EDITORIAL

AIDS Research: Charting New Directions

In 1983 these pages were used to announce that the Public Health Service had made the search for the cause, treatment, and prevention of AIDS (acquired immune deficiency syndrome) its number one health priority. At that time, the Centers for Disease Control, the Food and Drug Administration, and the National Institutes of Health intensified our laboratory research on a causative agent for AIDS. A possible association of human T-cell leukemia virus with AIDS had just been proposed.

Today, it seems most appropriate to use this same forum to report on the progress that has been made against this highly fatal disease and to chart new directions for AIDS research.

A most important milestone, of course, was the announcement by Health and Human Services Secretary Margaret M. Heckler, in April 1984, that Public Health Service scientists had found solid evidence that a form of human T-cell leukemia virus—HTLV-III—is indeed the probable cause of AIDS. Within the same time frame, our scientists acknowledged that a similar virus—LAV for lymphadenopathy-associated virus—discovered in 1983 by a French scientist, is probably identical to HTLV-III. Collaborative efforts between PHS scientists and investigators at the Institut Pasteur in France are underway to confirm whether or not HTLV-III and LAV are one and the same, or very closely related.

There have been other important payoffs from the concentration of PHS resources and manpower on the study of AIDS. These include the serological detection of antibodies to HTLV-III, a method of mass-producing the virus, and the impending production of assay kits to detect antibodies to the virus in the blood.

Since the production of virus-infected cells by the National Cancer Institute is primarily for research purposes, five private pharmaceutical companies will develop and distribute the actual test kits for AIDS. In June, representatives of the Public Health Service signed nonexclusive, royalty-bearing licenses with the competitively selected companies, giving them samples of the HTLV-III virus from which they will produce enough new virus to provide test material for a broad range of research needs and, ultimately, clinical use. All of the firms have a nationwide distribution system and a system for monitoring test results in blood banks and research laboratories.

Later, when the assay kits become commercially available, they can be used to screen blood donated for use in transfusions and for the production of blood products for hemophiliacs. Blood from donors with antibodies to the AIDS virus can then be rejected for use, further reducing the chances for transmission of AIDS to people needing blood or blood products.

A most significant result of our AIDS research commitment is the rapid accumulation of the kinds of information scientists need to undertake the development of an AIDS vaccine. Nobody knows for certain how long it will take to develop the vaccine, although the general speculation is that it will be available for clinical testing within 2 or 3 years.

The discovery of the probable cause of AIDS and the development of a blood test have considerably altered priorities within the Public Health Service's AIDS Operational Plan. In support of this changeover, the PHS Executive Committee on AIDS has been reconstituted as the PHS Executive Task Force, chaired by the Assistant Secretary for Health. The new coordinating body is made up of the heads of the five Public Health Service agencies and has separate panels on information, resources, and science. The chairpersons of the panels and representatives of the Office of the General Counsel and the Assistant Secretary for Legislation attend all biweekly meetings of the Task Force to review progress and plan strategies for the AIDS program.

To date, the PHS Executive Task Force has identified four major research priorities. These priority areas and some of the important considerations within each area are:

1. *Epidemiologic studies to determine the natural history of AIDS*. The Public Health Service's response to AIDS began in June 1981 with the investigation, and subsequent publication in the Centers for Disease Control's Morbidity and Mortality Weekly Report, of the first five cases reported from Los Angeles. Since then, CDC has provided regular updates on the spread of AIDS by time, place, and the number (but not names) of patients within certain population groups. These surveillance data, provided by State and local health departments and private physicians and carefully coordinated by CDC, have contributed greatly to the orderly development of our studies on the natural history of AIDS.

Also helpful to the AIDS effort has been the establishment of a mechanism for collecting specimens of blood, semen, feces, and saliva from several groups of persons considered at high risk for acquiring AIDS. These specimens can be stored for future examination and are considered particularly valuable because—if the donors do indeed develop AIDS—they will have been collected around the time the AIDS infection was first transmitted, a time that may precede diagnosis by months or even years. The value of the specimen bank has, of course, been enhanced by the development of the blood test for antibodies to the AIDS virus.

In summary, with reliable surveillance information, an established specimen repository, and a powerful new research tool for detecting viral antibodies, scientists are now armed to learn where and how the AIDS virus first appeared. Currently, investigators are pursuing leads on the natural history of AIDS that have been and are being developed in ongoing studies of the following populations:

- homosexual men with a large number of partners;
- individuals with hemophilia;
- Haitians living in New York and Miami;
- 7,000 homosexual men living in San Francisco;
- intravenous drug abusers;
- health care workers;
- family members and sex partners of AIDS patients;
- patients not belonging to known risk groups.

Investigations are focusing on determining the natural reservoir of the virus in man (tissue, cell type, and so forth); the degree of expression of the virus or viral antigens (if any) at various stages of the disease; the characteristics of factors existing in man that inhibit virus expression; and the degree of antiviral activity of the antibodies found in patients with and without the disease. The successful completion of this work will require the development of a series of special reagents and tests.

2. *Evaluation of the blood test.* The evaluation of a specific diagnostic test for AIDS, like the identification of the AIDS causative agent, will herald intensified medical research efforts to delineate the epidemiology of AIDS. Everything possible is being done, therefore, to expedite the formulation of protocols for the collection of blood specimens.

Initially, work on blood tests will be performed under an investigational new drug (IND) application held by the National Cancer Institute, or an IND held by companies developing the test kits. Prior to commercial distribution, any assay kit will require a product license from the Food and Drug Administration.

