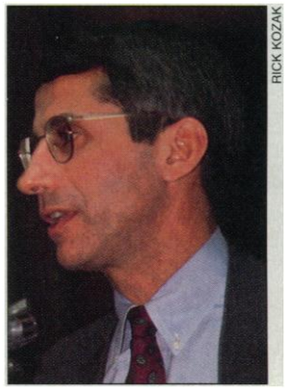
The HIV Vaccine Paradox

Last year, candidate HIV vaccines failed a critical laboratory test, but now a group of researchers is recommending that a clinical trial be conducted to determine if they are highly effective

Just as the thermometer started to dip last fall, a chill wind blew through the AIDS research world and threatened to send plans for large-scale trials of AIDS vaccines into the deep freeze. A battery of tests had revealed that the most promising potential vaccines might not provide protection against the strains of the virus that are most likely to be encountered in the real world. In recent weeks, however, warmer breezes have begun to blow, thawing some of the icy attitudes, and the trials may get the go-ahead after all.

The first sign of a climate change in the AIDS research community came last month when a group of influential researchers came up with a newly modified plan for vaccine trials. At a closed-door meeting on 21 to 22 April, the AIDS Vaccine Working Group for the National Institute of Allergy and Infectious Diseases (NIAID) concluded NIAID should scale back its old plans, which called for a massive trial in people at high risk of becoming infected to determine whether candidate vaccines are partially effective. Instead, the group urged smaller tests that could only detect much higher levels of efficacy. This recommendation leaves the National Institutes of Health wrestling with the uncomfortable—and unprecedented—decision of whether to recruit thousands of people into trials of vaccines few researchers believe will offer high levels of protection.

To make matters more perplexing for the administrators of the trials, the recent thaw was not triggered by compelling new data. Rather, the push to move ahead is rooted in a complex mix of scientific, medical, ethical, and financial dilemmas. And even some researchers in the group that is recommending going ahead with trials are uncomfortable with its advice. "There's a lot of uneasy feeling about proceeding," says David Ho, head of the Aaron Diamond AIDS Research Center. Dani Bolognesi of Duke University, co-chair of the working group, adds that expanded trials may be the only option short of deep-sixing the leading vaccine candidates. "It's an agonizing process to sit there and know you don't have what you want to have to take the next step, and at the same time not know how to get there," he says. Bolognesi, who could not attend the April meeting for personal reasons, says he is on the fence about whether to move ahead.



RICK KOZAK

Undecided. Anthony Fauci.

Because NIAID closed the meeting of the working group —whose members include NIAID staff, academic researchers, industry representatives, and AIDS activists—details of its recommendations have been sketchy until now. But the meeting was publicly discussed during a conference last week in Washington, D.C., that focused on the social, ethical, and political aspects of conducting domestic efficacy trials of HIV preventive vaccines (see box).* NIAID Director Anthony Fauci told the meeting that the working group was "virtually unanimous" in recommending that the more limited efficacy trials should move forward with the two vaccines that have advanced the farthest in NIAID-sponsored trials (see table). These vaccines, both containing genetically engineered forms of HIV's surface protein gp120, are being developed by Biocine (a joint venture between Chiron and Ciba-Geigy) and Genentech.

Fauci stressed, however, that the working group's opinion was by no means a final decision. Its recommendation will go to NIAID's AIDS Research Advisory Committee, a congressionally mandated group that will advise Fauci on the issue in mid-June.

NIAID-SPONSORED AIDS VACCINE TRIALS

Vaccine	Manufacturer	Treated Subjects
gp120, CHO expressed	Genentech	279*
gp120, CHO expressed	Biocine	412*
p120, yeast expressed	Biocine	62
gp160, baculovirus exp.	MicroGeneSys	145
gp160, vaccinia exp.	Immuno-Ag	124
live vaccinia w/gp160	Bristol/Oncogen	36
live vaccinia gp160	Bristol/Oncogen	
+ gp120, CHO exp.	+ Biocine	56
+ p120, yeast exp.	+ Biocine	28
+ gp120, CHO exp.	+ Genentech	28
+ gp160, vaccinia exp.	+ Immuno-Ag	14
octameric V3 peptide	UBI	54
live canarypox gp160	Connaught/ Pasteur Merieux	108
oral, V3 peptide cocktail	UBI	24**
live vaccinia w/3 HIV genes	Therion	42**

* This table lumps together subjects given vaccines that contain the same antigen from different HIV isolates and combined with various adjuvants.
**Projected enrollment
CHO = Chinese hamster ovaries gp = glycoprotein

SOURCE: NIAID/EMMES CORP.

