Chapter 2

Specific Findings

Chapter 2

Specific Findings

IS THERE AN ADEQUATE CORRELATION BETWEEN HTLV-III AND AIDS?

There is strong and increasing evidence that the newly discovered retrovirus HTLV-III (human T-cell lymphotropic virus, type III) (57,122,130,132) is the basic cause of acquired immunodeficiency syndrome (AIDS). HTLV-III is similar to, but nevertheless distinct from, two previously identified human T-cell lymphotropic retroviruses, HTLV-I and HTLV-II. HTLV-I and possibly HTLV-II cause T-cell leukemias (proliferation), whereas HTLV-III causes T-lymphocyte death (suppression). (Lymphocytes and other blood cells originate in the bone marrow. T cells or lymphocytes are white blood cells that mature in the thymus gland and mediate cellular immune reactions by helping ("helper T cells") or suppressing ("suppressor T cells") immune responses. B lymphocytes or cells are white blood cells that mediate humoral (e.g., antibody production) immune reactions and proliferate under stimulation from factors released by T lymphocytes.)

The genetic material of "retroviruses" consists of ribonucleic acid (RNA), not deoxyribonucleic (DNA), but when retroviruses infect cells, they are incorporated in the DNA of infected cells in a DNA form known as the "provirus. " When retroviruses invade cells, they can reverse the process of "gene expression" by which information contained in the cells' genes is transcribed from DNA to RNA and then translated to direct the synthesis of proteins. Through the production of the enzyme "reverse transcriptase, " retroviruses produce a DNA analog of their own RNA. The resulting DNA is then incorporated in the genetic structure of the invaded cell as the "provirus. " Subsequently, the genetic information in the incorporated DNA is "expressed" in the usual way to produce new retroviruses.

HTLV-III is essentially the same virus as other retroviruses that have been associated with AIDS—LAV or "lymphadenopathy-associated virus" (7), IDAV or "immune-deficiency -associated virus" ***(107)*** and ARV or "AIDS-related virus" (89). The mild confusion that has resulted from the giving of different names by researchers to what appears to be the same virus is primarily the result of scientific caution.

When a possible agent for a new disease is reported, early published accounts provide the details of the investigations, and the investigator assigns a name to the agent. As Broder and Gallo (23) have observed with respect to the viruses associated with AIDS: "In theory, each isolate might have been a different, newly discovered human retrovirus presenting as an opportunistic infection, with no bearing on the pathogenesis of AIDS."

French investigators named their first isolate "lymphadenopathy-associated virus" (LAV) because it was isolated from a patient with lymphadenopathy syndrome, and they named a subsequent isolate "immune-deficiency-associated virus" (IDAV) because it was isolated from a patient with AIDS. In a later report on two other patients, these investigators found isolates (or antibodies to them) that were similar to both LAV and IDAV (172). Gallo and his coworkers at the National Cancer Institute (NCI) named their isolates "HTLV-III" because they were closely related to, but distinct from, two other recently discovered human T-cell lymphotropic retroviruses that Gallo and his associates had been extensively studying. Gallo and his coworkers have now accumulated over ***90*** isolates of HTLV-III from around the world ***(23).*** Finally, when Levy and his associates published findings on their isolate, they chose yet another name, "AIDS-related virus" (ARV), even though they found that it cross-reacted with antiserum to the LAV isolated in France (89).

Investigators in a study that examined antibody reactivity to both HTLV-III and LAV have found the results to be identical (32). Gallo and his coworkers have also reported that they have found these variously named retroviruses "immunologically and morphologically indistinguish-

able from HTLV-III" (66). All of these isolates have now been cloned (1,66,91), and direct comparisons of the nucleotide sequences of the genomes of the various isolates are being conducted (56). In this memorandum, therefore, the various isolates will be collectively referred to as "HTLV-111."

HTLV-III attacks what is commonly referred to as the helper/inducer subset of T lymphocytes, the cells which are attacked (depleted) in AIDS. T lymphocytes are classified into various subsets, two of which are T4 and T8 (named after the monoclinal antibodies used to distinguish the antigenically distinct subsets from each other). Although T4 cells have commonly been identified with helper/inducer functions and T8 cells with suppressor/cytotoxic functions, both subsets contain cells that help and cells that suppress immune responses (133).

The primary defect in AIDS is an acquired, persistent, quantitative and functional depression in the T4 lymphocytes (45,133). Patients with lymphadenopathy syndrome have been found to have a selective depression in a subset of T4 cells, but to have normal numbers of cells in the subset of T4 cells that are the major helper subset for B cell responses ***(115).*** HTLV-III has a selective tropism for T4 lymphocytes (80), and the immune defects observed in AIDS are completely compatible with the cellular defects associated with HTLV-III infections (46).

Furthermore, the T4 cell membrane molecule that defines the T4 subset of T lymphocytes is now known to be an essential component of the cell-surface receptor for HTLV-III; i.e., interaction between HTLV-III and the T4 cell membrane molecule is apparently the way in which HTLV-III gains entry into the cell (39,81). These findings strongly suggest that HTLV-III tropism depends on the interaction of HTLV-III with the T4 molecule.

Most infectious retroviruses (including HTLV-I and HTLV-II) use receptors common to many cell types. HTLV-III, in contrast, appears to use the surface receptor molecule specific to the cells (T4 lymphocytes) most affected by HTLV-III infection (39). The T4 receptor molecule can be found on some types of white blood cells other than T4 lymphocytes. Such cells include macrophages and monocytes, which perform a scavenging or phagocytic function by engulfing foreign material and consuming debris and foreign bodies. These other white blood cells may also become infected with the virus (65a), adding to the compromised immune function in AIDS patients.

Brain cells and T lymphocytes are known to share some common cell surface molecules, and on the basis of this knowledge, some researchers decided to examine whether HTLV-III can infect brain cells. Their findings suggest that some of the neurological abnormalities found in AIDS, instead of being caused by "opportunistic" infectious agents or tumors, are directly caused by HTLV-111 infection (135). Although the investigators showed that infection was not due to infiltration of the brain by HTLV-III-infected lymphocytes, the brain cell type or types directly infected by HTLV-III—neurons, glial cells (cells which provide the supporting tissue of the brain), or macrophages (scavenger cells) —have yet to be determined. The finding that HTLV-III can directly infect brain cells and replicate in the central nervous system means that future drug treatment for HTLV-III infections will be made more difficult because many drugs will not enter the central nervous system if given orally or by intramuscular or intravenous injections.

HTLV-III also has unusual properties that make it especially virulent. When a retrovirus infects cells, its RNA is transcribed into DNA, which is then integrated into the genome of the infected cells. Normally, this viral DNA is present in the cytoplasm of the infected cells only for a short period of time before it is integrated into the cells' genome. With HTLV-III, however, a substantial amount of unintegrated viral DNA persists in the cytoplasm. Although a persistence of unintegrated viral DNA is unusual for retroviruses, when observed with certain animal retroviruses, it has been correlated with pathological effects on the infected cells (134).

Furthermore, when HTLV-III that is integrated in its "provirus" form in the genome of infected cells begins to reproduce, special viral genes direct the rate of reproduction. These special genes have been shown to increase the rate of gene ex-

pression of infected cells by 100 to 1,000 times the rate of expression of uninfected cells. Thus, HTLV-III is a very efficient reproducer, there being a high level of virus production in HTLV-III infections which is unusual in HTLV-I and HTLV-11 infections (140).

What is now known about the cellular mechanisms associated with infection with HTLV-III is compatible with certain characteristics in most of the population groups that have been identified as being at high risk for AIDS. For example, T cells that have been activated by antigenic stimuli, but not resting T cells, are especially prone to infection by HTLV-III ***(102).*** Homosexual and bisexual males who have frequent sexual intercourse with multiple partners are exposed to a variety of infectious agents that usually do not cause disease but do stimulate the immune system. Injections in intravenous drug abusers lead to stimulation of the immune system because of the injected drugs themselves and contamination with infectious agents. Injections with Factor VIII concentrates in hemophiliacs also lead to stimulation of the immune system.

There is also a correlation between exposure to HTLV-III and the development of AIDS. The HTLV-III virus has been cultured from patients with AIDS, AIDS-related complex, and persons at high risk for developing AIDS; HTLV-III has been observed by electron microscopy in the T cells of these groups; and antibodies to HTLV-III as well as HTLV-III antigens and the genes for HTLV-III have been isolated in these same groups. HTLV-III can now be recovered from over 90 percent of patients with AIDS-related complex (23); and, with the development of increasingly more sensitive tests, antibodies to HTLV-III can be detected in nearly all AIDS patients ***(77,127).*** In contrast, other possible viral agents, including HTLV-I, have been isolated in these patients at rates which indicate that exposure to these other viruses was only incidental and not related to AIDS (although some of these viruses maybe the cause of specific diseases associated with AIDS). These results are being duplicated in countries around the world: the United States and France ***(154),*** France and Zaire (25,26), France (97), Britain **(32,58), Denmark (103,104), Greece (118), Scotland (11), West Germany (9,71), and Japan (6).**

A further indication of the causal relationship between HTLV-III and AIDS is the chronological association between the emergence of AIDS as a recognized disease and increasing exposure rates to HTLV-III among groups at high risk for AIDS. Among homosexual men attending a sexually transmitted disease clinic in San Francisco, for example, the proportion of patients with antibodies to HTLV-III increased from 1 percent in ***1978*** to ***25*** percent in 1980 and to 65 percent in 1984 (154).

