The Search for an AIDS Vaccine

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THE GOAL OF THE PUBLIC HEALTH SERVICE is to have within the next few years an effective vaccine to protect people at risk of infection with HTLV-III, the virus that causes AIDS. For those who now have AIDS, others who may have developed AIDS-related symptoms, and still more who are already infected by HTLV-III and may be ill in the future, a vigorous drug development and treatment effort is under way.

The Public Health Service is committed to major initiatives to speed the discovery, development, and testing of drugs against AIDS—and to involve the external scientific and medical community and a growing number of AIDS patients in these efforts.

- In a joint project undertaken by the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID), drugs are being screened for their antiviral properties. So far, some 200 drugs have been screened, and several are now in early clinical testing at the National Institutes of Health and elsewhere. Several more antivirals have shown promise in preclinical testing and are being readied for clinical trials.
- The NCI and NIAID in December 1985 issued a request for applications for funding of National Cooperative Drug Discovery Groups. These groups will bring together research scientists from diverse disciplines and institutions who will combine their resources and talents into a single unit with the common goal of discovering new agents to inhibit HTLV-III and to restore or maintain immune functions. Such a program will enable these scientists to generate new strategies in drug development, conduct indepth biochemical and pharmacological studies, and identify new treatments worthy of development to clinical trials. The awards will be made in September 1986.
- The NIAID has also issued a solicitation for the establishment of AIDS Treatment Evaluation Units around the country. At these units, antiviral drugs, immune modulators, and antibiotics will be tested in patients with AIDS and AIDS-related complex. We hope within a year to have up to 2,000 patients in treatment. The best minds—both inside and outside the government—are also being brought together to establish criteria for deciding when a drug has shown enough promise in early tests to warrant compassionate release on a broader basis, even though the ultimate value of the drug still must be established by further testing.
- Finally, to speed information about new AIDS therapies to researchers and physicians, the National Cancer Institute has added data on treatment protocols to its Physician Data Query (PDQ) system, which already provides similar cancer treatment information. The AIDS portion of the PDQ system, when fully operational, will provide immediate access—through personal computers or word processors with telephone hookups—to information on the most promising AIDS therapies, locations of experimental treatment projects, and the names of AIDS specialists.

In the search for effective antiviral drugs, a major consideration is whether or not a drug that is active against the virus can be given by mouth, since it is likely that the drug would have to be taken over long periods, and possibly for life. Because not only the immune system, but the brain as well, is an important target for HTLV-III, the drug must also be able to cross the blood-brain barrier.

An example of a drug that inhibits the virus, that can be given orally, and that does penetrate to the brain is azidothymidine, or AZT, which is

manufactured by Burroughs-Wellcome. AZT was assayed in February 1985 by scientists of the National Cancer Institute, who found it to be active against HTLV-III in the test tube. The Food and Drug Administration approved AZT for experimental use in patients within 5 days of the manufacturer's application, and preliminary clinical testing began in July 1985 at the NIH Clinical Center, Duke University, and the University of California at Los Angeles. The purpose of this phase I trial was to identify potential toxic effects and establish what dosage can be tolerated. Phase II—a placebo controlled, randomized study—is expected to begin shortly.

While AZT has shown promise, it is still much too early to draw conclusions about the drug's ultimate safety and efficacy. But what has been learned from the early trial does give us some cautious optimism that an agent or agents can eventually intervene in patients with AIDS.

The search for therapies to restore immune function has not as yet yielded clear results; however, another part of the treatment picture is brighter, since several agents have given evidence of effectiveness against major opportunistic illnesses.

On the vaccine front, production of an HTLV-III vaccine presents numerous challenges. Unlike other virus vaccines, neither an attenuated nor a killed whole HTLV-III vaccine would be acceptable because of the undesirable presence of genetic material.

The fact that many differences have been found in the composition of the protein coats of various isolates of HTLV-III also has seemed to pose a problem for vaccine development. However, scientists have been able to identify the specific antigenic regions in precise molecular detail. Subunit proteins of the viral envelope that may stimulate antibodies capable of neutralizing the live virus have been purified and produced in the laboratory in large amounts, and the NCI researchers have been carrying out animal testing of these viral subunits in various combinations. Antibody responses have been demonstrated, and these antibodies neutralize HTLV-III in the test tube. The vaccine preparations are now being tested in rhesus monkeys. The next step will be to test the safety and efficacy of these preparations in the chimpanzee, followed by challenge with live virus.

To make sure that we have enough animals for the challenge studies, the Public Health Service is requiring that its own intramural scientists, and nongovernment scientists conducting PHS-supported AIDS studies, obtain prior written clearance from the PHS AIDS Animal Model Committee before using chimpanzees in AIDS research.

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Study of animals is an extremely important part of the vaccine development effort in other ways. For example, simian viruses having similar properties to HTLV-III have been found among certain monkey species. Use of these animals as models, and studies of other primates in which AIDS-like illnesses appear, may open additional paths to vaccine development. Also, genetically engineered viral protein products have been made by several interactive research and commercial groups and are being tested as vaccine preparations in animals.

Taking a different tack, researchers at the NIAID have inserted the HTLV-III envelope gene—which codes for the protein of the virus' outer coat—into vaccinia virus, a human virus with a known safety record. These scientists have found that when this recombinant vaccinia preparation is inoculated into mice, rabbits, and other animals, the envelope gene is expressed, and the resulting protein reacts with specific antisera. However, instability of the inserted gene has been a problem. Efforts are under way now to produce more stable recombinants in a different vaccinia strain.

No one would be happier than I if I could report that we have found all the answers to developing AIDS treatments and vaccines. But if I cannot, as the old saying goes, "a journey of a thousand miles must begin with a single step," we can say with assurance that we have behind us many steps, and that attainment of our ultimate goals seems much nearer.