We have to do something

Since 1987, AIDS vaccines have been tested in more than 1400 uninfected people, nearly all of whom have been at low risk of becoming infected with HIV. These early NIAID-sponsored trials were intended only to establish whether the preparations are safe and able to stimulate immune responses, not whether they can protect against infection. The Biocine and Genentech vaccines, NIAID believes, seem able to trigger the strongest, longest lasting immune responses.

One of the most vexing problems for AIDS vaccine developers is that no one yet knows which of the array of immune responses will protect a person from becoming infected. Many researchers, however, have faith in antibodies that latch onto HIV and prevent it from infecting cells. The Genentech and Biocine vaccines appear particularly adept at triggering such "neutralizing" antibodies. So these vaccines were expected to move into large-scale efficacy trials. At least that was the plan until last fall, when the candidate vaccines failed a crucial laboratory test.

Until then, these vaccines looked promising because sera from vaccinees had antibodies capable of neutralizing HIV grown in cell lines. But because viruses grown in laboratory cultures can change over time, last year researchers tested whether vaccinees' sera could neutralize "primary" HIV samples—virus isolated from infected people and never put into a laboratory cell line. To the

*HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials, 9–10 May, Washington, D.C.

Behavioral Conundrums

The AIDS research community is in a quandary over whether to move forward with large-scale trials of vaccines against HIV (see main text). As that problem is thrashed out, the researchers designing such trials face two major dilemmas related to the people who will receive experimental vaccines. Should researchers aggressively attempt to reduce high-risk behavior by those people, which may be the ethical course but could also undermine vaccine trials? And, even if that dilemma can be resolved, will enough people at high risk be willing to participate?

Last week, those two questions provoked heated discussion at a 2-day meeting in Washington, D.C., that brought together AIDS researchers, medical ethicists, and representatives from groups at risk of HIV infection. Hosted by the AIDS Action Foundation, a D.C.-based group that holds policy forums, the meeting repeatedly stressed the emerging view that behavioral research and vaccine development must be combined in an overall prevention strategy.

In fact, some at the meeting argued that behavioral research must take precedence. "There is a magic bullet: This virus can be avoided," said June Osborn of the University of Michigan's School of Public Health. "And there has never been a vaccine as good as that. Vaccine work must always be seen as an adjunct to the overall effort for prevention." But working out how social science and vaccinology fit together is tricky and contentious.

The most confounding quandary involves behavioral interventions, which the meeting participants roundly agreed must be part of a vaccine efficacy trial. But the interventions could complicate the aims of the trial. To prove that an AIDS vaccine works, researchers need evidence that people who receive the preparation do not become infected (or develop disease) as frequently as people who receive a placebo. But strong behavioral interventions could cloud differences between the groups.

To some directly involved in vaccine development, that isn't a problem. Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID), says if a vaccine trial fails because behavioral intervention works, the trial is a success. But not all agreed. Don Francis, a virologist who works with AIDS vaccine developer Genentech, hit a nerve when he criticized proposals to piggyback "Cadillac" behavioral interventions onto HIV vaccine trials. "We are testing the efficacy of a vaccine," said Francis; "we are not testing the efficacy of behavioral interventions." Francis argued that behavioral interventions should match the standards in the given community. "No more and no less," he said.

Several conference participants attacked Francis' point of view as "outrageous." But as conference organizer Derek Hodel of the AIDS Action Foundation pointed out later, much of the tension stems from the fact that many communities have no behavioral interventions whatsoever. And thus it would be unethical, he and others argued, to provide no counseling at all.

Even if behavioral intervention does not undermine vaccine efficacy trials, they could be crippled by a more immediate behavioral issue. Already, researchers have had trouble enrolling young gay men in vaccine research. A small-scale NIAID-sponsored trial of the Genentech and Biocine vaccines currently under way at five sites nationwide has not even meet its target of recruiting 60 people from this risk group. In a study of 375 intravenous drug users, Liza Solomon and colleagues at Johns Hopkins University in Baltimore uncovered some factors that make people reluctant to join vaccine efficacy trials. A whopping 84.3% of those interviewed said they were "likely" to enroll in the trials and 39% said they were "very likely" to do so. But when they were asked whether they would join a trial if they knew that after receiving the vaccine they would test positive for HIV antibodies (which would be expected following a vaccination), those likely to enroll dropped to 47% and those very likely plummeted to 19%.

