Redfield is declining all requests for interviews while the "informal investigation" is under way. But *Science* interviewed Redfield a few days before the investigation began. In the interview Redfield described his talk to the international AIDS meeting as a preliminary offering that was not intended to say whether the vaccine can actually prevent the onset of AIDS symptoms. "We're not trying to imply efficacy [for gp160]," he said.

Redfield's supporters in the research community contend the investigation was triggered by political forces surrounding the vaccine, which is made by the Connecticut biotech firm MicroGeneSys. With considerable help from high-powered lobbyists, including former Senator Russell Long, Congress recently added $20 million to the Defense Department appropriations bill for the Army to conduct a large-scale efficacy trial of gp160 (*Science*, 23 October, p. 536). That appropriation has evoked outrage on the part of National Institutes of Health (NIH) Director Bernadine Healy and AIDS researchers, who view it as an attempt to circumvent peer review. Editorials in *The Washington Post* and *The New York Times* have condemned the appropriation, and insiders suggest that the investigation of Redfield—long seen as an enthusiast for vaccine therapy generally and gp160 in particular—is fallout from the furor over the appropriation.

Whatever the political forces behind the investigation, the controversy over Redfield's Amsterdam presentation began in July at the conference itself, and the initial uneasiness originated with his colleagues. They were uncomfortable, say co-workers who insist on anonymity, because Redfield failed to share his analysis of the data with key members of his research team before presenting it. The data were drawn from a group of 15 patients infected with HIV, who were receiving gp160 as an experimental form of therapy. Using a new, ultrasensitive version of the polymerase chain reaction (PCR), Redfield's lab quantified the amount of HIV genetic material from those patients, then compared the results over time with data from a "natural history" study of untreated patients.



DARROW MONTGOMERY

Target. Robert Redfield's interpretation of results from the AIDS vaccine called gp160 is under investigation by the Army.

In doing the PCR work, Redfield's lab was attempting to measure the total amount of virus—the so-called "viral load"—in the patients' peripheral blood cells. Many AIDS researchers believe that if a therapeutic agent could decrease viral load in HIV-infected people, it might be effective in preventing AIDS symptoms. Of the 15 patients, Redfield said at the conference, 93% showed decreases or no change in their HIV genetic material. By contrast, 47% of the natural history group had increases in viral genetic material. In his Amsterdam talk, Redfield described the difference between the groups as statistically "significant."

The way Redfield presented his conclusions compounded the discomfort some of his colleagues felt. Some researchers in his own lab were concerned that his analysis of the data made it seem as though quantitative PCR is well understood and that the numbers generated by it had a clear clinical meaning; in fact, the method remains experimental and it is not known whether its results are clinically significant. As a result, one Walter Reed researcher calls Redfield's Amsterdam presentation "extremely misleading." That researcher, who insisted on anonymity, compared having quantitative PCR data to "knowing a noun or a verb in a sentence, that's all."

In August, Col. Donald Burke, Redfield's superior, asked a statistician at the Henry Jackson Foundation—a private foundation that has a contract to help the Army with AIDS research—to reanalyze Redfield's data. The statistician, William McCarthy, explained to *Science* that his analysis did not use the same yardsticks Redfield had chosen. One of the key differences is that Redfield had used what he called a "half-log" change (one-half an order of magnitude) in HIV genetic material as a threshold for recording an increase or decrease in viral load in a particular patient. But McCarthy said he "was told by biologists and virologists that [the half-log criterion] wasn't grounded in any biology and therefore it was just an arbitrary cut of the data." Using standard criteria, McCarthy reanalyzed the data for the 15 patients and found no statistically significant effect of gp160 treatment. A memo by McCarthy that came to a similar conclusion was leaked to the press and published in the *New Scientist*, further inflaming the controversy.

In the recent interview with *Science*, Redfield acknowledged that the half-log parameter was "arbitrary." But he added: "I stand by all the data that we did. We are extremely honest individuals. We are trying to share our data, probably much more openly than maybe some of our colleagues." Redfield said he had been open to revising his analysis and that in oral presentations at an NIH-sponsored AIDS vaccine conference held after the Amsterdam meeting, his group reported that the viral load changes after gp160 treatment were not significant.

Researchers who have worked with

Redfield suggest that while he may have been mistaken in his Amsterdam presentation, that is hardly a scientific sin. Gerald Eddy, the Jackson Foundation's laboratory director, argues that "if people were officially reprimanded for overexaggerating data in oral presentations, there wouldn't be many scientists left who had not been reprimanded in one way or another." Edmund Tramont, Redfield's former boss and now head of the University of Maryland's Medical Biotechnology Center, speculates that the real motivation for the investigation has more to do with the congressional appropriation than with Redfield. "If there weren't this $20 million, these goings on never would have happened."

Indeed, a Redfield colleague who is well informed of the details told *Science* that at least two forces have been unleashed on the Army by the legislation singling out MicroGeneSys's gp160. In the wake of the appropriation, the source said, the Navy and the Air Force—which have long been upset that all military AIDS research money goes to the Army before being distributed to other services—began calling for an investigation. An Army spokeswoman acknowledges that "information from the other services was one of several factors in the decision to initiate the investigation."

