Agencies Spar Over Vaccine Trial

The Department of Defense and the National Institutes of Health convened separate panels last week to discuss how to spend a $20 million appropriation to test a specific AIDS vaccine

When one government agency tries to tell another how to spend its money, sparks are sure to fly. And that's just what happened last week when the National Institutes of Health (NIH) and the Department of Defense (DOD) convened separate panels to decide what to do with $20 million Congress slipped into this year's defense budget for a controversial test of a therapeutic AIDS vaccine made by the Connecticut biotech firm MicroGeneSys. Congress had given the money to DOD, after all, but NIH Director Bernadine Healy was taking advantage of an opening in the legislation to offer her institution's unsolicited advice on how the test should be conducted. For much of the week, Washington's AIDS research community was awash with rumors that an angry DOD would thumb its nose at Healy's offering. By the week's end, however, tempers had cooled and it looked as though ultimately DOD and NIH would be able to agree, generally, that the $20 million ought to be spent testing several therapeutic vaccines, not just the one made by MicroGeneSys.

But that doesn't mean everyone is happy with the outcome. In fact, nobody is completely content with the $20 million gift. Many AIDS researchers feel that at the moment there's little justification for holding a large-scale efficacy trial of any therapeutic vaccines (which are designed to treat, rather than prevent, HIV infection). "If this legislation had not come along," top NIH AIDS researcher Anthony Fauci told the panel, "this would not have been a high scientific priority to us." In addition, DOD fears that the appropriation could skew its existing research program, which favors preventive vaccines. And then there's the possibility that, because of lack of funds, the MicroGeneSys "gp160" vaccine might wind up being the only one tested—which is what triggered researchers' outrage in the first place.

Congress made the $20 million appropriation last fall at the behest of lobbyists representing MicroGeneSys (*Science*, 23 October 1992, p. 536). The legislation contained a clause offering the NIH director and the Food and Drug Administration (FDA) commissioner a chance to object to the study. Healy seized this as an opportunity to assemble a blue-ribbon panel of FDA officials and leading AIDS researchers and activists to evaluate how this "highly peculiar" appropriation should be spent.

During two meetings in November, the panel concluded that although several therapeutic HIV vaccines appeared safe and broadened the immune responses of people already infected with the virus, there was scant evidence that any of these products might actually delay the onset of disease. Because of the urgency of the AIDS epidemic, however, the panel voted that DOD's money should not be turned away but used to fund a trial of several therapeutic vaccines. A subcommittee subsequently worked out the trial details, which were scheduled to be presented at a meeting on 28 January.

RICK KOZAK

Sorry, I can't tell you. Colonel Donald Burke told the NIH panel what his committee discussed, but not what it voted to do.

Though representatives from the Army (which directs AIDS research for the entire military) attended both meetings of the Healy panel, they kept tight lips about whether they would abide by its recommendations. So there was much curiosity when the Army hastily announced that its own panel would meet on 24 and 25 January. The rumor mill hummed: Was a preemptive strike afoot?

Living up to expectations, the Army meeting, held at the Walter Reed Army Institute of Research in Washington, opened with a shot across the bows of NIH and FDA. "There are those who would say this meeting is unnecessary because [the issue] has already been decided by NIH and FDA," Army Maj. Gen. Richard Travis told the 20 civilian and military scientists on the panel. "I would say it's been decided in their minds, but it has not been decided by this group."

It also quickly became clear that regardless of the scientific merits of the trial, the military was uneasy about the role Congress had thrust upon it. As panel cochair and chief Army AIDS researcher Colonel Donald Burke explained, the military's $44 million AIDS research program emphasizes prevention rather than treatment of HIV infection. "A $20 million appropriation is a big chunk of money for us," noted Burke, stressing that a large-scale vaccine therapy trial could take the military off its course of research into preventive vaccines.