Currently, antibodies to HTLV-III are found in approximately 75 to 90 percent of U.S. hemophiliacs, while percentages for hemophiliacs worldwide are 30 to 90 percent for Factor VIII users and 30 to 50 percent for Factor IX users (158). Since Factor VIII preparations from U.S. donors are used throughout the world, almost all studies have been done on patients receiving U.S. Factor VIII, at least in part. It is not clear that U.S. Factor VIII is a priori more infective than Factor VIII from other sources (160). However, in a study of Scottish and Danish hemophiliacs, 15.6 percent of Scottish patients, who were largely treated with Factor VIII concentrates produced in Scotland, versus 59.1 percent of Danish patients, who received both locally prepared concentrates and commercial concentrates made in the United States, were antibody positive to HTLV-III (105). In one longitudinal cohort study of hemophiliacs, no HTLV-III antibodies were detected prior to 1979 (from sera stored by a hematologist in Hershey, Pennsylvania). Subsequently, antibodies were first detected in 20 percent of sera collected during 1981 and 1982, and increased thereafter. By 1984, Factor VIII recipients had an overall positive rate of 74 percent, with 90 percent of frequent recipients of Factor VIII (at least twice a month) having positive antibodies (43,60).

Individual instances of a close correlation between HTLV-III and the development of AIDS have also been reported. For example, in one blood donor-recipient pair, both with AIDS, the virus was isolated from the donor's lymphocytes 12 months after he developed AIDS and from the recipient 1 month after she developed AIDS (47).

Other investigators have reported on three clinically healthy women intravenous drug abusers who were serologically positive for the virus and whose children developed AIDS, probably from transfer of the virus during pregnancy or the perinatal period (86).

Finally, studies in which chimpanzees were inoculated with serum and plasma from patients with AIDS or lymphadenopathy syndrome or with cultures of the virus have shown that chimps can be infected with HTLV-III ***(2,52,53,54).*** One chimp developed lymphadenopathy syndrome but no opportunistic infections, and the lymphadenopathy eventually disappeared (2,155). However, none of the chimps developed fulminant AIDS.

Thus, identification of HTLV-III as the basic causative agent for AIDS is now widely accepted by the scientific community, and current research is focusing on the relationship between exposure to the virus and development of the disease. Research on other possible causative agents has been refocused to examine the roles of these agents as "cofactors" in the causation of AIDS and of specific diseases associated with the syndrome.

HOW HAS THE PUBLIC HEALTH SERVICE (PHS) REDIRECTED ITS AIDS RESEARCH TOWARD HTLV-III WORK?

The discovery of HTLV-III has led to the rapid development of various methods to test for the virus's presence. The ability to grow HTLV-III in cell cultures plus the availability of tools from the field of molecular biology have made it possible to test people for the presence of antibodies to HTLV-III and for the presence of whole virus and fragments (antigens) of HTLV-III. Several diagnostic indicators for exposure to an infection with HTLV-III are identified below:

- ***Presence of antibodies to HTLV-III.*** Some tests for antibodies to HTLV-III use the whole virus as a source of antigens. Another approach is to fragment HTLV-III and use fragments to test for antibodies that may not be detected with whole virus preparations. Specific tests are now available to detect antibodies to the proteins that makeup the "core" of the virus and to the proteins that make up the "envelope" (surface) of the virus. These core and envelope antigenic proteins are specific enough to HTLV-III that they can be distinguished from the core and envelope proteins of HTLV-I and HTLV-II (7,32,89,122). Differentiation between antibodies to core and envelope proteins is important to the question of whether specific types of antibodies can protect against the development of AIDS, as well as to the related question of whether an effective vaccine can be developed (to be discussed later).
- ***Presence of antigens of HTLV-III.*** The presence of HTLV-III and fragments of the virus in people can be tested by using sera from other people known to have antibodies to HTLV-III.
- ***Presence of HTLV-III genes.*** The techniques of molecular biology allow the construction of genetic probes that can be used to search through the cytoplasm and nuclei of cells suspected of being infected with HTLV-III (66). (As noted above, when HTLV-III in its DNA form is integrated into the chromosomes of an invaded cell, it is referred to as being in its "provirus" form.) These methods have been used to show the integration of HTLV-111 into the genes of helper T cells and the presence of unintegrated HTLV-III DNA ***(66,134).*** Additionally, HTLV-III production by infected cells can be detected by very sensitive RNA hybridization methods so that individual infected cells can be visualized ***(68).***
- ***Culturing of HTLV-III.*** With the successful in vitro culturing of HTLV-III, it is now possible to take cells and sera from people to see if HTLV-III can be isolated and directly grown (89,108,122).

These diagnostic indicators are being applied to studies on AIDS, some of which are enumerated below.

Blood Studies

In April 1983, soon after the first cases of blood-transfusion-related AIDS had appeared, blood banks and plasma collection centers implemented donor screening procedures to exclude members of population groups at high risk for AIDS. Prior to the announcement of the discovery of HTLV-111 in April 1984, blood banks had been searching for "surrogate" laboratory tests that could be used to screen out blood that might transmit AIDS. Two of the tests that were considered were: 1) T4/T8 cell ratios because of the observation of lowered ratios in cases of AIDS and AIDS-related complex; and 2) the presence of antibodies to the core protein of the hepatitis B virus, because some of the groups (homosexuals, intravenous drug abusers) at high risk for AIDS also had a high risk for hepatitis B. The near availability of tests for detecting the presence of antibodies to HTLV-III has effectively made the usefulness of the search for surrogate tests of these types moot. Research grants sponsored by the National Institutes of Health (NIH) on surrogate tests have been reviewed and been reoriented toward cofactors research and/or toward the development of "second-generation" tests for HTLV-III ***(33).***

Screening of blood donors will be undertaken through tests to detect the presence of antibodies against HTLV-III as proof of past exposure to the virus (174). This blood test will augment, but not replace, blood donor screening procedures currently in place to exclude members of groups at high risk for AIDS ***(40).*** One reason is that researchers now know that some people who have the virus in their blood have not developed antibodies to it and are also symptom-free (129).

Since a proportion of the tests that are initially positive will be falsely positive, all positive tests for antibodies to HTLV-III in the serum of blood donors will need to be confirmed. PHS has addressed this issue of test reliability in its recommendations for blood and plasma screening (see box 2-A). In addition to the question of the reliability of tests for detecting the presence of antibodies to HTLV-III, there is the question of what antibody positivity means. Other than revealing past exposure to HTLV-III, does it mean that these people carry the virus? Will they develop AIDS? Answers to these questions are not known at this time. (These questions on test reliability and significance are also at issue in obtaining the informed consent of persons who will be tested and are addressed in the "Related Issues" section near the end of this chapter.)

The high risk of AIDS in hemophiliacs was presumed to be due to transmission in Factor VIII concentrates, the assumption being that standard methods for preparing Factor VIII concentrates were not sufficient to inactivate a presumed viral agent. There have recently been developed newer methods of preparation that use heat treatment at a sufficient level to inactivate some viral agents in Factor VIII concentrates (there is a trade-off in heat treatment between viral inactivation and preserving the biological activity of Factor VIII). With the discovery of HTLV-III, tests of inactivation of this specific virus could be conducted. Preliminary testing has shown that HTLV-111 is very sensitive to heat and that recent methods of heat-treating Factor VIII concentrates are capable of inactivating the virus in vitro. These findings are being investigated further ***(42,156).***

Other blood-related studies are discussed in the following section on epidemiologic work.

Epidemiologic Studies

Studies of different populations at risk for AIDS, their variations in associated risk factors and in clinical manifestations of AIDS, are of immediate relevance to our understanding of how the disease spreads, preventive strategies, and the possibility of early therapeutic interventions.

When AIDS was first recognized, tracking the development and spread of what was apparently a new disease had to be done without knowing what the cause of the disease was. Thus, it was necessary to survey specific illnesses—which were essentially limited to only one type ***of*** infection (Pneumocystis ***carinii*** pneumonia) and one type of cancer (Kaposi's sarcoma)—in the presence of immune suppression without known causes. This

Box 2-A.—PHS Recommendations for Screening Blood and Plasma Donations for Antibodies to HTLV-III

Initial Testing

Persons accepted as donors should be informed that their blood or plasma will be tested for HTLV-III antibody. Persons not wishing to have their blood or plasma tested must refrain from donation. Donors should be told that they will be notified if their test is positive and that they may be placed on the collection facility's donor deferral list, as is currently practiced with other infectious diseases, and should be informed of the identities of additional deferral lists to which the positive donors may be added.

All blood or plasma should be tested for HTLV-III antibody by ELISA (the name of the test procedure that is being used). Any blood or plasma that is positive on initial testing must not be transfused or manufactured into other products capable of transmitting infectious agents.

When the ELISA is used to screen populations in which the prevalence of HTLV-III infections is low, the proportion of positive results that are falsely positive will be high. Therefore, the ELISA should be repeated on all seropositive specimens before the donor is notified. If the repeat ELISA test is negative, the specimen should be tested by another test.

Other Testing

Other tests have included immunofluorescence and radioimmunoprecipitation assays, but the most extensive experience has been with the Western blot technique, in which antibodies can be detected to HTLV-III proteins of specific molecular weights. Based on available data, the Western blot should be considered positive for antibody to HTLV-III if band p24 or gp41 is present (alone or in combination with other bands).

Notification of Donors

If the repeat ELISA test is positive or if other tests are positive, it is the responsibility of the collection facility to ensure that the donor is notified. The information should be given to the donor by an individual especially aware of the sensitivities involved. At present, the proportion of these seropositive donors who have been infected with HTLV-III is not known. It is, therefore, important to emphasize to the donor that the positive result is a preliminary finding that may not represent true infection. To determine the significance of a positive test, the donor should be referred to a physician for evaluation. The information should be given to the donor in a manner to ensure confidentiality of the results and of the donor's identity.

