AIDS Vaccines: The Problems of Human Testing

A Pandora's box of ethical, legal and logistical problems, in addition to scientific concerns, awaits the first human trials of candidate AIDS vaccines.

By STEFI WEISBURD

Second in a two-part series

When researchers met at the National Institutes of Health (NIH) in March to discuss the progress and problems of developing an AIDS vaccine, they had a walking experiment in their midst. One of the workshop participants, the University of Paris researcher Daniel Zagury, had been the first human to inject himself with a candidate AIDS vaccine, along with several other volunteers in Zaire (SN: 3/18/87, p. 198).

It's unlikely that Zagury and his fellow volunteers will remain the world's only human test subjects of AIDS vaccines for very long. In the United States, for example, the Food and Drug Administration expects to approve the initial phase of human trials for some test vaccines this year (SN: 4/4/87, p.213). If all goes smoothly, thousands of people may eventually be involved in AIDS vaccine testing.

But while vaccine research is moving into the human arena, there are still serious scientific challenges in the way of developing a safe and effective vaccine against the human immunodeficiency virus (HIV), which causes the disease (SN: 5/9/87, p.297). And even if these challenges are met, it could be at least eight to 20 years before a vaccine is available to the public, according to Assistant Secretary for Health Robert E. Windom, who addressed the NIH workshop in Bethesda, Md.

Until then – and for that matter, long after – scientists and society will be faced with some equally serious ethical, legal and logistical questions, including:

- Who should be the first U.S. test subjects? How many people will be required and how long will the studies take?
- Should vaccine developers have to show that an inoculated animal is protected against AIDS infection before the vaccine is tried in humans?
- Will false hopes be raised by the prospect of a vaccine, leading people to be less careful about avoiding exposure to the AIDS virus?
- How will scientists balance their responsibility to teach test subjects how to avoid becoming infected by the virus with their desire to do rigorous efficacy tests, which, on scientific grounds, would require that subjects be exposed to the virus?

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- If and when an AIDS vaccine is developed, will U.S. manufacturers be able to wrestle with the long-standing liability problem of distributing vaccines to a litigious public?

"We must develop ethical and legal answers that are as sophisticated as the science that develops the vaccine itself," stressed NIH's Charles McCarthy at the recent workshop, which was convened in part to anticipate and address these concerns.

Participants at the workshop did not come to a consensus on the detailed logistical design of the three phases of human trials that are required in the United States. But the general feeling was that each Phase I trial – in which a candidate vaccine's safety and ability to invoke an immune response is tested – would involve fewer than 20 volunteers who are not homosexual men, intravenous drug users or other people thought to be at high risk of encountering the virus. In Phase II, anywhere from 40 to 200 people from both high- and low-risk groups might be studied to determine dosage and timing between doses. And in the final stage, Phase III, the efficacy of a vaccine would be evaluated.

AIDS "brings us to a new era of testing vaccine efficacy," David T. Karzon of Vanderbilt University in Nashville told the workshop. He and others predict that clinical trials of AIDS vaccines will be very costly and lengthy. They also anticipate that Phase III studies would need to involve an extraordinarily large number of subjects in order to yield meaningful statistics, because it can take more than five years for a person infected with HIV to develop clinical signs of the disease.

In contrast, "essentially all the vaccines that have been developed before have dealt with diseases that were acute and had some way of expressing themselves as a disease in a reasonably short period of time," says June Osborn, dean of the School of Public Health at the

University of Michigan in Ann Arbor.

HIV's long incubation period is one reason why some researchers think it's essential to develop a vaccine that blocks infection by the virus, rather than arresting the virus at a later stage. But because HIV can enter the body in a latent form hidden inside cells, some researchers question whether this will be possible. If it is not, scientists may try to develop a vaccine that prevents postinfection disease, or at the very least, blocks the transmission of the disease from one person to another. But no one yet knows if even these are realistic goals.

Almost all researchers think it is crucial that vaccine trials be carefully controlled with the use of placebos. Many also believe the trials for some types of AIDS vaccines may have to be controlled with the use of other vaccines against other diseases. This is important because scientists will need to know which immune responses are due to an AIDS vaccine, which are part of the immune system's natural variability and which might result from vaccination in general.