As for the details of how the trial should be conducted, the Army was particularly concerned that the Healy panel had not considered which vaccines were ready to be tested for efficacy. Specifically, the military panel wanted to know which companies had enough product available, and what data they had accumulated on safety and the ability to stimulate immune responses.

After the panel heard presentations from several researchers testing MicroGeneSys' gp160 and from four other vaccine manufacturers, it closed the meeting for a vote on how to spend the $20 million. Three days later, at the Healy panel meeting, Burke recapped the DOD deliberations—but withheld the final vote. This drew sharp barbs from Healy, who denounced the Army's "secretiveness." In particular, Healy was concerned that DOD might not stage a multiproduct trial, as her panel had stipulated.

In fact, the Army has refused to divulge what its panel decided pending a review by the secretary of defense. *Science* has since learned, however, that the DOD panelists voted 10 to 9 against conducting a large-scale test of the MicroGeneSys vaccine alone. But attendees who insisted on anonymity said that because the vote was close and because the military didn't want to offend Congress by flat-out rejecting its proposed trial, the panelists reformulated the question. The second version was a trial of the MicroGeneSys vaccine along with any other vaccines that met minimum requirements—and this time the vote was 15 to 4 in favor.

But the panel stipulated that "full imple-

mentation of all aspects of the trial will depend on adequate resources." And just how costly such a multiproduct trial might be became clear at the Healy panel meeting. The subcommittee that had been asked to design such a protocol came up with a "large, simple trial" that it estimated would cost from $34 million to $53 million. It would involve 18,000 patients divided into three groups based on their number of CD4 white blood cells. Substudies would attempt to clarify how well changes in "surrogate markers" (such as a person's CD4 count and amount of HIV) predict clinical outcomes—a critical question to AIDS research.

Without knowing what the DOD panel had decided, Healy acknowledged that such a trial may be too expensive for DOD to fund. "If the Department of Defense says we only have $20 million, we have to give them some options," she told her panel. This led the panel to slash the trial's size in half, restricting entry to people who have a mid-range of CD4 cells (200-500). The substudies also were dropped, unless more funds surface. On the basis of that reconfiguration, Healy's panel unanimously voted to approve the multivaccine trial, bringing the NIH panel into general agreement with DOD.

In spite of the unanimous vote, however, some of the panelists expressed deep scientific reservations about the entire enterprise. Said David Ho of New York's Aaron Diamond AIDS Research Center: "I don't think we're going to be happy because we've been given a task of coming up with a proposal for a project that NIH has decided has a low priority." And, despite the overall emphasis on a multivaccine trial, the Army's Burke conceded that there's "a possibility" that when DOD looks at the real costs, there may only be enough money to test one preparation: the one from MicroGeneSys. That's a dim prospect to the AIDS research community, but it might be the net effect of all the political and economic constraints surrounding the controversial appropriation. Whether that is, in fact, the outcome will be known before 6 April, which is the deadline by which DOD must tell Congress what it plans to do.

–Jon Cohen

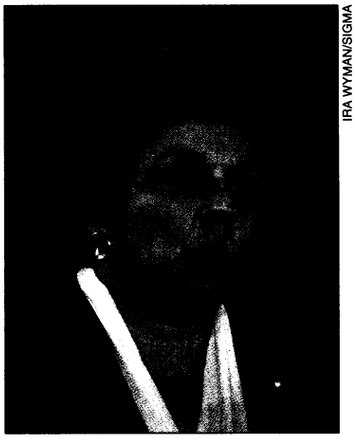
AIDS RESEARCH

Reorganization Plan Draws Fire at NIH

At last summer's international AIDS conference in Amsterdam, a fledgling activist outfit called the Treatment Action Group (TAG) issued a two-volume critique of AIDS research at the National Institutes of Health (NIH). The heavyweight report (nearly 200 pages) sank without a trace at the conference. But over the past 6 months, it's resurfaced to receive serious attention in another venue: the United States Senate. So seriously has it been considered there that TAG's recommendations form the basis for legislation that would dramatically overhaul how NIH coordinates and funds AIDS research by drastically strengthening the hand of its Office of AIDS Research (OAR). The legislation has stirred concern at NIH—where institute directors see their power being eroded—and it is making waves for new Secretary of Health and Human Services (HHS) Donna Shalala before she's had time to get her sea legs.

