AIDS Vaccine Trials: Bumpy Road Ahead

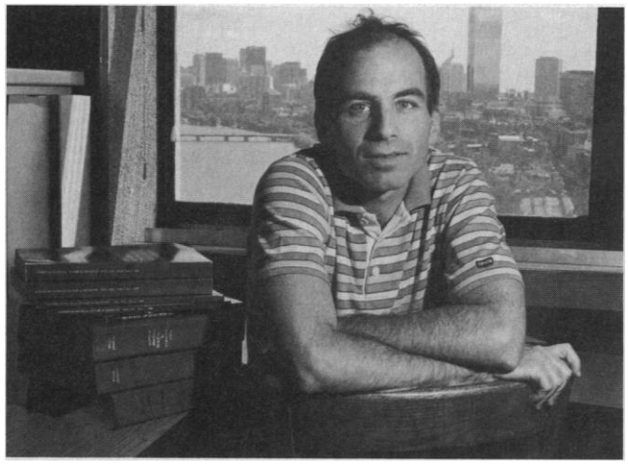
As real life tests of an AIDS vaccine come closer, thorny questions of where they should be held and who will get the benefits are facing the international community

CURRENTLY HANGING ON THE WALLS OF the marble-columned edifice that houses the National Academy of Sciences (NAS) in Washington, D.C., is an art show titled "Contentious Terrain." The paintings of twisted American landscapes in their asymmetrical frames provided a fitting backdrop for a 13 February NAS meeting on international trials of AIDS vaccines that itself covered some highly contentious ground.

The problems on the meeting's agenda—how to guarantee developing countries access to potential AIDS vaccines, where to hold key upcoming tests of vaccine efficacy, and which of the big institutional players should coordinate such an effort—are touchy. So touchy that the meeting's sponsor, the International Forum for AIDS Research (IFAR), a branch of the Institute of Medicine, barred the press from most of the day-long, invitation-only proceedings. But through a series of interviews, *Science* has distilled some of the pertinent discussion at the meeting. William Mayer, director of IFAR, says that his group is trying "to make people face up to the issues that really need to be faced up to."

Perhaps the most sensitive of those issues is the one people in the field call "distributive justice." In more straightforward terms, the issue boils down to who takes the risks and who gets the benefits. Deriving statistically significant data that prove a vaccine's efficacy is difficult: Researchers need a large population varied in gender and age that is at high risk for infection. The length of the trial is dependent on all of these variables. That's why researchers, who want to conduct a sound trial expeditiously, are looking toward developing countries, where HIV infection is spreading rapidly through the general population. "Obviously one of the reasons for testing a vaccine in developing countries is there is more chance of its being challenged [by HIV infection]," says Mervyn Silverman, president of the American Foundation for AIDS Research and an attendee at the IFAR meeting. Silverman is quick to add, however, that trial participants must still be educated about infection prevention.

Suppose the international agencies involved choose Zaire as one of the trial countries. If an HIV vaccine proves itself effective there, the first quandary is fairness: How will the people of Zaire be able to afford such a vaccine at free market prices? But if the people of Zaire receive the AIDS vaccine free or at reduced price, due to financial support from the developed world, shouldn't other Third World countries get the same treatment? And if they should, how could such generosity be put into practice: Who's going to foot the bill? Who's going to distribute the vaccine?



Access route. *Third World countries think access is the key issue in AIDS vaccine development, says Larry Gostin.*

Wrestling with such questions at the IFAR meeting were 50 representatives of some 20 organizations, including influential officials and researchers from the World Health Organization (WHO), the National Institutes of Health, the Centers for Disease Control (CDC), the U.S. Public Health Service, the U.S. State Department, the U.S. Army, the Pan American Health Organization, academia, philanthropic foundations, think tanks, and industry. By all accounts the tone of the meeting was not acrimonious, but it was clear that the terrain to be traversed in testing an AIDS vaccine is full of potential pitfalls.

