Will There Be an AIDS Vaccine?

Research is speeding ahead, but there are many scientific roadblocks in the way of developing a safe and effective AIDS vaccine

By STEFI WEISBURD

First in a two-part series

Ever since 18th-century physician Edward Jenner used a dairymaid's cowpox lesions to successfully inoculate a boy against smallpox, vaccines have been indispensable in the fight against infectious diseases.

It's no wonder, then, that people might turn toward a vaccine in hopes of stemming the modern-day plague of AIDS. Indeed, as a National Academy of Sciences publication "Mobilizing Against AIDS" stated last year: ". . . the only hope for halting the spread of the disease completely is widespread immunization." With an estimated 5 million to 10 million people worldwide now thought to be infected by the AIDS virus, many research groups and companies are working at a feverish pace to develop a vaccine against the deadly disease.

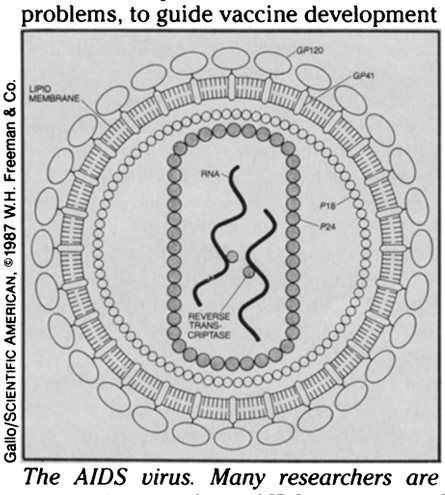
But these researchers have some extremely difficult, if not impossible, scientific hurdles to overcome, because the AIDS virus, also known as the human immunodeficiency virus (HIV), is like no other virus for which vaccines have been developed.

"It's the first time we've considered a retrovirus for a human vaccine," says John Nutter, who heads the Prevention Branch of the AIDS Program at the National Institute of Allergy and Infectious Diseases. "It's a whole new ball game." The genetic material of a retrovirus is RNA, rather than DNA; it uses its RNA as a template to make DNA, which is then inserted into the chromosomes of a cell. When the virus, which can lie dormant for long periods of time, becomes active, it can then hijack the cell's replication machinery for the life of the cell.

Moreover, unlike most other viruses, HIV is extremely complex genetically and has the capacity to mutate to a worrisome multitude of variants. It attacks T4 white blood cells, which are at the heart of the body's immune response. And like a wolf in sheep's clothing, it can enter the body completely hidden inside cells – an ability that may make vaccination against the cellular route of infection impossible.

As a result, there is no guarantee that researchers will ever be able to make a safe and effective AIDS vaccine. And whether they succeed or not, scientists as well as the community at large will have to grapple with some thorny ethical and legal problems during vaccine testing and possible distribution.

In an attempt to foresee some of these problems, to guide vaccine development and testing and to discuss scientific obstacles, AIDS vaccine researchers and policy makers met at the National Institutes of Health (NIH) in Bethesda, Md., in March. What was clear at the workshop is that while researchers have sorted out important areas to study, they are raising considerably more questions than they can answer.



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The AIDS virus. Many researchers are attempting to make an AIDS vaccine out of bits of the virus, such as the glycoprotein (GP) 120 on the outer coat, which can be easily "seen" by the body's immune system. But since these proteins vary greatly, some scientists are focusing on more stable inner proteins, such as the P17 protein (not shown), which lies inside, but close to the outer membrane.

The purpose of a vaccine is to put the immune system on alert against a specific disease. Among the body's main lines of defense against invading viruses and other pathogens are antibodies. These protein molecules recognize and destroy viruses by binding to viral proteins, which act as antigens, or substances that trigger an immune response. A vaccine exposes the body to a harmless form of viral antigen and helps program the immune system to quickly recognize that antigen and mobilize against it in the future. Should a virus carrying that specific antigen later invade the body, the immune system will produce specific antibodies that attack the virus.

Traditionally, researchers have made vaccines either from whole viruses that have been killed or from a viral strain that does not cause disease. In this way, vaccines have been used successfully to combat a variety of viral diseases, including measles, polio, smallpox and yellow fever.

AIDS researchers, however, are leery of whole-virus vaccines because they do not want to take the chance that live, virulent AIDS viruses could find their way into vaccine preparations. They are also not sure whether there are any truly harmless variants of HIV or if it is possible to render an AIDS virus irreversibly

benign.

Moreover, the AIDS virus contains nucleic acids that, when inserted near a human oncogene (a cancer-causing DNA segment), could prompt cancerous tumors to form. Whether researchers consider a whole-virus approach or one in which antigenic parts of the virus are purified from viruses grown in tissue cultures, "our ability to remove the last little bits of nucleic acid certainly isn't up to par at this point," notes Robert J. Gerety at Merck Sharp & Dohme Research Laboratories in West Point, Pa.