Maintaining Confidentiality

Physicians, laboratory and nursing personnel, and others should recognize the importance of maintaining confidentiality of positive test results. Disclosure of this information for purposes other than medical or public health could lead to serious consequences for the individual. Screening procedures should be designed with safeguards to protect against unauthorized disclosure. Donors should be given a clear explanation of how information about them will be handled. Facilities should consider developing contingency plans in the event that disclosure is sought through legal process. If donor deferral lists are kept, it is necessary to maintain confidentiality of such lists. Whenever appropriate, as an additional safeguard, donor deferral lists should be general, without indication of the reason for inclusion.

Medical Evaluation

The evaluation might include ELISA testing of a follow-up serum specimen and Western blot testing, if the specimen is positive. Persons who continue to show serologic evidence of HTLV-III infection should be questioned about possible exposure to the virus or possible risk factors for AIDS in the individual or his/her sexual contacts and examined for signs of AIDS or related conditions, such as lymphadenopathy, oral candidiasis, Kaposi's sarcoma, and unexplained weight loss. Additional laboratory studies might include tests for other sexually transmitted diseases, tests of immune function, and where available, tests for the presence of the virus, such as viral culture. Testing for antibodies to HTLV-III in the individual's sexual contacts may also be useful in establishing whether the test results truly represent infection.

SOURCE: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, "Provisional Inter-Agency Recommendations for Screening Donated Blood and Plasma for Antibody to the Virus Causing Acquired Immunodeficiency Syndrome," *Morbidity and Mortality Weekly Report* 34:1-5, Jan. 11, 1985.

conservative "surveillance" definition of AIDS made it easier to identify populations at high risk, but it excluded other possible AIDS-related clinical conditions and probably underestimated the extent of AIDS.

The availability of various tests for HTLV-III should allow for a more accurate definition of AIDS and a more precise delineation of the natural history of the disease, clarifying whether antibodies that can protect against progression to full-blown AIDS exist and under what conditions a protective effect might occur. Use of the blood test for HTLV-III will also enhance epidemiologic studies of known high-risk groups such as homosexual and bisexual males with multiple sex partners, intravenous drug abusers, recent immigrants from Haiti, and hemophiliacs.

In the blood area, a large study supported by the National Heart, Lung, and Blood Institute (NHLBI) is focusing on immunologic consequences of transfusions. A component that has been added to the study deals with the collection and preservation of 200,000 serum samples from blood donors to be tested when the HTLV-III screening test becomes available (33). (There are 200,000 samples being collected on the assumption that the rate of HTLV-III-antibody-positive tests in the donor population will be approximately 0.5 percent, thereby yielding about 1,000 HTLV-III-antibody-positive donors.) The NHLBI-supported study will provide information on the extent of HTLV-III antibodies in the blood donor populations in cities in which AIDS is highly prevalent, as well as on the immunologic status of both donors with positive tests and recipients of their blood. The study should also provide important information on the natural history of exposure to HTLV-III in the blood donor and in the recipient following blood transfusion.

Identification of HTLV-III as the basic etiologic (causative) agent of AIDS has opened new avenues to epidemiologic studies of AIDS on a worldwide basis and has provided a plausible, though preliminary and controversial, explanation of the origins and spread of the disease from equatorial Africa to other parts of the world (12,120). AIDS cases in Africa have been found in epidemiologic patterns that differ from those in the United States, where AIDS is still occurring predominantly among homosexual and bisexual males. In Zaire, the male-to-female ratio of AIDS cases in one study was approximately 1:1 ***(120);*** and in a study in Rwanda, **9 of 17 patients were female** (170).

HTLV-III is probably already prevalent in the general population of some African countries. In Uganda, antibodies to HTLV-III have been found in preserved sera collected in 1973 of 65 percent of 65 children of approximately 6 years of age (131), although there have not yet been any reported AIDS cases from Uganda. Sera collected in ***1980*** from 100 Zairian mothers used as a control group to compare HTLV-III-antibody-positivity with that of known AIDS patients were positive for HTLV-III in five cases, and at least one AIDS case may have occurred as early as 1977 (26). A study of female prostitutes in Rwanda has found approximately 20 percent to have antibodies to HTLV-III (16).

Finally, a study among 250 outpatients in a hospital in rural Zaire found that 12.4 percent had antibodies to HTLV-III (12). The presence of antibodies was higher in children than in adults. One researcher's hypothesis about the reason for the difference in positive antibody rates between the younger and older patients is as follows. When the older patients were younger, the incidence of positive antibodies among them and their peers was higher and probably similar to that of the younger patients. However, over the years, some of the older patients' peers with positive antibodies died of unrecognized AIDS, probably of opportunistic infections such as parasitic diseases, which would not have been distinguished from primary parasitic deaths in rural areas. A further hypothesis is that HTLV-III was probably endemic in rural areas and entered the urban population only recently with the immigration of persons from rural to urban areas. Alternatively, a related and cross-reactive virus that is distinct and does not cause AIDS could account for their rural pattern of antibody positivity (16).

Another factor to consider in searching for the origins of AIDS is that HTLV-III has been shown to be more similar morphologically and by the nucleotide sequence of its genes to an animal

retrovirus known as "visna" virus than it is to the other two members of the HTLV family, HTLV-I and HTLV-II (63). Visna virus causes a chronic degenerative disease of the central nervous system in sheep and belongs to a subfamily (Lentiviruses) of retroviruses that infect ungulate (hoofed) mammals, particularly domestic sheep, goats, cattle, and horses. (Findings described earlier that HTLV-III can infect the brain (135) provide further evidence of a relationship between HTLV-III and the Lentivirus subfamily of retroviruses.) Thus, HTLV-III might have been initially transmitted from domestic ungulates, and the epidemiologic evidence from central Africa provides a clue as to when and where that initial transmission might have taken place.

The contribution of a number of cofactors—i.e., factors or agents which are necessary for or which increase the probability of the development of disease in the presence of the basic etiologic agent of that disease—to the actual development of AIDS is also being investigated in epidemiologic and other studies. Results of animal studies and studies of the prevalence of HTLV-III antibodies and virus in humans suggest that not everyone exposed to HTLV-III virus develops fulminant AIDS. Thus, it is assumed that other factors may play a role in making people susceptible to development of the disease, primarily through alterations of the immune system. There are a number of hypotheses about what these risk factors might be. Factors currently under investigation in U.S. populations include the following ***(8,35,95,110,138,165/173):***

- presence of cytomegalovirus;
- presence of Epstein-Barr virus;
- presence of other herpes viruses;
- exposure to hepatitis;
- iatrogenic effect of steroids and other medicines (e.g., psychoactive drugs);
- use of alcohol and other recreational drugs (e.g., heroin, cocaine, marijuana, methadone);
- cigarette smoking;
- antigenic stimulation as a result of various sexual practices;
- ethnicity;
- particular underlying diseases; and
- psychosocial risk factors (e.g., life satisfaction, self-esteem, depression, coping mechanisms, sense of control, social support, stress).

The resources that PHS is devoting to the investigation of cofactors are discussed below in the section entitled "How Adequate Are PHS's Resources Devoted to AIDS?"

Treatment Protocols

The development of effective treatments for AIDS is urgent, as there is already a serious worldwide epidemic, By the end of 1984, the total number of U.S. AIDS cases that had been reported to the Centers for Disease Control (CDC) was approximately ***7,000;*** and the number of reported cases has been doubling every year—almost 900 cases prior to December 1982, more than ***2,000*** cases in 1983, and about ***4,000*** cases in 1984. Seventy-three percent of AIDS patients diagnosed before January 1983 have died ***(157).*** Furthermore, extrapolations from trends in the incidence rate of AIDS ***(67)*** suggest that an additional ***40,000*** new cases can be expected in the United States in the next 2 years (125). There have already been over 500 cases in the rest of the Americas, 600 in Europe, and several thousand in central Africa (125).

Approaches for treating patients with AIDS include the following:

- treatment for opportunistic infections and cancers;
- reconstitution of the immune system through bone marrow transplants and lymphocyte transfusions;
- immunologic enhancement with T-cell growth factor (TCGF), interferon, and immunoregulatory agents such as isoprinosine and imuthiol; and
- agents directed against the HTLV-III virus itself ***(84).***

Prior to the discovery of HTLV-III, treatment was directed at the specific opportunistic infections and malignancies associated with AIDS. Treatment of the immune deficiency itself proceeded along two fronts: 1) attempts to restore

immune functions; and 2) the use of known antiviral agents, on the presumption that the epidemiologic pattern of AIDS pointed to an infectious agent, most likely a virus.

Although the discovery of HTLV-III has not affected treatment protocols for associated opportunistic infections and malignancies, it has affected treatment protocols for the underlying immune deficiencies associated with AIDS. Early treatment methods for immune deficiency involved the use of general antiviral agents (e. g., gamma interferon) and attempts to restore immune functions through methods such as lymphocyte transfusions and administration of TCGF (also known as interleukin-2). These "shotgun" methods were not successful. Which antiviral agents would be effective and when they should be administered were not known, The timing of the administration of antiviral agents is probably crucial since they may have to be administered before HTLV-III invades cells. Lymphocyte transfusions were analogous to pouring water in a leaky bucket (since the virus would destroy these cells), and TCGF stimulated T cells, a condition now known to enhance T-cell infectivity by HTLV-III.