Osborn and others also argue that there is a need for long-term follow-up studies to ensure that there are no unexpected adverse side effects. Many workshop participants noted, however, that it would probably be impossible to continue long-term studies with placebos: If a vaccine were shown to be at all beneficial, every study participant would want to ensure that he or she received a vaccine and not a placebo, and scientists could not ethically withhold a vaccine from anyone in the study.

McCarthy warns that the demand for a vaccine in that case would be many times greater than that for azidothymidine (AZT), a drug that appears to prolong the lives of some AIDS victims. When some benefit had been shown for AZT, placebo-controlled trials of the drug were halted just seven months after they had begun (SN: 9/27/86, p.196).

AIDS vaccine researchers are concerned about many other issues, including how and when testing in children might be conducted, how vaccines developed in the United States would be tested or distributed in other countries and the need to give trial participants a certificate assuring insurance companies and employers that their HIV antibodies are due to a vaccine and not to exposure to the virus. They also worry about how they could anticipate what kinds of tests should be performed on trial participants before they fully understand the workings of the AIDS virus and the immune responses necessary to defeat HIV. And they debate what should be expected from animal studies and at what point in human studies the results from animal work should be required (see box).

One ethical dilemma voiced by many at the workshop is the problem of wanting to balance the welfare of the test volunteers against the need for scientifically sound trials. "What will make this the hardest vaccine trial in history," says Osborn, ". . . is that as soon as you've established an investigator-investigatee relationship, you're honor bound to use that relationship to maximize the safety of the participant, and that means teaching them how not to come into any contact with the virus." But if trial participants avoid exposure to HIV, the vaccine will not be given a good run for the money.

This is a much greater problem for AIDS trials than for the past development of vaccines against other pathogens, for two reasons. First, AIDS is much deadlier than most other viral diseases, and exposure to HIV carries greater risk. Second, most pathogens for which vaccines exist are transmitted through casual contact, so preventive education played a lesser role.

"This is a nightmare for vaccine trials," Osborn says, "because you have a strong ethical obligation to take the very best test subjects and turn them into the very worst."

Assume, however, that an AIDS vaccine is developed, its trials go well and there is still a market for it when it is finally developed. Would manufacturers be able to obtain liability insurance so that they could produce and distribute an AIDS vaccine without great financial risk?

Because of the unusually complicated nature of the AIDS virus, the urgency to develop a vaccine against it and the potential for a vaccine's unforeseen side effects, it's likely that the development of an AIDS vaccine will bring to a head long-standing legal problems associated with distributing vaccines in this country – especially since plaintiffs injured by vaccines have been increasingly successful in suing companies for damages. As Richard M. Cooper, an attorney at Williams & Connolly in Washington, D.C., noted at the NIH workshop, "there is no vaccine that confers legal immunity."

A poignant example is the swine flu vaccine. In 1976, an increasing litigious judicial atmosphere, compounded by a trend in the courts holding manufacturers responsible for warning patients of all foreseeable risks, caused the insurance industry to refuse coverage of the swine flu vaccine. Without insurance, the manufacturers would not release their vaccine. Following an outbreak of swine flu, Congress then stepped in with $135 million to purchase the vaccine, and after considerable haggling with insurers, the U.S. government ended up assuming all liability. According to NIH's McCarthy, $4 billion in liability claims have been brought against the government for injuries and deaths caused by the vaccine.

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nization programs," Cooper told the audience, "it may nevertheless be a relevant precedent for an AIDS vaccine."