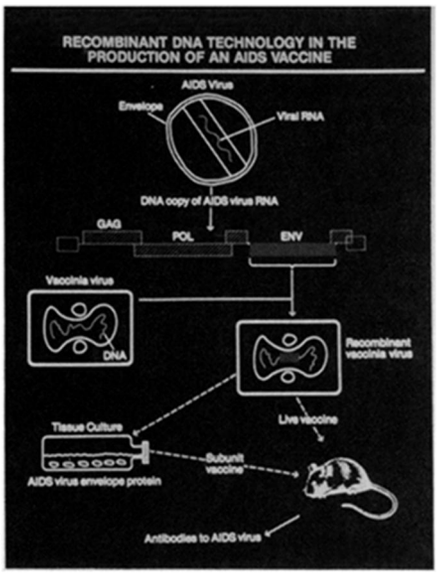
However, says Nutter, "from a research basis, we're going to have to take a look at [this approach] to at least find out what does happen when we administer a whole killed viral particle into an experimental animal." And he adds that "this is something we may have to come back to" if the other approaches fail.

To get around the problems of whole viruses, researchers are trying to isolate specific HIV protein antigens with genetic engineering techniques. For example, a few research teams at the NIH conference reported on how they have taken the HIV genes that code for particular proteins on the virus's outer envelope and inserted them into the genetic machinery of *E. coli* bacteria, hamster ovary cells and insect cells. These other systems then produce the specific protein antigens without all the other potentially dangerous baggage contained in the AIDS virus. The intention is to use the resultant proteins as a vaccine after they have been mixed with an adjuvant, a substance that enhances the effectiveness of the proteins to provoke an immune response.

Another approach being taken is to insert HIV genes into harmless forms of other live viruses such as the vaccinia (cowpox) virus (SN: 4/12/86, p.228). This other virus would not only produce the desired AIDS antigens but would also present the antigens to the immune system in a more "natural" fashion, which might provoke a wider spectrum of immune responses. Two advantages of using a vaccinia virus, noted George Todaro of Oncogen, a division of Bristol Myers, in Seattle, Wash., are that health care workers around the world are familiar with it, and it is a big virus, enabling researchers to insert many genes.

But the big question about these subunit approaches is whether a vaccine made from parts of the AIDS virus can trigger the kind of immune response that successfully fights off an AIDS infection – and, if so, which antigens or combination of antigens should be targeted.

A few research teams have shown that chimpanzees (which can be infected by the AIDS virus, but do not develop the disease) injected with a few subunit vaccines do produce "neutralizing" antibodies. But when one participant at the NIH workshop asked if anyone knew of any studies showing that these chimps were protected from infections after they had been injected with HIV, the auditorium was silent (although some researchers argue that the chimps were "challenged" with an unrealistically high level of HIV).



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Researchers are taking about half a dozen different approaches to developing an AIDS vaccine. Here, specific AIDS virus genes are implanted into a vaccinia virus, which then produces some AIDS virus proteins. The hope is that when the vaccinia viruses expressing the AIDS proteins are injected into the body, they will "teach" the immune system to recognize AIDS viruses.

Moreover, it's not clear in humans whether antibodies to the AIDS virus are sufficient to stave off the disease, because there are people who have produced neutralizing antibodies to AIDS after being naturally infected by the virus, but who still developed full-blown AIDS. Some researchers at the workshop noted, however, that it takes several weeks for people to develop these antibodies; perhaps if the immune system were prepped with a vaccine to produce the antibodies before infection, the AIDS virus could be fought off.

Assuming this were the case, researchers would still have to determine which antigens should be included in a vaccine. And a major stumbling block here is that scientists don't fully understanding how the virus works and what natural defenses the body has against it.

Unlike victims of many other viruses for which vaccines have been found, AIDS patients do not recover from the disease, notes Gerety, who was involved in the development of a hepatitis B vaccine. With hepatitis B, he says, scientists were able to identify the antibodies that provide immunity by examining the blood of the infected patients who recover. (About 90 percent recover completely.) But "for the AIDS virus," says Gerety, "no one really knows [what the protective antibodies are]." And that, he adds, is why researchers are taking so many different routes to developing a vaccine.

Researchers stress that a successful vaccine – in addition to producing neutralizing antibodies that, by binding to free viruses, kill them and prevent them from infecting cells – must also stimulate the body to attack already-infected cells. The ability to kill infected cells is part of a larger process called cell-mediated immunity, in which virus- and foreign-material-eating macrophages, antibody-producing B cells and other immune cells are directed by T4 cells to do their various jobs.