With the discovery of HTLV-III, more specific therapeutic approaches are now possible. First, the availability of HTLV-III cell cultures makes possible an in vitro test of possible anti-HTLV-111 drugs. One such drug, suramin, has been shown to protect T-lymphocyte cell cultures against the cytopathic effects of HTLV-III through inhibition of the reverse transcriptase of HTLV-III ***(23)*** and is undergoing limited clinical trials at NIH. Another drug, ribavirin, a general antiviral agent, has also been shown to inhibit HTLV-III in vitro (99). Finally, French investigators report that they have tested another chemical, HPA-23 (heteropolytungstate, an inorganic cryptate), which inhibits the reverse transcriptase enzyme of murine (mouse) retrovirus in vitro and in vivo. Four patients, three with AIDS and one with lymphadenopathy syndrome, have been treated with ***HPA-23,*** and virus replication has been inhibited, though not completely (106).

Strategies directed at the virus itself can also encompass more than inhibition of reverse transcriptase activity. Eventually, it might be possible to use antibodies against HTLV-III to prevent or modulate infection (passive immunization). Moreover, since HTLV-III invades cells, antibody infusions will probably have to be used before or at the time of initial infection, perhaps in conjunction with a vaccine to confer more permanent immunity (if such a vaccine proves possible). When passive immunization would be most propitious is not known, but the epidemiologic studies now under way may eventually answer this question. Another possibility would be to couple toxins with antibodies against HTLV-III.

Approaches directed at disrupting HTLV-III'S life cycle might take place at the following points: 1) binding of the virus to the target cell surface, ***2)*** entry into the cell, 3) transcription of RNA to DNA (the target of reverse transcriptase inhibitors), 4) integration of the virus into the cell's genes, 5) transcription of DNA to RNA (in preparation of the virus's replication and release from the cell), ***6)*** transfer of the virus to the cell surface, and 7) disruption of the cell and release of the virus (180). Studies described earlier, which showed that the T4 molecule on T4 lymphocytes was necessary for HTLV-III to infect the cell, used monoclinal antibodies against the T4 molecule to see if binding of HTLV-III to the T4 lymphocyte would be blocked (39,81). This blockage was in fact shown and might constitute a possible method of inhibiting infection by HTLV-III. Whatever the mode of attack against the virus, successful therapy depends on whether or not infected cells die in a short period of time and on whether there is a regenerative capacity of T cells. It is not realistic to expect that all of the virus will be eradicated. Therefore, the hope is that the immune system can handle a minimum of infection, and lifetime treatment against the virus may be needed (180).

Finally, attempts at reconstitution of the immune system ***(85)*** may be more successful if done in conjunction with specific agents against the HTLV-III virus.

Animal Models

Chimpanzees have been successfully infected with the AIDS virus and have developed immunologic abnormalities and lymphadenopathy, but

no opportunistic infections or tumors characteristic of AIDS (2,52,53,54,155). Other possible animal models are being screened by testing for the effect of HTLV-III on the animals' T lymphocytes in cell cultures.

At NIH, prior to the discovery of the AIDS virus, three chimps were sequentially infused with plasma from three different patients with lymphadenopathy syndrome, Kaposi's sarcoma, and life-threatening opportunistic infections, respectively. Two chimps developed antibodies to HTLV-III (specimens were stored and subsequently tested when an HTLV-III test became available), and one of the two chimps developed a transient severe lymphadenopathy 26 weeks after inoculation, which persisted until 58 weeks after inoculation ***(2).*** At CDC, two chimps were inoculated with concentrated HTLV-III and autologous lymphocytes that had been infected in vitro. The virus has been found to grow and persist in the chimpanzees' lymphocytes, and the chimps have produced antibodies to the virus; however, neither chimp has developed any clinical illness or lymphadenopathy (52). In another study using tissues and plasma from AIDS patients, chimpanzees were similarly infected and antibodies produced. Infection and antibody production also occurred in chimps inoculated with whole blood from chimps previously infected and shown to have produced antibodies. Except for one infant chimpanzee which died 5 months after inoculation (cause of death under investigation), all 23 of the inoculated chimps have remained clinically well for periods of between 2 and 15 months (53,54). These chimpanzee inoculation studies, in addition to having promise as an animal model, may indicate that AIDS is not an inevitable consequence of HTLV-III exposure or even infection.

Primates other than chimpanzees, including rhesus, stumptailed, cynomolgus, and bonnet macaques, the capuchin, the squirrel monkey, and the patas monkey, have also been inoculated with HTLV-III. Rhesus monkeys have recently been shown to undergo infection by HTLV-III, but have not produced antibodies and have remained clinically well (48,53,54). Other animal species that might serve as animal models are being screened before inoculation studies are initiated. Lymphocytes provided by the National Institute of Allergy and Infectious Diseases (NIAID) from 25 animal species are being studied in cell cultures by NCI to see if they can be infected by the virus. In the case of those which are successfully infected in vitro, the animals themselves will be inoculated (121).

WHAT ABOUT EFFORTS TO DEVELOP AN AIDS VACCINE?

In general, "live" vaccines produce better immunity because of prolonged stimulation from viral reproduction. Noninfectious "inactivated" vaccines, on the other hand, require frequent booster shots. Noninfectious vaccines can be made either from whole inactivated organisms or from parts ("subunits") of the organism that have antigenic properties which stimulate immunity. Neither live virus vaccines for AIDS nor whole inactivated preparations containing the genetic material of the AIDS virus currently hold much promise: 1) because it is not known what constitutes an "inactivated" virus in the case of HTLV-III; and 2) because the genetic structure of HTLV-III contains segments that may cause cancer by activating normal cellular genes involved in the initiation of tumors. Thus, only "subunit" vaccines against AIDS are under serious investigation, albeit through a variety of methods including the use of live viruses other than HTLV-III.

When a foreign organism invades the body, several different antibodies are produced, each directed at specific subunits of the organism that the body's immune system recognizes as different antigens. Only some of these antibodies will be directed at subunits of the organism that are crucial to the organism's life cycle. "Subunits" that stimulate the production of neutralizing or protective antibodies are necessary to produce an effective vaccine. Such subunits are usually the proteins that make up the "envelope" (external coat),

as opposed to the "core" of the virus. One way to determine which antigenic subunits may produce a protective antibody response is to produce antibodies against individual antigenic subunits and determine whether these antibodies neutralize infectious virus in cell cultures (in vitro testing).

The three-dimensional structure of a viral antigen is probably crucial for eliciting the proper antibody response; i.e., without the proper three-dimensional configuration of the viral antigen as it appears on the whole virus, antibodies would be produced against a viral subunit, but might not "fit" the viral antigen as it actually appears on the whole virus and therefore might not inactivate the virus. After they are synthesized, envelope proteins have carbohydrate molecules attached to them which help to determine their three-dimensional structure. (This modification is referred to as "post-translational modification, " and the attachment of a carbohydrate molecule to the protein molecule is called "glycosylation.") Thus, HTLV-III subunit proteins produced for use as vaccines may need to be glycosylated or treated by some other method to approximate the three-dimensional configuration of the virus's original subunit.

Relevant to the possible development of a vaccine to protect against HTLV-III is the experience with a vaccine against feline leukemia virus. Feline leukemia virus attacks T cells in cats and can cause either immunosuppression or cancer. There are three subgroups of the virus, one of which does not occur naturally but develops in cell cultures when either of the two naturally occurring types is cultured. All three subgroups produce an envelope glycoprotein of the same molecular weight (gp70), but each subgroup's glycoprotein is structurally distinct from the others.

The first experimental vaccines for feline leukemia virus used either the inactivated viruses themselves or the T-cell tumor cultures infected with the viruses. Both types resulted in immunosuppression in cats because of the presence of p15E (an envelope protein with a molecular weight of ***15,000).*** Another feline leukemia vaccine was developed by altering the culture medium in which the virus-infected T cells were grown; the incomplete viruses or fragments that resulted proved to be about 90 percent protective against the virus in cats themselves. The envelope proteins produced by this method were: 1) the gp70s of the three subgroups of feline leukemia virus, which neutralized the virus in vivo and prevented viremia; and 2) another protein (FOCMA, or feline-oncornavirus-associated cell membrane antigen) formed by lymphosarcoma cells infected with the virus, which prevented solid tumor formation. FOCMA maybe identical to or immunologically similar to the gp70 of the nonnaturally occurring subgroup of the feline leukemia virus. Field trials of this subunit feline leukemia vaccine are being completed, and the vaccine may be available sometime in 1985 ***(44).***

Experience with the subunit feline leukemia vaccine is relevant to the development of an AIDS vaccine because: 1) HTLV-III may contain subunits that may be detrimental to the patient; and 2) if there is a subunit that elicits protective antibodies, it is likely to be a high molecular weight envelope glycoprotein. Of the several protein subunits in HTLV-III, natural human HTLV-III antibodies predominantly recognize an antigen of ***41,000*** molecular weight (p41). This observation has led to opposing preliminary conclusions by researchers. On one hand, some researchers have suggested that p41 may be of use for prophylactic measures in persons at risk for AIDS (71). However, antibodies to p41 can be found in all AIDS cases, even when different isolates of the HTLV-III virus have been identified. Antibodies to p41 may therefore be a good diagnostic indicator of infection with HTLV-III, but p41 may not be the antigen for vaccine development. Another suggestion, therefore, is that a more specific antigen needs to be identified and that places to look for antibodies might include lymphadenopathy patients who get better; selected long-term partners of AIDS patients who are well; hemophiliacs, many of whom have high positive titers of antibodies to HTLV-III; and patients with only Kaposi's sarcoma and no opportunistic infections ***(48).***

NIH has taken the lead in developing an AIDS vaccine, at both NCI and NIAID. NIAID would usually be the primary institute involved in vaccine development, but in the case of AIDS, NCI

has the most experience with human retroviruses. Vaccine development is being pursued both intramurally and through extramural funding of non-Federal researchers.

