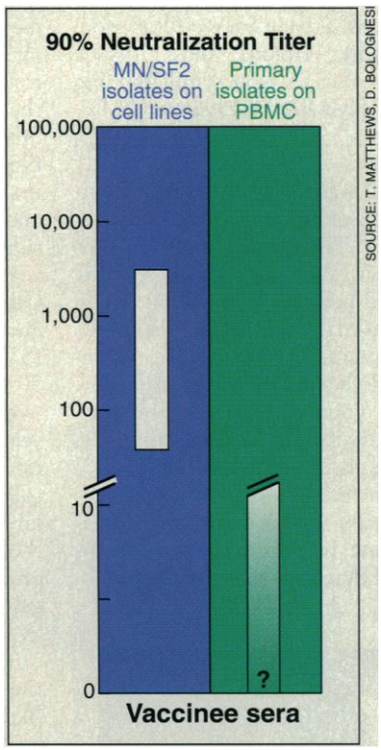
Jitters Jeopardize AIDS Vaccine Trials

Developers had planned on efficacy trials in humans by the end of this year, but discouraging results from the toughest vaccine tests yet have thrown those plans into limbo

AIDS vaccine developers, spurred by the urgency of the pandemic, have been pushing forward—gingerly—with plans for large-scale tests of vaccines. Their goal has been to try experimental preparations in people who are at high risk of becoming infected with HIV, to determine if the vaccines actually can prevent infection. Early lab tests, while they haven't provided any strong leads, haven't thrown up any serious obstacles either: These vaccines appear safe and capable of stimulating immune responses. So the developers have been joined in their drive for efficacy trials by the National Institutes of Health (NIH), which last year revealed plans to begin the tests in December 1993.

But discouraging findings reported last week at an annual AIDS vaccine conference have dealt these researchers a serious setback. In the toughest laboratory test that experimental AIDS vaccines have yet faced—which analyzes a preparation's ability to trigger a key immune response against HIV—almost all have failed. Although the results are preliminary, and some researchers raised questions about the accuracy of the assay used to judge the vaccines, the news caused dismay and confusion among the researchers. "It certainly does make me anxious about going forward with large-scale efficacy trials," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID).



Real-life letdown. While HIV vaccinee sera can neutralize lab-grown viruses *(blue)*, they are ineffective against isolates taken directly from HIV-infected patients *(green)*.

Anxiety at NIAID, the world's largest funder of vaccine research, could portend trouble for its partners in the vaccine effort. The World Health Organization (WHO), which is planning with NIAID to stage efficacy trials in four developing countries, could find itself with different criteria than its Bethesda partner for moving forward. Vaccine manufacturers, who have scaled up their operations to begin such trials, fear that NIAID foot-dragging could jeopardize their investment. "There's a lot riding on trying to resolve this issue," says Duke University's Dani Bolognesi, a prominent AIDS vaccine researcher.

The troubling results, reported last week at NIAID's 6th Annual Conference on Advances in AIDS Vaccine Development in Alexandria, Virginia, centered on a battalion of immune warriors known as neutralizing antibodies. While many antibodies can bind to HIV, only neutralizing antibodies can prevent the virus from infecting cells. To assess whether vaccines can raise neutralizing antibodies, researchers run a laboratory test that mixes blood from a vaccinated person with HIV. If neutralizing antibodies are in the blood, HIV will be locked out of healthy cells. One of the reasons that AIDS vaccine efficacy trials have had a green light until now is because just such neutralizing antibodies have been found in the blood samples taken from volunteers participating in several different HIV vaccine trials.

There is, however, a drawback to this sort of assay: It relies on HIV that was grown in continuous laboratory cell lines, and even though antibodies may protect against this lab-adapted virus they may be ineffective against a real-world strain of HIV. A more realistic test is to use HIV that has been freshly harvested from patients, because these "primary field isolates" are believed to be much closer to the type of HIV that would infect a vaccinated person.

This field isolate test was the focus of three new studies presented at the meeting. "We all had anticipated that [neutralizing antibody] titers evident against the lab strains would translate to field isolates," says Duke's Bolognesi. Unfortunately, the scientists were in for an unpleasant surprise. First, Bolognesi's collaborator, Thomas Matthews, reported that he and his co-workers analyzed blood from 40 people given six different vaccines. While most of the samples beat back lab-adapted strains of HIV, not one could neutralize a field isolate. "The obvious implication is that the immunogens used to date don't induce the breadth of response needed to neutralize primary isolates," Matthews said, adding with dark humor: "We hope we don't know what this means."

But the next presentations began to make the meaning depressingly clear. John Mascola of the Walter Reed Army Institute of Research offered another sobering description of how his group also failed to find neutralizing activity against primary isolates when they tested 34 of the blood samples the Duke group analyzed. Mascola was followed by Kathelyn Steimer from California's Chiron Corp., who had focused on people who had received a vaccine jointly being developed by Chiron and CIBA-GEIGY. After testing blood samples on lab isolates, Steimer and co-workers selected the five vaccinees that had the strongest neutralizing antibodies. They then tested these blood samples against primary isolates and, once again, could find no activity.

In workshops and hallway talk, researchers tried to digest the bad news. They debated the vagaries of the neutralizing antibody assays and noted that the differences between the lab-adapted and primary isolates may be the result of everything from laboratory artifacts to different conditions used in the different tests. They also noted that one study presented at the meeting contained hints of success: Barbara Potts from New York's United Biomedical Inc. (UBI) showed that blood from one person injected with UBI's vaccine neutralized a field isolate.