Test kits will be made available to both public and private hospitals and blood banks, with the understanding that the data resulting from the tests will be reported to the Public Health Service for scientific evaluation. These data will make possible fuller evaluations of the significance of positive and negative results obtained with blood samples. The evaluations will involve both extensive testing of samples and patient followup. For example, a negative test result for antibodies in persons suspected of harboring HTLV-III virus may require repetition because sufficient time may not have gone by for the possible generation of antibodies. A positive result for the blood test, implying that at some time in the past the person has experienced infection with the virus, would also need to be replicated to minimize the possibility of a "false positive" result.

As yet, none of these results can definitively indicate whether or not active infection is still present. It is therefore desirable to develop an additional test for presence of the virus particles, because some infected patients may not be able to make antibody effectively. Accordingly, intensive research is in progress with a view to the elaboration of a practical test to detect the actual viral antigen(s).

3. *Development and evaluation of a vaccine, including the development, if possible, of an animal model of AIDS.* Efforts to develop a safe and effective AIDS vaccine are underway within the Public Health Service laboratories that are cooperating in this project. The National Cancer Institute has established a committee for vaccine development, and the National Institute of Allergy and Infectious Diseases, a veteran of many years' experience in vaccine development, has assigned investigators and facilities to the AIDS vaccine program. Vaccine research is also bringing Food and Drug Administration laboratories into collaborative studies of inactivation processes, immunogenicity *in vitro* and in animal models, the safety of cell substrates or R-DNA production systems, and, eventually, effectiveness in clinical trials.

The presumptive vaccine will be tested first in laboratory animals. Upon the successful completion of these tests, the next step would be clinical trials of the vaccine as an investigational new drug, under Food and Drug Administration guidelines. The goal is to determine the safety and efficacy of the vaccine as quickly as possible, but under safely controlled conditions, before its release for use in the general population. Ultimate large-scale production of the vaccine would, like the production of the test kits, be undertaken by private industry.

The establishment of an animal model has been a major step in the process to control most human ill-

nesses, especially those of an infectious nature. Although AIDS is clearly an infectious disease, attempts to isolate the AIDS virus by inoculating a wide variety of laboratory animals with AIDS materials have not yet been fruitful.

Identification of the probable cause of AIDS by other methodology has increased rather than diminished the search for an animal model that could be successfully inoculated with the AIDS virus and subsequently used to test the AIDS vaccine. Accordingly, collaborative efforts have been initiated with the Yerkes Primate Center and the New England Primate Center for inoculation in various primate species. Because of the concern regarding the use of primates in AIDS research, the animals will only be used in well-designed, carefully planned studies.

4. *Studies of therapeutic intervention, especially in the early phases of the disease, as identified in the epidemiologic studies. Bioethical and biosafety issues will also be explored.* Despite the wealth of new data now available on AIDS, it has not been possible to translate this into help for people who already have the disease. Ameliorating the suffering of AIDS victims, especially those in the early stages, is a continuing challenge. Based on the discovery of the AIDS virus and test, discussions have begun within the Public Health Service Executive Task Force on what might be done immediately in terms of treating the disease, *even in the absence of positive efficacy of animal model vaccines or treatment*. These discussions are by no means complete, and many issues relating to potential therapies need to be further defined, developed, debated, and evaluated within the Task Force and the scientific community at large.

Scientists are optimistic that isolation of HTLV-III will enhance opportunities for evaluation of chemotherapeutic agents and antiviral or immunologically active biological substances such as the lymphokines and toxin-tagged monoclonal antibodies. Public Health Service agencies will be working with each other and with potential manufacturers to speed the development and licensure of promising therapeutic substances.

By its nature, AIDS is a disease with many and complex bioethical and biosafety issues that must be thoughtfully addressed. At a recent workshop sponsored by Public Health Service agencies, these issues were explored with representatives of the nation's major blood banks and bioethicists from the Hastings Center and the Kennedy Institute of Ethics.

Discussions focused on the ethical, legal, and psychological implications involved in projected clinical studies of AIDS and in the application of the blood test. Workshop participants agreed on the urgency of establishing mechanisms whereby appropriate studies can be done with due consideration for the sensitive issues involved. They also explored a number of approaches that would provide adequately for patient safety while protecting everyone's right to privacy. Followup meetings will be required to develop precise guidelines to ensure that individual rights, including confidentiality of research results, will be respected in all AIDS projects involving the use of human subjects.

The AIDS battle is far from won. As in all things scientific, a few answers raise a thousand new questions. Yet I think that all who have taken part in the fight against AIDS can take some satisfaction from having reached the end of the beginning of the struggle, and can enter the next phase with confidence of final victory. It is important to emphasize that at no time in the history of medicine has so much progress been made, in so short a time, in understanding a complex illness. The Public Health Service and the scientific community should take great pride in their accomplishments.

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LETTERS TO THE EDITOR

Outcome of Out-of-Hospital Births Should Not Be Measured by Birth Weight

We take issue with Declercq's conclusions regarding the safety of out-of-hospital births in the United States (*Public Health Reports, January–February 1984*). On the basis of his observations that the proportion of low birth weight deliveries is slightly higher in hospital births (7.1 percent) than in out-of-hospital births (6.9 percent), Declercq concludes that public policy and attitudes toward home births should be liberalized. This suggests that Declercq has mistakenly treated a confounding variable, namely birth weight, as a measure of outcome. Although women choosing to bear their offspring out of the hospital may indeed be at different risk for low birth weight offspring than women delivering in hospitals, it does not follow that birth weight is directly influenced by where a woman chooses to give birth. Birth weight, therefore, is an inappropriate outcome variable for a study attempting to compare the safety of hospital births with out-of-hospital births. As Declercq points out, the most likely explanation for the birth weight differential in favor of out-of-hospital births is referral of high-risk patients to hospitals.