Proposed by Senator Edward Kennedy (D–MA), who chairs the Senate's Committee on Labor and Human Resources, the controversial AIDS reform is tucked into the NIH reauthorization bill. A version of the bill, without the AIDS provisions, was vetoed by former President George Bush last year because it would have lifted the ban on therapeutic research involving human fetal tissue. The bill became a top priority for the Senate to push through under President Bill Clinton, and, indeed, it was the first piece of legislation introduced in the Senate this year.

The AIDS portion of the revamped bill gives OAR control over NIH's $1.1 billion AIDS budget. OAR currently coordinates AIDS research at all 21 institutes under the direction of Anthony Fauci, whose main job is heading the National Institute of Allergy and Infectious Diseases (NIAID). While OAR can tell an institute that a certain project is redundant or unnecessary, the office does not touch AIDS money, which travels directly from Congress to each institute. In addition to beefing up OAR's funding role, the bill would increase responsibilities for the agency's director, require a strategic plan to guide budget decisions, and establish a discretionary fund OAR can use to bankroll "emergency" AIDS research and fill gaps in existing programs. And those are just the kinds of things the activists had called for. "The TAG report is the genesis of this legislation," says a staffer for Senator Nancy Kassebaum (R–KS), the ranking minority member of the labor committee.



IRA WYMAN/SIGMA

No objection. HHS Secretary Donna Shalala supports the bill.

When contacted by *Science*, Fauci and several other institute directors said they had no comment on the legislation. Yet on 22 January, the day after Kennedy introduced the bill, the NIH institute directors held an emergency meeting with NIH Director Bernadine Healy, and insiders say some voiced heated objections. The directors agreed to detail their complaints in a formal memo to Healy, which she forwarded to Shalala that Friday afternoon.

Neither NIH nor HHS will publicly release the memo, and, in a highly unusual move, Shalala's office even declined to give it to a Senate staff member. But *Science* has learned that a key concern was the increased budgetary authority delegated to OAR. The institute directors said they would not object to OAR being given authority in the planning process to hash out with each institute which projects deserved what funding. But they balked at the notion of having all AIDS funding pass through OAR. Their chief argument was that—by adding another layer in the process whereby funds are delivered—the measure would create delays in the awarding of contracts and grants.

The next day, 23 January, National Cancer Institute director Samuel Broder worked with HHS and Senate staff to modify the legislation. In the draft of the bill that Kennedy's committee unanimously marked up on 26 January, OAR will have no say over the funds that institutes already have committed to AIDS research projects. This "commitment base," which funds 3- to 5-year projects, accounts for about 80% of the AIDS budget. OAR will, however, control funding of all new and competing programs; moreover, each year about 20% of the committed money frees up, meaning that after 5 years, OAR will control the entire NIH AIDS budget—a prospect that many researchers find disturbing. "It adds another layer of bureaucracy," says AIDS researcher Dani Bolognesi of Duke University. "I think it's going to be a disaster."

Kennedy has already received positive letters from more than a dozen scientists, however, including Mathilde Krim of the American Foundation for AIDS Research, former Food and Drug Administration official Ellen Cooper, and Arthur Ammann of the Pediatric AIDS Foundation. AIDS activist Gregg Gonsalves, who co-authored the TAG report with Mark Harrington, says OAR needs the budgetary authority to compel reforms. "We're quite concerned that OAR will remain a paper tiger without teeth to enforce its plans," says Gonsalves. TAG member Derek Hodel of the AIDS Action Council, a Washington,