NIH is conducting both supportive and direct activities related to vaccine development (55). Supportive activities include: 1) large-scale production of HTLV-III to characterize its various antigens and immunogenic properties (and to provide adequate quantities of virus for other activities); and 2) isolation and characterization of the virus's envelope proteins. Related activities include the development of an animal model to test the efficacy of future vaccine candidates, as well as epidemiologic and serologic investigations of the natural history of AIDS to determine whether or not protective antibodies exist, when in the natural history of AIDS such antibodies appear, when a vaccine would have to be given, etc. Several activities directed at vaccine development at NIH are discussed further below.

Subunit Vaccine From Cultured Virus

Viral proteins can be produced either by breaking up whole virus or by changing the conditions under which the virus is grown so that greater amounts of specific viral fragments may be preferentially produced. The latter technique has been used to produce a new subunit vaccine against feline leukemia virus and could be used to produce an AIDS vaccine. The feline leukemia vaccine and associated hazards were discussed above.

Recombinant DNA Vaccine

An alternative to using whole virus as a source of a subunit vaccine is to use recombinant DNA techniques to make a vaccine. Once the gene(s) for the viral protein(s) is identified, it is (they are) cloned and inserted into bacteria, yeast, or mammalian cells, which then produce the protein(s).

The genes for several proteins (p41, p55, and p54) of unknown specificity from at least three different isolates of HTLV-III have already been cloned and inserted into bacteria and yeast (55). One hypothesis is that the glycosylated envelope proteins gp120, gp100, and gp46 are the most likely candidates for an AIDS vaccine (74).

Mammalian cells and, to some extent, yeast cells (but not bacterial cells) have the ability to glycosylate (add carbohydrate molecules) to these proteins and are the favored method of synthesis for subunits that need post-translational modification. (The Merck Institute for Therapeutic Research at West Point, Pennsylvania, for example, is close to licensing a vaccine for hepatitis B that uses yeast-cloned hepatitis B virus surface antigen (101), and Biogen plans to begin human clinical trials for a similar vaccine in early ***1985 (13).)***

A related method of preparing an AIDS vaccine would be to synthesize the viral proteins directly, based on the nucleotide sequences of their genes. It is now known which nucleotide sequences code for each of the 20 amino acids from which all proteins are made. To obtain the proper three-dimensional configuration, however, glycosylation or other methods would probably be needed.

Infectious Recombinant Vaccine

If the gene(s) coding for the proper subunit of HTLV-III could be inserted into other viruses that are not harmful to humans, these viruses themselves could then be used in vaccinations. The result would be a live vaccine with more sustained antibody production than an inactivated vaccine but without the hazard of using live, whole HTLV-III virus for continual stimulation of antibody production.

The vaccinia virus (which has long been used to vaccinate against smallpox) has already been used for the insertion of genes from a number of viruses and one parasite, including hepatitis B (111,137), rabies (78), herpes simplex, influenza viruses, and "malaria. The recombinant vaccinia virus has been shown to be capable of producing rabies virus glycoprotein; i.e., following insertion of the gene for the rabies envelope protein, the vaccinia virus (which propagates in the cytoplasm of infected cells rather than in the nucleus) not only can produce the rabies envelope protein but also adds carbohydrate molecules to the protein, resulting in production of a rabies glycoprotein that produces protective antibodies ***(78).*** Some of these infectious recombinant vaccines have been tested in animals but not in humans.

Much of the work on recombinant vaccinia virus has been done by researchers at NIAID and their collaborators, and work with HTLV-III genes in vaccinia virus is being conducted through NIAID. Meanwhile, NCI has also issued requests for proposals for the development of human recombinant viruses other than the vaccinia virus. One reason is that many people have been previously exposed to the vaccinia virus through smallpox vaccinations, and if revaccinated with an HTLV-III-gene-containing vaccinia virus, their antibody-producing responses would be short (anamnestic rather than primary responses). Possible alternatives to the vaccinia virus are the adenoviruses, and NCI reports that William Jarrett, the discoverer of feline leukemia virus, is interested in examining antibody production in dogs with a dog adenovirus in which HTLV-III genes would be inserted. Another possibility would be to use herpes viruses (48).

Anti-Idiotype Vaccine

Contact between an antigen and an antibody can be envisioned as a precise fit between two pieces of a three-dimensional puzzle. If a second antibody were made against a particular antigen's antibody (the "idiotype"), the second antibody (the "anti-idiotype") would have a part that mimics the part of the antigen that was in contact with the first antibody. And if the first and second antibodies came from the same animal species, they would differ only in that part which comes in contact with the antigen; the rest of the molecules of these antibodies would be identical. Therefore, the anti-idiotype, when used as a vaccine in the animal species from which it was derived, would elicit an antibody response only to that part which was identical to the original antigen.

In addition to the specificity of the elicited antibody response, the fact that this anti-idiotype vaccine would consist mostly of a molecule that would be recognized as "self" would mean that it would not be removed from the body as quickly as it would be if the antibody had come from another animal species. Therefore, if such a vaccine were made with human monoclinal antibodies, it would be present in the body for a longer period and produce more of an immune response. Furthermore, since no part of the anti-idiotype would have been made from the actual virus (either from the whole virus or from its genes through recombinant DNA methods), there would be no possibility of infection from the virus or its products.

An experimental anti-idiotype vaccine has been developed in mice against reoviruses (another family of RNA viruses), and the researchers are now applying their methods to HTLV-III (182). Successful immunization of mice against the bacterium ***Streptococcus pneumonia*** with an anti-idiotype vaccine has also recently been reported (100).

Prospects for a Successful Vaccine

A subunit vaccine, made through purification from whole virus, special culturing techniques, or through the use of recombinant DNA technology is the most likely vaccine candidate to be first available. However, it ***is*** not known at this time whether an effective vaccine against HTLV-III can be made. The virus has only recently been discovered, and investigations into the relationship of the natural history of the disease with specific immunologic responses, which may answer the questions of whether or not protective antibodies exist and under what circumstances, have just begun.

An additional question for vaccine development is the variation among the different isolates of the HTLV-III. In contrast to HTLV-I, which has been found to have only a few minor variations despite its worldwide distribution, HTLV-III isolates have been found to have many variations. Variations have been observed in the sequences of the nucleotides that make up the genes (1,23,66,91). These imply either a large number of subtypes or the possibility of sequential mutations analogous to some animal retroviruses. As noted earlier, HTLV-III is related to visna virus, an encephalitis-inducing retrovirus of sheep, which can change its envelope proteins antigenically ***(63). On*** the other hand, no heterogeneity has been seen so far in a given HTLV-III isolate, nor has heterogeneity developed in culture. Most of the heterogeneity is seen in the genes coding for the envelope pro-

42-575 0 - 85 - 3

teins, and it is not yet known whether the genetic heterogeneity results in significant antigenic differences (178),

An emerging issue is the question of who might benefit from a vaccine. Testing of high-risk groups for exposure to HTLV-III has shown a rapid increase in the percentage of persons exposed-up to ***65*** percent for some groups of homosexual and bisexual males (154), nearly ***90*** percent in some intravenous drug abusers (141), and up to ***90*** percent of hemophiliacs who regularly use Factor VIII concentrates ***(43,60,79).*** On the other hand, cases of heterosexual transmission and transmission between family members are being reported (28,86,126), and the disease transmission pattern in central Africa appears different from that in the United States, with relatively more female patients in central Africa and significant rates of the presence of antibodies to HTLV-III in the general central Africa population (12,120,170). Furthermore, since HTLV-III has now been isolated from semen and saliva (65,73,181), the population at risk may change or may include more groups those than currently identified in the United States.

One way that AIDS may get into the general population is through female prostitutes. Seventeen of sixty-five AIDS cases not known to belong to any risk group are now known to have had frequent contact with prostitutes. There are approximately ***200,000*** drug abusers undergoing treatment in public clinics at any one time, totaling about 400,000 over the course of a year. This number excludes about 1.5 million drug abusers who are in private treatment or who are occasional users. About ***20*** percent of female drug abusers resume drug use within 1 year after treatment in methadone clinics, and about 31 percent of female drug abusers admit to prostitution. Thus, female drug abusers are habitual users and many are very active sexually (in part to support their addiction). U.S. cities with large numbers of drug abusers and where AIDS is most prevalent include New York, Miami, San Francisco, and Los Angeles, which are also popular tourist areas, hence intensifying the probability of spread through female prostitutes ***(62).***

Finally, there is the question of the private sector's interest in developing and marketing an AIDS vaccine. There has been great interest by the private sector in developing and marketing blood tests for HTLV-III, but the technical difficulties involved in developing and producing an effective and safe vaccine, and product liability issues concerning vaccine-related injuries may make an AIDS vaccine much less attractive commercially than the markets for screening and other diagnostic tests for AIDS. Although the private sector seems interested in all AIDS-related products, it remains to be seen whether the interest generated in the marketing of a blood test will carry over into the vaccine area. If an AIDS vaccine proves feasible, the Federal Government may need to assume production activities in addition to the development activities it is currently undertaking,

HAS THE DISTRIBUTION OF NEW INFORMATION AMONG RESEARCHERS AND REGULATORS BEEN ADEQUATE AND TIMELY?

Whether information about AIDS has been generated and disseminated on an adequate and timely basis has been an issue of recurrent concern. As the new syndrome, later to be called AIDS, began to surface, there was relatively fast coordination and dissemination of information among PHS agencies and outside researchers. In September 1981, only 6 months after the first clusters of an unusual syndrome involving Kaposi's sarcoma and ***Pneumocystis carinii*** pneumonia were reported to CDC, NCI and CDC cosponsored a workshop on AIDS at which a significant amount of information about the syndrome's epidemiology and virology was shared with 50 intramural and extramural participants ***(164).*** In the intervening months, CDC, NCI, and NIAID researchers had

begun to reorient some of their intramural research, and the first patients with the syndrome had been admitted into NIH's Clinical Center.