In the end, the meeting offered few answers, but the participants agreed that it did put important questions front and center. "The meeting accomplished everything we set out to do," said organizer Hodel. "This was a dialogue that I don't think has happened before between the various disciplines and a community of prevention service providers." And it's a dialogue that is sure to intensify as efficacy trials move closer.

–J.C.

surprise of many researchers, the sera had next to no effect on primary HIV isolates, plunging the field into depression (*Science*, 12 November 1993, p. 980).

In spite of these results, Genentech and Chiron made a strong pitch at the working group meeting to move ahead with large-scale trials. Several attendees told *Science* that researchers from the two companies pointed out that industry had invested a great deal of money under the assumption that NIAID planned to support large-scale trials. In addition, both companies reported some success in preventing infection in chimps.

A few details of the recent chimp studies emerged at the D.C. conference last week. Duke's Bolognesi mentioned new data about chimpanzees injected with these vaccines and then "challenged" with an HIV isolate, SF-2, that the researchers believe has never been passaged in a cell line. Though the experiments were begun only a few weeks ago, preliminary tests suggest the vaccines thwarted HIV infection, Bolognesi said; control chimps readily became infected. Alan Schultz, head of NIAID's AIDS vaccine branch, said there is also unpublished evidence showing that sera from some of the chimps that were apparently protected was not able to neutralize HIV grown in cell lines—suggesting that the in vitro assay whose results threw the community into despair last fall may not be a reliable predictor of what happens in vivo.

Researchers at last week's meeting were treating the new chimpanzee data cautiously. NIAID's Fauci called the new results "more fortification to move ahead," but he and others stress they are preliminary and only involve a few chimps. And in the end, the working group members were swayed not by new data but by the pressure to move ahead with a trial, according to those present at the meeting. "It was extraordinary how unanimous the feeling was that, in some manner or form, we have to do something," said Fauci, who attended the working group meeting.

Smaller, cheaper, better?

The trial the working group now visualizes would require a significant revision of NIAID's old blueprints for HIV vaccine testing. NIAID had mapped out trials to assess whether a vaccine can protect 60% to 80% of vaccinated people. A test designed to assess that level of protection for two vaccines would probably take 3 years and between 8000 and 10,000 people, half of whom would receive a placebo. NIAID estimates it would cost between $1000 and $2000 per person, per year—for a total of at least $24 million and perhaps as much as $60 million.

The idea pitched by the vaccine working group was to test the vaccines in a 3-year trial involving only about 4500 people. If a vaccine were only 60% effective, a trial on this scale would not be able to show it because the number of infected people in the vaccinated group would be too close to the number of infected people who received a placebo shot. But if either vaccine were 80% to 90% effec-

tive, the difference between the treated and untreated groups should be detectable.

The most obvious advantage of a scaled-back trial is that it would cut costs in half. And Sten Vermund, head of NIAID's AIDS vaccine trials and epidemiology branch, argues that doing a trial now would offer other benefits. For example, he says, the trials may reveal that a particular vaccine is effective against a subset of HIV strains. "What if a vaccine is 100% effective against 30% of the viruses?" he asks. "That would be extremely important." The trials might also reveal some clinically important facts, such as which immune responses correlate with protection. Finally, says Vermund, not conducting the trials carries risk, too. "What if they provide some efficacy and we never find out?"

The other side of the argument, NIAID's Fauci explained at the meeting last week, is that there is a danger—besides wasting money—to staging any large trials. It would be "catastrophic," he said, if people who enroll in HIV vaccine trials assume they are protected and engage in more high-risk behavior. And there also is a remote chance that an HIV vaccine will make the immune system *more* vulnerable to becoming infected; such "enhancement" has been seen with vaccines designed to prevent dengue.

Fauci, who will make the final decision about whether now is the time to stage efficacy trials of these vaccines, says he's not "totally convinced" by the arguments for pushing ahead, especially since he thinks there is "little chance" the preparations will be more than 30% effective. And he's particularly uneasy about the inherent illogic in receiving bad news about vaccines and then staging trials that can only detect high levels of success. "That's why I'm having considerable trouble with that concept," he says.

Fauci is not alone. Some leading investigators view the move toward large-scale trials of drugs and vaccines that are expected to have only limited effectiveness as evidence that research priorities are misplaced. As Harvard virologist Bernard Fields wrote in a "back-to-basics" manifesto in the 12 May *Nature*, "The focus on drugs and vaccines made sense a decade ago, but it is time to acknowledge that our best hunches have not paid off and are not likely to do so." In an interview with *Science*, Fields said he would not back a large, expensive efficacy trial now with these products. "I think the likely outcome is it's very unlikely to be positive."