Osborn warns that AIDS, with its long incubation period, "will make the swine flu look like a picnic." Scientists don't know the cause of most neurological diseases, she says, so if anything goes wrong neurologically during that time in people who have been vaccinated, it will be blamed on the vaccine. "I'm not speculating," she says. "Manufacturers will be sued to the teeth by the time they've had two years' worth of trials.... Whether [neurological diseases] are causally re-

The challenge of testing chimps

By far, the most heated debate at the recent AIDS vaccine workshop at the National Institutes of Health revolved around the use of chimpanzees in testing the viability of candidate AIDS vaccines. Until recently, chimps have been the only known animals that can be infected with the AIDS virus—in other words, when the virus is injected into a chimp it will replicate in the chimp's body. However, the chimpanzee is not a perfect model for the human immune system, because while some chimps injected with the AIDS virus have had temporarily enlarged lymph nodes, the animals do not appear to come down with the disease. Another problem is that research chimps are in short supply.

These two problems are forcing scientists to consider how much they can expect to learn from chimp studies and whether there are certain tests that a candidate vaccine should be required to pass in chimps before being tried on humans. Most researchers who voiced an opinion at the NIH meeting felt that chimpanzees could be used at the very least to test the safety of vaccines. According to Gerald Quinnan of the FDA, they might also be used to test the "quality of the immune response" — whether, for example, a vaccine induces the production of antibodies to the virus.

But the big question at the meeting was whether vaccine developers should have to show that inoculated chimps are protected against infection when the animals are "challenged" with injected doses of the virus. Two groups at the meeting reported that they had tried such challenge studies but had failed to demonstrate protection (although in one study, the levels of AIDS antibodies rose more rapidly in inoculated animals than in control chimps).

However, Peter J. Fischinger at the National Cancer Institute notes that these studies may not have been fair tests, because the chimps were given very high doses of the AIDS virus, much higher than what is probably necessary to infect the animals. He says no one knows exactly what the natural exposure level is for chimps (or for humans), but he expects that more realistic challenges will be conducted soon.

"If you get protection from primary infection in chimpanzees — whose immune system is very similar to that in man—then chances are that you may be able to replicate that in man as well," he says.

But what should researchers do if chimps cannot be protected from infection after being injected with a candidate vaccine? And at what point in human studies should certain results from chimp studies be required?

"My feeling from the conference is that we'd be willing to go through the very early stages of [human] testing," says Harold Jaffe of the Centers for Disease Control (CDC) in Atlanta. "But there was a lot of uneasiness about going into large-scale trials in people who are really at high risk for infection [before protection is shown in chimps]. The danger is that they may be falsely reassured in getting a vaccine and it won't work, that they'd fail to modify their behavior and get infected. That would be a disaster."

According to Robert Couch at the Influenza Research Center in Houston, who chaired one of three working groups at the conference, many people in his group also wanted to see some sort of protection demonstrated in chimps before scientists proceeded with large-scale field evaluations. But there was also a sentiment, he says, that human investigations should not be precluded on the basis of chimp studies alone.

This was somewhat echoed by Quinnan, who says he has "a great problem with some of the opinions expressed here because I don't know if the chimpanzee challenge is a relevant model [for humans]." Without that information, he says, trying "to establish requirements for the outcome of chimp testing — [in order] to determine whether we go ahead with any [human] phase of the study—at this point seems to me to be very difficult."

Some of the pressure of deciding how to use the few available chimps may be relieved by the recent work of the CDC's Patricia Fultz. She has found that some rhesus macaque monkeys can be persistently infected with one kind of AIDS virus, called LAV-2 or HIV-2 (SN: 5/16/87, p.312).

Fultz says she does not yet know if the monkeys injected with HIV-2 will develop the disease. But even if they don't, they could still aid research because they are easier and less expensive to handle than chimps and there are about 100 times more of them. And while the chimp's immune system is somewhat closer to the human immune system, Fultz feels that macaques, like chimps, provide a valid model for assessing whether vaccines can protect against infection. With macaques, she says, "we will be able to test many more prototype vaccines than we would have been able to using the chimps."

In addition to using animals to test candidate vaccines directly, scientists can use animals to learn more about the pathology of the human AIDS virus by studying the pathology of related viruses that naturally infect animals and sometimes make them ill. For example, simian T-lymphotropic viruses, similar to human AIDS viruses, have been found in captive macaques suffering from an immune deficiency and in healthy wild African green monkeys.