The reason IFAR felt it was time to lead a forced march across this landscape is that several recent developments have brought efficacy trials of an AIDS vaccine—the final stage of vaccine testing—much closer to practical reality. During the last 12 months, the number of AIDS vaccines to receive the Food and Drug Administration's permission to enter clinical trials jumped from two to six. And after initial failures with a variety of candidate vaccines, several experimental preparations have now demonstrated limited efficacy in monkeys and chimpanzees. Finally, researchers have already initiated small Phase I and Phase II trials of nine experimental AIDS vaccines in the United States and Europe. These are not to be confused with the critical phase of vaccine testing about which meeting attendees wrangled.

Phases I and II test a vaccine's safety and its capacity to evoke an immune response. These trials are less controversial because they are not set up to measure the vaccine's effectiveness against an actual viral challenge. But now that they're going well—and the animal data have become more encouraging—WHO officials have, since January, been scouting sites for the Phase III efficacy trials.

No one at the IFAR meeting was willing to predict on the record when a Phase III trial might begin in a developing country, but several insiders who did not wish to be named said the time frame was 2 to 5 years. And since getting experimental sites set up is bound to be tricky—both organizationally and politically—the international groups responsible are getting started now. According to Michael Merson, head of WHO's Global Program on AIDS, this is "the most urgent issue right now."

To that end, WHO representatives have been approaching various ministries of health to learn which countries want to participate in AIDS vaccine trials. WHO plans to conduct site visits in interested countries and, through a newly formed steering committee that will meet for the first time in April, eventually select six or seven sites. The steering committee also will decide which vaccines to test. "We're not

discouraging other vaccine trials," WHO's David Heymann assured attendees of the IFAR meeting. "We're only trying to spend money wisely."

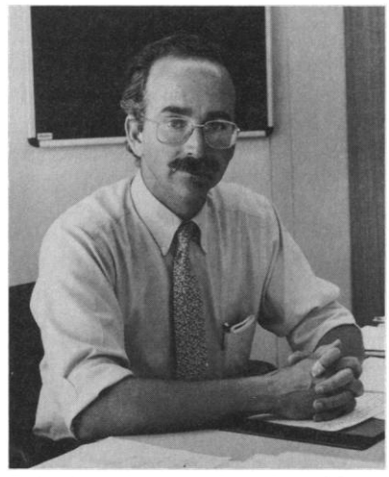
But choosing a group of sites isn't the only potential problem in the Phase III AIDS international vaccine trials. Another difficulty that will have to be negotiated is the plethora of big organizations with a vested interest in vaccine work. The CDC has AIDS epidemiologists, clinicians, and lab workers on the ground in Zaire, Thailand, and the Ivory Coast. Could there be turf battles over which group should lead the research? "I don't think anybody would work independently," says Helene Gayle, chief of the CDC's international AIDS branch. "It is not a competitive process." Indeed, CDC already collaborates with WHO in Zaire, and Gayle adds that nearly every vaccine developed over the past 20 years has involved the CDC and an international trial.

Yet CDC and WHO aren't the only institutional players in the international vaccine effort. NIH funds research at various sites around the world and brings scientists from developing countries stateside for training. And, unlike the CDC, NIH is actually developing AIDS vaccines rather than simply organizing trials. What's more, the National Institute of Allergy and Infectious Diseases now conducts clinical trials of commercially made AIDS vaccines. Another interested party is the U.S. Army, which has deep pockets and a long history of testing vaccines in developing countries. The Army currently is running clinical trials in the United States with commercial AIDS vaccines and has a program to develop its own.

Although this overlap suggests the need for some direction from above, several attendees at the IFAR meeting said they were uncomfortable with the idea of one organization playing gatekeeper. Still, Jonathan Mann, former head of WHO's Global Program on AIDS, and now director of the International AIDS Center at the Harvard School of Public Health, sees WHO providing the "international umbrella." Mann says a government's politics, both internal and external, can easily derail a clinical trial. Because WHO is not a branch of any government, he says it is well poised to negotiate with local ministries of health, evaluate sites, weather shifts in political regimes, and guarantee ethical excellence.