"That's terribly important," says Maurice R. Hilleman of Merck Sharp & Dohme, "because [HIV can be transmitted] either as a free virus or inside infected cells. . . . There are no vaccines that I know of that vaccinate against cells that are infected."

How best to elicit a cell-mediated response, and how important such a response is in comparison with neutralizing antibodies, remain open questions. Another significant problem, adds Hilleman, is that HIV can get through the blood-brain barrier into the central nervous system. From there, the virus can launch an attack with relative ease, because antibodies have a hard time getting through this barrier.

One of the most important potential obstacles to making an AIDS vaccine is the extreme variability of the virus, particularly of its envelope proteins. While most viruses have only a few variants, HIV has a great many. Not only are there substantial differences in the genetic makeup and envelope proteins of viruses isolated from different people, notes Hilleman, but viruses within the same individual keep changing.

As a result, antibodies that neutralize one HIV variant may not recognize the envelope antigens of another. A key question to resolve, says Gerety, is whether the number of variants is finite. If so, he says, it might be possible to make an effective vaccine from a constellation of antigens. (Other researchers call this an antigen cocktail.) "The idea of making a multivalent vaccine is not foreign," Gerety says, but "viruses that have the ability to change in unpredictable ways like this one [can] make it very difficult."

Researchers would like to find a common denominator for all the variants by targeting some part of the virus that doesn't change. One common quality of all HIV variants is that they recognize and infect T4 cells. With this in mind, many of the researchers have been focusing on one particular surface antigen called GP 120 (SN: 3/8/86, p.151), thought to be involved in binding to a molecule called the CD4 receptor on the T4 cells. By generating antibodies to this antigen, some researchers hope to disable HIV's ability to infect T4 cells.

A novel vaccine approach that could possibly be used to block binding sites of either the HIV or T4 cells uses "anti-idiotypes" (SN: 4/12/86, p.231). As discussed at the NIH workshop by Ronald C. Kennedy of the Southwest Foundation for Biomedical Research in San Antonio, Tex., an anti-idiotype is made in two steps. First the virus is injected into an animal and the resultant antibodies produced by the animal are collected. These antibodies are then injected into a second animal, which produces anti-idiotypes, or antibodies to the antibodies. The idea is to use anti-idiotypes, which mimic the antigenic structure of the virus but not its genes or other dangerous components, as a vaccine.

In the same way, anti-idiotypes could be made that mimic the structure of CD4 receptor sites; these anti-idiotypes would then tie up the binding site on HIV. Kennedy says he and his colleagues have demonstrated in chimps that anti-idiotypes have potential as a vaccine for hepatitis B. As for AIDS, he says that work by his laboratory and, independently, by a group in England suggests that anti-idiotypes can neutralize different virus variants.

But June Osborn of the University of Michigan in Ann Arbor worries about "going the receptor route" in general, because the CD4 receptor is found not only on T4 cells but on many other cells as well, especially in the central nervous system. In trying to interrupt HIV attachment to the CD4 site, she says, researchers may be adversely affecting other important processes.

Another way of dealing with the variability problem is to focus on internal proteins, which seem to be more stable than those on the virus's outer coat. Most researchers have avoided the core proteins because they are thought to lie too deep within the virus to be seen and attacked by antibodies. However, Allan L. Goldstein of George Washington University in Washington, D.C., told the NIH workshop that research by others has shown that one internal protein called P17 lies closer to the outer envelope than once supposed, and it may be exposed enough to make an effective vaccine.

Using yet another technique, Goldstein's group has made a vaccine by directly synthesizing P17 proteins. He says they have been encouraged enough by animal studies to have applied in February to the Food and Drug Administration to begin human tests.

If experience with the hepatitis B and influenza viruses is any gauge, says Hilleman, there may be some hope for solving the variability and infected-cell problems of AIDS. For influenza, a highly variable virus, he says "there appear to be some constant regions in the surface-membrane antigens that have something to do with immunity." And from hepatitis B research, he adds, "we learned that the internal coded antigens can appear on the surface membranes [of cells] and provide a basis for recognition of infected cells."

In spite of all the scientific barriers that must be surpassed, the NIH workshop was infused with optimism. Some scientists think this optimism is misplaced. Some believe that by instilling people with what may turn out to be false hopes, this confidence is even dangerous. But whether or not a vaccine is indeed developed, all scientists have been duly impressed at the speed with which the HIV's workings are being unraveled.

"Even though [the study of AIDS] is just a few years old," remarks Hilleman, "it's just miraculous how much is known now about its molecular virology and viral replication." And even if scientists fail in their attempts to make a vaccine, he says, the work will have tremendous importance to the biological sciences in general: "AIDS may be to virology what space exploration has been to the development of new products such as electronics and computers." □

Coming later this month: Ethical and legal issues of a possible AIDS vaccine

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