Since 1981, individual researchers and PHS agency managers have coordinated the dissemination of information about AIDS in a variety of ways. PHS units other than CDC, NIAID, and NCI began to be involved as more became known about the disease. Most, if not all, of the PHS institutes and agencies have had internal working groups or committees meeting on AIDS with varying levels of intensity depending on research developments. In addition, there have been numerous interagency meetings and conferences on AIDS, attended by PHS researchers and PHS-funded grantees. The Assistant Secretary for Health, PHS, arranged for journals to expedite their review process so that AIDS research results could be published more quickly. NIAID took the lead in publishing the ***AIDS Memorandum,*** a compilation of nonreviewed research on AIDS, and an AIDS bibliography to speed up the dissemination of information to researchers. Furthermore, interagency task forces have worked on developing recommendations on blood donation (153) and on the blood test for HTLV-III (159).

At the PHS management level, former Assistant Secretary for Health Edward Brandt established a PHS Executive Committee on AIDS in May 1983 (21). The committee was chaired by an individual from CDC (not chosen to be a CDC representative per se) and had representatives from all five PHS agencies: CDC, NIH, the Food and Drug Administration (FDA), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), and the Health Resources and Services Administration (HRSA). The committee's function was to coordinate PHS efforts, but in practice, the committee served primarily as a way in which PHS's central management was apprised of progress in AIDS research.

With the announcement of the findings of NCI's work on HTLV-III in April 1984, Assistant Secretary Brandt reconstituted the PHS Executive Committee into the AIDS Executive Task Force, chaired by him, for the following purposes:

- to develop and implement a strategy for PHS efforts in AIDS;
- to determine and allocate the resources required to accomplish the strategy; and
- to develop policies and procedures for informing the public, Congress, and the scientific community about PHS's efforts.

Three panels were established to accomplish these purposes: 1) a science panel, 2) a resources panel, and 3) an information panel (18). In September 1984, four specific task forces ***were*** also established: 1) one on vaccine development and therapeutic intervention, chaired by the Director of NIH with representatives from NIH, CDC, and FDA; 2) one on epidemiology and prevention, chaired by the Director of CDC with representatives from CDC, NIH, FDA, and ADAMHA; **3) one on blood and blood products, chaired by the Director of FDA's Center for Drugs and Biologics with representatives from** FDA, NIH, CDC, and ADAMHA; and 4) one on psychological, psychiatric, and addictive aspects, chaired by a representative from ADAMHA with representatives from ADAMHA, NIH, CDC, and FDA. The Science Advisor to the Assistant Secretary for Health was designated the PHS coordinator of these task force activities. The Science Advisor also coordinates the private sector production of the blood test for HTLV-III and chairs committees concerned with animal studies, bioethics, and biosafety, and the utilization of the blood test (21).

The PHS task forces and committees continue to meet on a regular basis. Since the discovery of the probable AIDS etiologic agent, formal information-sharing activity on a management level has increased substantially, and centralized coordination of activities is also on the increase. Members of the Epidemiology and Prevention Task Force not only have agreed to distribute articles prior to publication, but have also agreed to discuss studies at the planning stage **(96) in order to avoid unnecessary redundancies and to ensure that all the necessary areas are being** covered. The Task Force on Psychological, Psychiatric, and Addictive Aspects is discussing participation by the National Institute of Mental Health (NIMH) in the NHLBI study of blood donors (138). As before, however, information sharing among individual laboratories and researchers continues both formally (e.g., HTLV Symposium, Dec. 6-7, 1984 (161)) and informally.

The Office of Technology Assessment (OTA) has identified five factors which may have impeded the generation and dissemination of new information about AIDS. First, NCI has not fully shared HTLV-III supplies with CDC, perhaps slowing the comparison of LAV and HTLV-III. Second, the announcement by the Secretary of the Department of Health and Human Services (DHHS) Margaret Heckler of NCI's discovery of HTLV-111 provided overly optimistic assessments concerning the usefulness of a blood test and prematurely committed the Federal Government to require use of the test for antibodies to HTLV-III in blood and plasma collections. Third, in the context of a public health emergency, the grant application and approval process for extramural research works slowly. Fourth, Federal regulations covering commercial development of drugs, biologics, and devices mean that much information is not subject to full public scrutiny. Finally, the coordination of PHS resources could be improved, as discussed in the section below entitled "How Adequate Are PHS's Resources Devoted to AIDS Prevention and Treatment?"

NCI and CDC Sharing of HTLV-III Culture Samples

At about the same time that the Assistant Secretary for Health established the first PHS Executive Committee on AIDS in May 1983, the Director of NIH established an NIH Coordinating Committee. Part of the reason for establishing the NIH Coordinating Committee was that CDC and NIAID were collaborating with the French researchers who had just published findings implicating a new virus they called "lymphadenopathy-associated virus" or LAV (7) as the cause of AIDS, but neither CDC nor NIAID was aware of similar work that had been going on in NCI's Laboratory of Tumor Cell Biology under Dr. Robert Gallo (179).

CDC had received samples of LAV from the French researchers in May 1983 (the month in which their findings were published) and again the following month, but had not been able to culture it. In February 1984, CDC again received the virus from the French researchers, and this time, CDC was able to culture it (38). In late April 1984, DHHS Secretary Heckler announced the discovery of HTLV-III and prospects for a blood test and vaccine (70). Gallo and his coworkers had their results published in May 1984 and sent CDC their cultures later that month. CDC had difficulty growing the cultures in bulk and asked for more culture materials from the PHS Science Advisor, who was coordinating the production of the blood test for HTLV-III and arranging for transfer of large amounts of HTLV-III cultures to the commercial companies who would develop the blood test. Subsequently, CDC was given a small, but in its view insufficient, additional amount. At the end of 1984, CDC signed a purchase agreement with NCI for 100 liters of material (38).

One consequence of CDC's use of the French instead of the NCI virus cultures was that the research papers published by CDC and their collaborators, in which evidence of the AIDS virus was presented, referred to "LAV" instead of to "HTLV-III." This situation might have been avoided, and comparisons of the "LAV" and "HTLV-III" isolates might have taken place sooner, if PHS had arranged for sharing of NCI culture materials with CDC with as much attention as PHS has given to transferring bulk quantities of the cultures to the five commercial firms developing blood tests for AIDS under NCI's license.

DHHS Announcement of the Discovery of HTLV-III

The announcement by DHHS Secretary Heckler in April 1984 of the discovery of HTLV-III was a dramatic and extremely positive assessment of the implementation of NCI's research into the HTLV-III virus (70a). The announcement called AIDS "a disease with two names," the other name being "Fear," announced that an "arrow" had been aimed and fired at AIDS and had hit the target "only two or three rings away from the bulls-eye, " and concluded that "(y)et another terrible disease is about to yield to patience, persistence and outright genius. "

Secretary Heckler's announcement indicated that a blood test could be widely available within about 6 months and that a vaccine might be ready for testing in about 2 years, and most attention

has focused on these two developments. In addition, however, Secretary Heckler committed the Federal Government to the use of the blood test in screening blood and plasma donations. The Secretary's announcement indicated that the blood test could "identify AIDS victims with essentially 100 percent certainty" and thus should prevent transfusion-related AIDS, including AIDS in hemophiliacs. The announcement also indicated that the blood test would allow prompt and early diagnosis of people who may have been infected by HTLV-III.

In trying to reassure the public of progress against AIDS, Secretary Heckler appears to have been too optimistic regarding the use of the blood test to screen for possible AIDS carriers. The Secretary's announcement also did not take into account the social implications and ethical dilemmas that would have to be addressed when persons who might be carriers of HTLV-III were identified through a blood test.

As mentioned earlier in this memorandum, it is now known that the blood test for antibodies to HTLV-III will not detect all persons exposed to the virus, because some persons who have the virus in their blood do not produce antibodies and can also be symptom-free (129). Furthermore, studies of hemophiliacs for antibodies to HTLV-111 have shown that most hemophiliacs have already been exposed to HTLV-III *(43,60);* thus, only new hemophiliacs (and the minority of present hemophiliacs not yet exposed) will benefit from blood and plasma screening.

Aside from these limitations of the blood test are the difficult issues of what to tell persons who are found to have antibodies to HTLV-III and who should have access to lists of HTLV-III antibody-positive persons. In July 1984, the New York State Council *on* Human Blood and Transfusion Services advised the New York State Health Commissioner that mandatory testing of blood donors for viruses associated with AIDS was premature (114). Following this action, the five-member New York City Board of Health, in a resolution approved unanimously on October 17, 1984, recommended that the blood test be given only in the context of controlled research programs which preserve the confidentiality of participants (113a). The Board of Health noted that although the test "provided the opportunity for great scientific strides," unanswered questions mean that the test carries a "threat of mental anguish for those who receive the results." These issues do not seem to have been raised and addressed prior to Secretary Heckler's announcement in April 1984.

Funding of Extramural Research

Another coordination issue is whether or not NIH funding of extramural research on AIDS could have taken place more quickly. The policy question here is not so much whether extramural funding of specific research areas was tardy within the time frame of established processes, but whether the usual processes through which extramural research is funded can and should be accelerated in public health emergencies.