Even if the AIDS Research Advisory Committee recommends going ahead, Fauci says he may not follow its advice. The Food and Drug Administration also must give the trials a green light, as it oversees all clinical trials. Asked which way he is leaning, Fauci replied: "To be honest with you, I don't know."

–Jon Cohen

CAREER ENDINGS...

Early Retirement Program Cuts Deep Into UC Faculties

For many U.S. universities, last year's court-ordered end of mandatory retirement for professors brought a new worry: that their aging faculty members would refuse to move over and make room for the next generation. But the nine campuses of the University of California are facing just the opposite problem, at least in the short term. In July, a record 941 UC faculty members will retire, many of them before reaching the age of 60. This unusual behavior is the result of a generous "golden handshake" that UC offered its faculty in a desperate effort to trim the payroll to offset cuts of $341 million in state funding over the past 3 years.

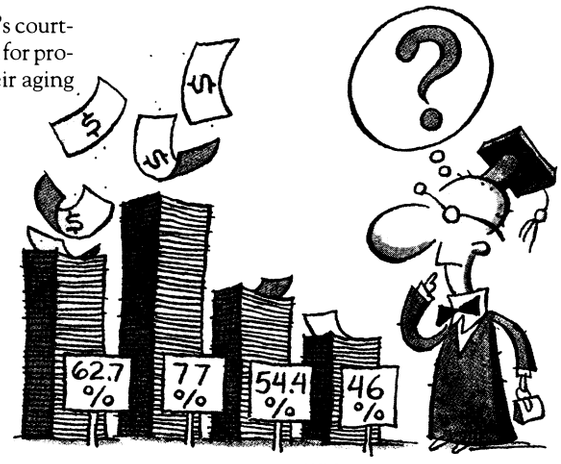


ILLUSTRATION: TERRY E. SMITH

Tempting. With VERIP-3, a professor retiring at age 57 with 27 years of service gets 77% of his or her salary.

This year's voluntary early retirement incentive program, known as VERIP-3, is the third such program in as many years. And it is cutting deep into the heartwood of the UC faculty. More than one third of UC's eligible faculty—those over 50 with 5 or more years of service—took the deal. And that includes many senior professors valued for their teaching and leadership. "People in their mid-50s are generally in the peak of their academic careers," says Marjorie Caserio, vice chancellor for academic affairs at UC San Diego. "To lose those people is to lose the core of the faculty."

That's the bad news; the good news is that most of the retirees will—in the tradition of professors emeritus—continue to serve the university in some way rather than heading for the sunbelt or the trout stream. And many of the youngest ones will carry on as if nothing had changed; the only differences will be that they will give up tenure and their salaries will be paid by UC's overflowing retirement fund rather than its operating budget. "I will teach, I will run my lab, I will do everything exactly the same way I did before," says Berkeley engineering professor Edwin Lewis, 60. "My reasons for taking VERIP were purely financial."

Indeed, many professors like Lewis simply found VERIP-3 too good to refuse. The annual pay of a retired UC professor is determined by a formula based on the professor's age at retirement and number of years with the UC system. The first two VERIPs altered that formula in a way that was attractive to faculty over 60 and netted 1045 faculty retirements. But further budget cuts forced UC to cook up VERIP-3, the sweetest deal yet. It contains an age credit making it tempting to faculty as young as 57, and allows some faculty in their mid-60s to earn nearly 100% of their pre-retirement salary. Those who receive part-time salary from research grants may earn more than before they retired.

But while individual professors benefit, some departments are hard hit. "The VERIPs, while they provide an easy system-wide [budget] fix, programmatically can be devastatingly capricious," says Dave Shelby, assistant dean of biological sciences at UC Davis. Three rounds of VERIP "essentially halved" the plant biology section at Davis, he says. "The program in which we have some of our most internationally known strength, just by virtue of the age distribution, was most dramatically affected."

Berkeley chancellor Chang-Lin Tien was so concerned that his campus, with a slightly older faculty than the others, would be decimated by VERIP-3 that he insisted on a reduced age credit for Berkeley faculty, making the deal less tempting to those younger than 58. Tien says that move retained 20 to 30 professors who might have retired.

But the campus still had some key losses, such as Nobel-laureate chemist Yuan T. Lee, who left to head the Taiwan Academy of Sciences. Lee's departure represents the worst fear of many campus administrators: that top faculty would be enticed to "cash in on retirement and leave and go to some other institution," says UCSD's Caserio. Each campus has a story or two of the professors