Another factor, says a well-placed source, was the Army's desire to head off an investigation by Senator Sam Nunn (D–GA), who played a key role in allocating the $20 million. Nunn, when introducing the measure on the Senate floor, said that according to "Army medical experts" the large-scale trial of the MicroGeneSys gp160 should happen "as soon as possible." Now Nunn, who has yet to name the Army experts, is modifying his stance. In a 23 October press statement Nunn denied he had been interested in any particular product and that in putting forward the measure he was only attempting to bring the Army's AIDS research program "back to approximately the same level as previous years." That statement, however, does little to explain Nunn's motivation, since before adding the $20 million, Congress had already boosted the Department of Defense's 1993 AIDS research budget to $50 million—$5.6 million more than was appropriated in 1992.

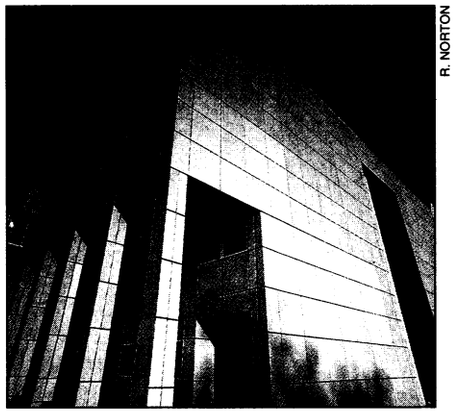
What all this means for Robert Redfield won't be settled for 60 days or more. When the investigation is concluded, the matter could be dropped, a letter of reprimand could be issued to Redfield (and possibly others in his lab), or, if serious wrongdoing is judged to have occurred, those involved could be court martialed. In the meantime, a blue-ribbon panel organized by Bernadine Healy was scheduled to hold its first meeting on 5 November to discuss the $20 million appropriation, and it's clear the last word on these matters has yet to be spoken.

–Jon Cohen

SCIENCE IN IRELAND

Brussels Provides Funding Lifeline to Irish Research

DUBLIN—If you took a walk around Dublin's Trinity College this summer, it wouldn't have taken you long to realize to whom Ireland's scientists owe their allegiance nowadays. At Trinity, there aren't too many flagpoles flying the Irish tricolor, but the European Community's (EC) distinctive emblem—a circle of 12 gold stars on a blue background—was proudly displayed at the construction site of a new 4-story biotechnology institute that will open later this fall. Faced with an impoverished government that provides next to no money for basic research—and certainly can't afford by itself to bankroll major campus building projects—Ireland's researchers have turned to Brussels for funding. And while scientists in southern European countries like Greece and Portugal, where research money is equally hard to come by, have also looked to the EC, no one has succeeded in playing the Brussels system as well as the Irish.



R. NORTON

Courtesy of the EC. Trinity College's new biotechnology institute.

Most European scientists hoping to build a research empire don't make Brussels their first stop when looking for money—the EC's research budget is still less than 4% of the total science spending of its member governments. But by turning to the EC for grants, Irish scientists who might otherwise be tempted to leave the Emerald Isle in search of greener research pastures abroad are finding it possible to hold their own. Indeed, some have managed to thrive. Take Trinity's genetics department: In 1980, it was a quiet backwater, teaching students, carrying out small research projects, but influencing virtually no one. Today, however, it commands the respect of Europe's top researchers in the field. "In terms of excellence per unit of resource, they're near the top," says evolutionary geneticist Steve Jones from London's University College.

Trinity's geneticists gladly acknowledge their debt to Brussels. Department head David McConnell says he was so demoralized about the Irish government's low spending on science that, in the late 1970s, he was on the point of leaving for the United States. "Then I heard about EC funding and I guessed there was one more chance to get science going in Ireland," he says. It was a chance that McConnell and his colleagues seized with both hands. "The level at which we operate here is hugely dependent on an influx of funds from the EC," says bacterial geneticist Kevin Devine. His group, for instance, currently rakes in about $68,000 a year from Brussels to study how *Bacillus subtilis* ensures that copies of its plasmids get transmitted to both daughter cells at each cell division; and next year, he expects to land another $67,000 EC contract to sequence 25 kilobases of the *B. subtilis* genome. Then his EC funding will easily surpass the $85,000 he's getting each year from EOLAS—the Irish government's main science and technology agency—to support the sequencing work and study bacterial gene expression.

It's a similar story throughout the department. "I think everybody has had EC money at some point," says evolutionary geneticist Paul Sharp. And for researchers like Ken Wolfe, who joined the Trinity faculty in January after finishing a postdoc at Indiana University, EC funding is literally the only lifeline. When Wolfe returned to Ireland, he was given a few thousand dollars to set up his lab—nowhere near enough to buy sufficient equipment and reagents to pursue his work in mammalian molecular evolution. To make ends meet, Wolfe has become a high-tech equivalent of the traditional Irish laborer, churning out DNA sequences under contract for the EC's yeast genome project (*Science*, 24 April, p. 462). Because the EC pays more to its contract sequencers than the basic cost of doing the work, Wolfe can use the difference to equip his lab.

Although Wolfe and his Trinity colleagues are all doing fundamental research, many of the EC programs that they've tapped for funds were set up primarily to help industry. Most European academics grumble about the EC's bias toward applied research, but then they haven't had to deal with EOLAS. More than three-fourths of the money that the country's main science agency channels to Ireland's universities is spent on applied projects, and