NIH research grants take about *16* months from conceptualization to awards, and contracts take about 14 months. The first round of extramural grants awarded by NCI/NIAID was funded through cooperative agreements (which have been used only in the last 2 years), in which researchers from the funding agency participate to some extent in the research activities for better control of the studies. Almost immediately after the NCI-CDC workshop on Kaposi's sarcoma, NCI's Division of Cancer Treatment, together with NCI's Clinical Division and NIAID, began to develop requests for applications (RFAs) to investigate multiple aspects of AIDS. These RFAs were developed and funds set aside during the first half of 1982, and the RFAs issued in August 1982. Proposals were received in October 1982, and awards were made beginning in January 1983. A second round of RFAs was issued by NCI and NIAID in May 1983, directed at biological agents in AIDS. These RFAs were awarded in March 1984, at about the time (April 1984) that the announcement of the discovery of HTLV-III was made by DHHS Secretary Heckler. (All grantees were contacted to make sure they were aware of Gallo's findings *(29)).* Thus, these grants took a total of *14* months, in part because of negotiations with the Office of Management and Budget (OMB) over the specific language used in the agreements (29).

Some steps have been taken to speed up the normal process. For example, mail balloting has been used instead of face-to-face meetings by reviewers. Or researchers working in relevant areas have had their grants (or contracts) augmented to direct their ongoing research specifically at the AIDS problem. Nevertheless, a period of at least several months is probably still necessary to fund new research projects, given the time needed to conceptualize the problem in researchable terms, to review the work statements, including outside experts such as an institute's advisory body, to allow respondents adequate time to develop and write their proposals, and to evaluate and rank each proposal. In addition, the more the usual process is shortened, the more serious will be concerns over the quality (and therefore, usefulness) of the research activities funded. Nonetheless, the extramural grants process for AIDS research was not significantly accelerated over the usual grants process, and the process needs to be examined to see if bureaucratic processes can be streamlined without compromising the quality of research that is funded.

Federal Policy on Commercial Development

The general policy in this country is to leave the commercial development of technologies, including technologies derived from Federal biomedical research, to the private sector. Once under commercial sponsorship, research and development activities are considered proprietary and will not be made public unless voluntarily released. Under the Federal Food, Drug, and Cosmetic Act, this restriction applies when the sponsor of a new drug has applied to FDA for Investigational New Drug (IND) status to conduct clinical investigations. Thus, for example, FDA cannot divulge even the protocols being used by the five companies under license from NCI to develop AIDS screening tests to Federal researchers not directly involved in these activities; FDA is also enjoined from discussing when such trials will be completed and marketing approval granted. Federal researchers, on the other hand, will generally share their research, including their research materials, their primary concern being the qualifications of the private researchers and the quality control processes they have established (e.g., whether or not their laboratory facilities meet standards for containment of infectious agents).

In the case of AIDS, the sharing of information developed by commercial firms was enhanced in small part because PHS selected the companies that would get the HTLV-III culture developed in the NCI laboratory. Thus, for example, Dr. Gallo met with the five companies soon after they received the materials to discuss their use. However, other laboratories have cultured the virus and sold or given it to companies other than the five selected by PHS, and the status of those companies' activities is formally unknown to any Federal researcher except at FDA. As an illustration, a company (Cellular Products of Buffalo, New York) not among the five licensees of NCI may be among the first companies to market an HTLV-III test; and another company (Centocor of Malvern, Pennsylvania) claims to be the first to successfully express polypeptides (small proteins, presumably antigenically similar to proteins of HTLV-III) specific to antibodies to HTLV-III and has filed a patent on the method of production (14).

Conclusion

The involvement of multiple organizations in similar research activities that are addressed at different aspects of a common problem is arguably the best scenario for research. However, this scenario means that researchers are constantly striving to keep abreast of the work of others. In addressing the problem of AIDS, information has been shared through the informal networks that exist among PHS agencies and among their researchers. This sharing has been augmented by coordinating committees, external advisory committees, conferences, and cooperative agreements on funding extramural research and conducting intramural research.

Although most of these sharing and coordinating activities would have taken place regardless of any directive from PHS central management, there have been instances in which PHS (or departmental level) guidance could have led to better coordination. PHS might have directed NCI

to share virus culture with CDC, and Secretary Hecklerfs announcement of the discovery of the etiologic agent for AIDS could have been more restrained.

Other possible impediments to the generation and dissemination of information are matters of more generalizable policy concerns that can only be raised in this memorandum. A systematic examination both of the methods by which the research grants and contracts process could be accelerated in public health emergencies and of the policy of keeping the research activities of commercial developers confidential may be needed.

HOW ADEQUATE ARE PHS'S RESOURCES DEVOTED TO AIDS PREVENTION AND TREATMENT?

As evidenced by the preceding discussions, PHS has accomplished a great deal with respect to AIDS: PHS grantees "discovered" AIDS as a syndrome; PHS has conducted surveillance of AIDS; and PHS investigators and others have made significant scientific advances, including the discovery of the probable etiologic agent for AIDS. PHS is currently coordinating development of a blood test for HTLV-III antibody; and research on treatment, vaccine development, and the many remaining questions about the natural history of the disease is progressing. It has not always been clear, however, that the amount of support for AIDS activities has been equivalent to the needs identified by PHS agencies (see, e.g., ***146).*** Thus, OTA was asked to address whether PHS has devoted sufficient resources to its AIDS activities.

Resources for AIDS can be examined at two levels: 1) specific funding for AIDS activities, and ***2)*** overall funding for specific PHS agencies. Although funding for AIDS research has been substantial, particularly in fiscal years 1984 and 1985, the history of specific funding for AIDS has been marked by continuing tension among the individual PHS agencies, DHHS, and Congress. Individual PHS agencies have consistently asked DHHS to request particular sums from Congress; the Department has consistently submitted requests for amounts smaller than those suggested by the agencies; and Congress typically has appropriated amounts greater than those requested by the Department. Except when prodded by Congress, DHHS has maintained that PHS agencies should be able to conduct AIDS research without extra funds, by obtaining money from their other activities. However, cutbacks and threatened cuts in overall funding and personnel levels have restricted the ability of affected agencies to redirect resources. The Administration has not pursued the option of seeking an appropriation for the Public Health Emergency Act, which established a revolving fund to be used for urgent government response to public health emergencies (Public Law ***98-49; see 146).***

In large part, PHS agencies' responses to the AIDS crisis have been facilitated by the transfer of money and personnel from other activities. By DHHS directive, the response to AIDS has concentrated on research into the biology of AIDS. Psychological and social factors related to AIDS, the service needs of AIDS patients, and public education and prevention have not been considered funding priorities.

The U.S. budget process has effects on PHS agencies apart from the amount of resources they can devote to AIDS activities. PHS agencies have been unable to plan their activities adequately because they have not known how much funding and staff will be available to them. Furthermore, the uneven distribution of resources has intensified competition among agencies, particularly now that an etiologic agent for AIDS has been discovered and there are many directions for research to take concurrently (e.g., treatment, vaccine development, cofactor research, natural history studies) and several areas in which agencies have overlapping expertise. The distribution of resources to activities not directly involving the etiologic agent remains an issue. Of particular importance is the question of whether sufficient resources are being devoted to the investigation of

factors affecting the transmissibility of AIDS, treatment, public education, and prevention.

Five issues concerning the allocation of funds for AIDS to PHS remain open:

- the extent to which progress in other disease areas has suffered as a result of diversions to AIDS activities;
- the wisdom of limiting the priority status of AIDS primarily to biomedical research;
- the manner in which limited resources can be allocated among agencies;
- the particular problem of personnel ceilings; and
- the extent to which agencies will be able to pursue AIDS work adequately in the face of further cutbacks.

Specific Funding for AIDS Activities

As shown in table 1, Congress has consistently earmarked funds for AIDS activities at a level higher than that requested by the Administration, although not necessarily at levels requested by in-

Table 1.—History of AIDS Funding, Fiscal Years 1982 to 1985 (thousands of dollars)

	PHS agencies' request	President's budget request	Earmarked in congressional appropriate ions and/or actually obligated
Fiscal year 1985:			
President's budget request	$55,242[a]	$60,589[b]	
Proposed budget amendment	35,809[a]	—[d]	$87,356[f]
Estimated funds redistributed	—	—	10,070
Total	$91,051	$60,589	$97,426[b,e]
Fiscal year 1984:			
President's budget request	$39,827[f]	$39,827[g]	$48,345
Supplement to original appropriation	20,076[a]	0	9,475[h]
Estimated funds redistributed	—	—	3,640
Total	$59,903	$39,827	$61,460[i,j]
Fiscal year 1983:			
President's budget request	of	0[k]	
Supplement to original appropriation	N. A.[l]	—	$2,000
Estimated funds redistributed	—	—	26,736
Total	N.A.	—	$28,736[j,m]
Fiscal year *1982:*			
President's budget request	of	0[n]	—
Supplement to original appropriation	of	0[n]	500
Estimated funds redistributed	—	—	5,055
Total	0	0[n]	$5,559[m]