But will it be able to handle the price problem and other ethical hurdles? No matter which institution winds up leading the vaccine trials and no matter which countries are chosen as test sites, the final program will no doubt involve a product developed in a rich country being tested in a poor one. And that problem is at the heart of the many efforts to formulate ethical guidelines for AIDS vaccine testing that is now under way. WHO is developing an ethical checklist for AIDS vaccine trials. WHO's Geneva neighbor, the Council for International Organizations of Medical Sciences (CIOMS), is establishing new ethical guidelines for international human epidemiological research. And the U.S. Public Health Service (PHS), parent to both the NIH and CDC, also has a new policy for international HIV research in the works.

Even with all these hurry-up efforts, the ethics are falling far behind the science in AIDS vaccine trials, says attorney Larry Gostin, head of the Boston–based American Society of Law & Medicine and a professor at the Harvard School of Public Health. "I'm terribly afraid that when there is a safe and efficacious vaccine it will be too expensive for the Third World," says Gostin, who works for CIOMS, WHO, and PHS. "Would that happen, it would be a tragedy of world proportions.... From an ethical standpoint, to place a research burden on Third World countries and not make plans [to make the final product accessible] is unconscionable."



Patent exchange. *Jonathan Mann wants vaccine developers to donate patents to international organizations.*

Gostin is particularly concerned that none of the new ethical guidelines or policies mandates distributive justice. "I have had the opportunity to interview numerous people in this area," says Gostin. "Virtually every Third World country thinks distributive justice is the central issue. Those in Western countries don't have the same sense of urgency. They understand that it's a problem, but they aren't planning its solution."

One stumbling block for the U.S. government, notes Gostin, is that it doesn't want to interfere with the private sector. "This is a very public thing and the ground rules need to be different for negotiating pricing," says Gostin. "I'm trying to avoid the problem with AZT, where there was a lot of governmental help testing and getting the drug to market. Once it got there, there was no interference with profit motive."

And Mann, who left WHO last March, says, "The issue of vaccine accessibility was one of the reasons I handed in my resignation." Mann doesn't believe WHO was giving the matter serious enough consideration. Merson, who replaced Mann, says WHO hopes to hold a meeting later this year with the companies that are developing AIDS vaccines to discuss access and distribution.

Almost everyone agrees that access to an AIDS vaccine for the world's poor is an important goal. But even if that goal receives a sympathetic audience, ultimately somebody has to foot the bill for any largesse that might be required—and that's not quite as easy a subject to agree on. Some favor a two-tiered pricing scheme in which developed countries pay more for a vaccine and thereby subsidize others. And since last June, Mann has been floating a novel idea he thinks would work better than a tiered setup: patent exchange, in which the developers of an AIDS vaccine donate the patent to an international organization. In return, the developers receive the right to extend the patent on an existing drug, a right they can use for their product or trade as a commodity.

Ronald St. John, deputy director of PHS's National AIDS Program Office, supports a less ingenious but perhaps even more radical solution: take AIDS vaccines out of the private sector altogether. St. John says he would like to see the 14 developed countries sign a treaty to fund and distribute an AIDS vaccine. "Nobody is going to get very far as long as a vaccine is treated as a commodity," says St. John. "As long as you treat it that way, you're in an economic free market box."

Ideas like this will get far more discussion than they received at the pioneering meeting at the NAS—and they will create an enormous number of headaches—but everyone is banking on one thing: that the scientific obstacles studding the road to an efficacious AIDS vaccine, obstacles that still humble researchers, are surmountable. International trials may even add to the scientific complications—for example, would a vaccine developed using HIV strains prevalent in the United States and Europe be successful in a Third World country where different strains prevail? But international trials are coming inexorably closer, and the IFAR meeting, says director Mayer, "advanced the cause of doing the trials right."

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