However much animals can help in the development of an AIDS vaccine, some researchers urge that animals be used to their fullest before human trials get very far, and they hope that scientists resist public pressures to race ahead with human testing. "[We] ought to do extensive animal testing because there have been immunological surprises in the past that one would like to avoid," says Maurice Hilleman of Merck Sharp & Dohme Research Laboratories in West Point, Pa.

He cites as an example the case of the measles vaccines, in which many people who had received one of two types of vaccines in the 1960s became very ill later when they either were naturally exposed to measles or were given a live-virus vaccine; the two vaccines, says Hilleman, induced immune responses that were incomplete or were out of context with the natural play of events and produced immunological damage rather than protection. Another example is the vaccine developed for the feline leukemia retrovirus, which is closely related to the the human AIDS retrovirus. Hilleman says scientists found that vaccines could act to suppress the cat's immune system and actually enhance the effects of the disease.

Adds Merck's Robert J. Gerety, "We have to move slowly. Vaccines go into healthy people. We don't want to have difficulties in humans that set us back because there are some concerns about Phase I studies that were done without all the data in hand on chimps [or other animals]. This is not an area that can be compromised." — *S. Weisburd*

lated or not, it won't matter because when the smoke has cleared, there'll be so much wreckage, it will be a trivial question."

What Osborn, who has been a vaccine adviser to the Food and Drug Administration for the last 15 years, and others would like to see established is a national vaccine liability program. "We're the only country in the industrialized world that does not have a national solution to the vaccine liability problem," she says. This is the reason why each vaccine now in use in the United States is made by only one manufacturer, she adds.

"Even with the AIDS monster staring straight at them," Osborn says, the Reagan administration has opposed national vaccine liability legislation. So far, the only vaccine legislation approved by Congress is the National Childhood Vaccine Injury Act, which passed last November as part of the Omnibus Health Legislation. This act creates a no-fault compensation scheme for children who suffer injuries from mandatory childhood vaccines, as an alternative to conventional litigation. Cooper says that Congress must enact a special tax on vaccines for this scheme to become operational. The administration opposes both the program and the tax.

According to Mona Sarfaty, associate health staff director for Sen. Edward M. Kennedy (D-Mass.), the potential liability problems of an AIDS vaccine were discussed at a recent hearing on AIDS and senate staff members are now "exploring" the possibility of proposing liability legislation for AIDS.

Perhaps the most progressive government action taken so far to reduce the liability risks involved in developing and distributing an AIDS vaccine is legislation enacted in California last year. According to Cooper, this legislation protects the manufacturer of an FDA-approved AIDS vaccine from some, but not all, kinds of liability and establishes a compensation fund for AIDS vaccine victims (financed by a surcharge on the sale of these vaccines in California) to cover those cases in which a manufacturer is not held liable. "The statute also creates a program to provide grants for research on an AIDS vaccine, and a guarantee by the State of California to purchase 500,000 units of an FDA-approved AIDS vaccine," Cooper told the workshop.

Beyond the liability problems and other concerns, Osborn worries about the impact the well-publicized AIDS-vaccine efforts themselves may have on the behavior of the public. "I can't for a minute argue that this research shouldn't go forward as fast as possible," she says. "And I think there are situations in other countries where straightforward preventive activities [are less viable and a vaccine would be even more urgently needed]." But in the United States, she says, we have an important opportunity to educate people to avoid becoming infected with the virus.

Echoes Maurice Hilleman of Merck Sharp & Dohme Research Laboratories in West Point, Pa., "I think it will be a couple of years before we have much of a fix on whether a vaccine is feasible or not." But the spread of AIDS could be stopped tomorrow, he says, if certain sexual practices and intravenous drug use were halted.

Osborn argues that when some people hear there is a vaccine on the horizon, they become more careless in their behavior. "I get very frustrated because we can get thousands of people to pay lots of attention to discussions of vaccines, but we can't get anybody at the federal level to talk about direct preventive education," she says.

"We must not work under the assumption that our responsibility is to develop a vaccine at all costs, whether it's a good idea or not," she told her colleagues at the close of the NIH workshop. "Our [foremost] public health responsibility is to bring the epidemic under control." □