Still, few researchers could dismiss the negative data. "If it turns out that the data is real, any of the products that are presently in clinical trials are not going to be effective," predicts UBI's Wayne Koff, who formerly headed NIAID's AIDS vaccine branch and believes that even the vaccine he is working on needs many more ingredients to be effective. Duke's Matthews thinks action must be taken immediately: "Efficacy trials need to be put on hold right now until this primary isolate question is sorted out."

And that is exactly what NIAID is doing. As John Killen, acting director of NIAID's

Division of AIDS, announced at the meeting, NIAID will conduct "a formal and thorough review" next spring of the field isolate issue and decide whether to launch efficacy trials in the United States by the end of 1994.

The hesitation may seem like appropriate scientific caution, but it has infuriated at least one major vaccine developer. Jack Obijeski, head of the AIDS vaccine project at South San Francisco's Genentech, says his company now has more than 200,000 doses of HIV vaccine ready to go because it thought NIAID was committed to moving forward. "To leave that vaccine on the shelf, something that might help someone, we think that's ridiculous," says Obijeski, who doesn't believe the primary isolate question should override other positive animal and human data from experiments with Genentech's vaccine. "If that's the case, this is a monumental disincentive for Genentech....What needs to be forthcoming is for NIH not to dwaddle about, one step forward, one step back. That's what makes CEOs nervous." He cautions there are many other projects competing with the AIDS vaccine work for company resources.

Jose Esparza, head of AIDS vaccine development at WHO, says developing countries, which will have more than 90% of the world's new HIV infections by 2000, cannot wait for a complete answer to the field isolate question. "Vaccine development is very empirical," says Esparza. "For every point you try to prove there's a counterpoint....I think a trial will give you more information than 1000 lab experiments." WHO, in fact, already is helping Brazil, Uganda, Rwanda, and Thailand prepare for efficacy trials and has run into what he sees as a much more formidable obstacle: Vaccine manufacturers have little interest in tailoring vaccines specifically for these countries—which have different strains of HIV—when the market is uncertain. "There's a need here to encourage manufacturers to make strain-specific vaccines," says Esparza.

The head of the United States military's AIDS vaccine program, Donald Burke, concurs with this view. For more than a year, Burke has been trying to find a company willing to make a vaccine for the strain of virus circulating in Northern Thailand, where he is helping to lay the groundwork with Thai officials for efficacy trials. "I don't want to close the door, but none of the manufacturers has made a commitment up to this point," says Burke.

NIAID's Margaret Johnston ended the conference with the reminder that "none of us are willing to wait for the ideal vaccine" before starting efficacy trials. But if the field isolate findings hold up, expect a heated debate about the risk of jumping in versus the risk of standing still.

–Jon Cohen

SCIENTIFIC MISCONDUCT

Popovic Is Cleared on All Charges; Gallo Case in Doubt

A federal appeals board last week roundly criticized the government's 4-year effort to find scientific misconduct against AIDS researcher Mikulas Popovic—and, by implication, against his former boss, Robert Gallo of the National Institutes of Health (NIH). In clearing Popovic of any wrongdoing, the appeals board, which consists of three lawyers, also threw into question the government's case against Gallo (see box, p. 982). "One might anticipate," the appeals board wrote in a strongly worded, 79-page decision, "that from all this evidence, after all the sound and fury, there would be at least a residue of palpable wrongdoing. That is not the case."

CHRIS SANDERS

Nothing wrong. An appeals board rejected misconduct claims against Mikulas Popovic.

"How could it happen," the board asked itself, "that such a massive effort produced no substantial evidence of its premise?" Its answer: Investigators had initially concentrated on the big issues—allegations that Gallo's lab misappropriated the French LAV virus, a patent dispute, and disputes with other scientists. But the issue of misappropriation was dropped early in the investigation, and in the end, the board said, the items of alleged misconduct brought before it were "largely vestigial."

Popovic was a cell biologist in Gallo's laboratory in the early 1980s, a period marked by Gallo's attempt to identify and isolate the AIDS virus. The two scientists coauthored four groundbreaking papers in *Science* on the subject (4 May, 1984, p. 497). Since then, however, it has become clear that the virus Gallo and Popovic reported was virtually identical to a virus isolated by researchers at the Pasteur Institute, leading to allegations of misappropriation and deception. In the 4 years since those allegations were spelled out in a lengthy article by *Chicago Tribune* investigative reporter John Crewdson, two federal bodies—the NIH Office of Scientific Integrity (OSI), and its successor, the Office of Research Integrity (ORI), within the Department of Health and Human Services (HHS)—have conducted nearly continuous investigations of the two scientists. Early on, OSI determined that it lacked the evidence to conclude misappropriation rather than inadvertent contamination. OSI and later ORI issued reports on the case, the last of which

A SCORECARD ON POPOVIC

Charge	Board's Ruling
1. The sentence "The concentrated fluids [cell cultures from individual patients] were first shown to contain particle-associated RT [reverse transcriptase]" is false and misleading because Popovic did not test the individual fluids before pooling them.	1. ORI's charge assumes—without evidence—that Popovic concentrated the fluids before pooling them, despite Popovic's "reasonable" testimony to the contrary. ORI did not prove that Popovic actually drafted or approved the sentence, nor that he would have recognized that it could be misinterpreted. No misconduct.
2. Several experiments in Popovic's paper are marked "ND-not done" in a table, despite evidence that they were done.	2. ORI did not prove that "not done" can only reasonably mean "not performed." It could also mean not completed, not done properly, or not determinable, all of which would have been accurate reportings of the true results. No misconduct.
3.Popovic's "10%" entry in a table was improper considering that the only recorded data was a technician's reading of "very few cells" for the relevant slide.	3. Popovic's testimony that he had independently read the slide before inserting the 10% figure was "credible [and] corroborated" by the technician and other evidence. No misconduct.