Notes:
a Source: E. N. Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, "(Proposed FY 1984 and FY 1985 Amendment for Acquired Immunodeficiency Syndrome," memorandum to the Secretary of Health and Human Services, May 25, 1964.
b Source: E. N. Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, Washington, DC, letter to Office of Technology Assessment, U.S. Congress, Dec. 20, 1984.
c By subtraction.
d T. be determined, In hearings before the House Energy and Commerce Subcommittee on Health on Sept. 17, 1984, the Assistant Secretary for Management and Budget testified that fiscal year 1965 supplemental AIDS funding would be addressed in connection with the submission of the 1986 budget in February 1985.
e Includes $8350,000 for FDA which cannot be obligated until requested by the president.
f Actual figure not known, but assumed to be the same as the President's budget request.
g Source: U.S. Congress, House Committee on Government Operations, *The Federal Response to AIDS* (Washington, DC: U.S. Government Printing Office, 1963).
h Source: U.S. Congress, House of Representatives, "Making Supplemental Appropriations for the Fiscal Year Ending September 30, 1984, and for Other Purposes, Conference Report 96-977 (to accompany H.R. 6040), Aug. 10, 1964.
i Source: W. H, Little, Office of the Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, Rockville, MD, personal communication, Dec. 28, 1964.
j Amount represents actual obligations, including funds redirected from other activities,
k No request for funds specifically for AIDS was made until May 1983 (U.S. Congress, House Committee on Government Operations, *The Federal Response to AIDS* (Washington, DC: U.S. Government Printing Office, 1963)). As of April 1983, PHS planned to spend $14.5 million on AIDS from existing allocations (U.S. Congress, House Committee on Government Operations, *The* Federal *Response to AIDS* (Washington. DC: US. Government Printing Office, 1983)).
l N.A. = Not available. CDC, but not NIH, identified funds needed, DHHS did not request them. Congress appropriated an additional $2 million for CDC's AIDS research in December 1962 (US. Congress, House Committee on Government Operations, *The Federal Response to AIDS* (Washington, DC: U.S. Government Printing Office, 1963).
m Source: W. H, Little, office of the Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, Washington, DC, Personal communication, Oct. 26, 1964.
n N. request for funds specifically for AIDS was made until May 1983.

dividual agencies. The Administration has maintained that AIDS activities can be funded from overall agency funds supplemented by appropriations initiated by Congress (see, e.g., 70). The Administration has continued to maintain this despite the fact that the special panel for AIDS resources established in the Office of the Assistant Secretary for Health (OASH) investigated and approved the amounts requested by individual agencies.

AIDS was not discovered until March 1981, so in fiscal year 1981, there was, of course, no opportunity for the Administration to request money for AIDS work in its initial budget requests. However, although the need for additional resources was becoming clear in late 1981 and 1982, no requests for funds were made in those years, not even through requests for transfer authorities. In August 1982, Congress appropriated additional funds for AIDS research in fiscal year 1982, primarily for CDC. Again in December 1982, Congress appropriated an additional $2 million for fiscal year 1983 CDC AIDS research, based on material prepared by CDC but not officially presented to Congress (146). The Administration did not acknowledge the need for funds specifically for AIDS until May 1983, when the Assistant Secretary for Health requested the authority to transfer funds across agency lines (19).

More recently, AIDS activities have been considered in the President's budgets, although at lesser amounts than those considered necessary by affected agencies. The Administration's initial budget request for fiscal year 1984 AIDS activities was for $14,461,000, compared to then estimated fiscal year 1983 expenditures of $14,132,000 (145). By August 1983, the expected spending level for fiscal year 1983 had risen to $25 million, but the Administration's official request for AIDS research and surveillance for fiscal year 1984 rose from $14.46 million to $17.7 million, $7.3 million less than expected fiscal year 1983 spending levels (146). Subsequent to congressional hearings, the Administration's request for fiscal year 1984 more than doubled, to $39.8 million (145). In contrast, Congress earmarked $48,345,000 for fiscal year 1984 AIDS research (150). It is not known what the desires of the affected agencies were at that point, but at least $3,045,000 was redirected from other areas to meet the needs of AIDS activities, as shown in table 2.

When the discovery of the agent for AIDS was announced in April 1984, the Assistant Secretary for Health asked PHS agencies to reevaluate the needs of their AIDS activities, for both fiscal years 1984 and 1985. On the basis of the agencies' reevaluations, which were assessed for reasonableness by the newly formed PHS AIDS Resources Panel, Assistant Secretary Brandt forwarded a memo to Secretary Heckler requesting a total supplemental appropriation of $20,076,000 and 4 full-time equivalents (FTEs) for fiscal year 1984 and a budget amendment of $35,809,000 and 37 FTEs for fiscal year 1985 (20).

The Assistant Secretary's requests were not forwarded to Congress by the Department, although several Members of Congress received copies of Assistant Secretary Brandt's memo. Instead, DHHS Secretary Heckler directed Assistant Secretary Brandt to use "resources currently available to the Public Health Service" and to review the funding status of AIDS after the passage of the second supplemental appropriations bill for 1984 and the regular appropriations bill for 1985 (70). The Secretary noted that PHS had been able to increase spending for AIDS by about $2.5 million over the funding levels in the fiscal year 1984 DHHS appropriations act, implying that funds were available in the agencies.

Despite the Department's inaction, Congress passed a supplemental appropriations bill in 1984 that included $9,475,000 for AIDS research. This was about half the amount initially requested by the affected PHS agencies (see table 3).

The President's initial budget request for AIDS for fiscal year 1985 was $55,242,000 (150). No changes were made in allocations to the various PHS agencies as a result of the discovery of the etiologic AIDS agent. (As discussed below, funds were redirected within agencies as a result of the discovery of the AIDS agent.) Table 4 compares the President's budget request for PHS agencies' AIDS activities for fiscal year 1985 and the amounts suggested by Congress in its final appropriation (Public Laws 99-473 [Continuing Resolution] and 98-619 [Appropriations]).

Table 2.--PHS Agencies' Estimated Obligations for AIDS Activities in Fiscal Year 1984

Agency	(1) Estimated obligations	(2) PHS estimate of funds redirected (included in column 1)
Centers for Disease Control (CDC)	$13,750	
Food and Drug Administration (FDA)	798	$398
National Institutes of Health (NIH):		
National Cancer Institute (NCI)	***16,627***	2,150
National Heart, Lung, and Blood Institute (NHLBI)	***4,871***	154
National Institute of Dental Research (NIDR)	***81***	—
National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)	1,510	145
National Institute of Allergy and Infectious Diseases (NIAID)	19,616	198
National Eye Institute (NEI)	60	—
Division of Research Resources (DRR)	1,356	—
Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA)	2,791	—
Health Resources and Services Administration (HRSA)	—	—
PHS total	$61,460	$3,045

Notes:
[a] Includes supplemental appropriations and $3,045 million redirected; Source: E. N. Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, Washington, DC, letter to Office of Technology Assessment, U.S. Congress, Dec. 20, 1984.
[b] Source: M. Gonzales, Public Health Service, U.S. Department of Health and Human Services, Washington, DC, personal communication, Nov. 8, 1964. Figures are approximate, and based on the difference between AIDS obligations at two points in time, one earlier (approximately July 1964) and one later (approximately August 1964). The assumption made by PHS was that any increases in obligations between the two points in time would have had to represent a redirection of funds initially obligated to other activities into AIDS activities (W. H. Little, personal communication, Dec. 28, 1984). Further estimates of the amounts redirected to AIDS from other activities in fiscal year 1964 have not been calculated by PHS.

Table 3.— Supplemental Funds for PHS Agencies' AIDS Activities in Fiscal Year 1984: Agencies' indications Compared to Congressional Appropriations[a]
(thousands of dollars)

Agency	Agency indication	Administration's request	Congressional appropriation
CDC	$3,200	$ –	$1,750
FDA	2,600	—	—
NIH:			
NCI	3,900	—	2,000
NIAID	8,330	—	4,150
NIDR	81	—	—
DRR	790	—	400
ADAM HA:			
NIMH[d]	375	—	375
NIDA[e]	800	—	800
HRSA	-	—	—
Total	$20,076	$ –	$9,475

Notes:
[a] Initial agency indications were not forwarded to Congress by the Department of Health and Human Services.
[b] Source: E. N. Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, "Proposed FY 1964 Supplemental and FY 1985 Amendment for Acquired Immunodeficiency Syndrome, " memorandum to the Secretary of Health and Human Services, May 25, 1964.
[c] Source: U.S. Congress, House of Representatives, "Making Supplemental Appropriations for the Fiscal Year Ending September 30, 1964, and for Other Purposes, " Conference Report 98-977 (to accompany H.R. 6040), Aug. 10, 1984.
[d] NIMH = National Institute of Mental Health.
[e] NIDA = National Institute on Drug Abuse.

Table 4.-Amounts Identified for PHS Agencies' AIDS Activities for Fiscal Year 1985: President's Budget Request Compared to Congressional Appropriations or Estimated Actual Obligations (thousands of dollars)

	Amounts identified for AIDS activities				
		Congressional appropriations			
Agency	(1) President's budget[a]	(2) Total[b c] (3)+(4)+(5)	(3) Conference levels before Cranston Amendment and redistribution	(4) Cranston Amendment[b d]	(5) Estimated redistribution needed[d]
CDC	$12,020	$23,200[e]	$12,000	$11,200	—
FDA	475	8,825[f]	8,825	—	—
NIH:					
DRR	779	1,731	1,731	—	—
NCI	18,951	26,851	21,351	—	$ 5,500[g]
NEI	61	300	300	—	—
NHLBI	8,459	8,884	8,884	—	—
NIAID	16,228	23,262	17,389	1,303[h]	4,570[h]
NIDR	35	411	411	—	—
NINCDS	1,150	1,150	1,150	—	—
ADAMHA	2,431	2,812	1,990	822	—
HRSA	—	—	—	—	—
PHS total	$60,589[i]	$97,426[h]	$74,031	$13,325	$10,070

Notes:
[a]Source: E N Brandt, J,, Assistant Secretary for Health, Public Health Service U.S Department of Health and Human Services, Washington, DC, letter 'o Off Ice of Technology Assessment, U S. Congress, Dec. 20, 1964
[b]Sources: W H Little, Office of the Assistant Secretary for Health, Public Health Services, U.S. Department of Health and Human Services, Washington, DC, personal communication, Oct 26, 1964; and E N Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, letter to Office of Technology Assessment, U.S. Congress, Dac 20, 1984.
[c]Includes Cranston Amendment and estimated redistribution needed
[d]Included In total congressional appropriations
[e]Includes $4.5 million for addition to CDC virology building
f Contingent on President's request fOr $8,350,000
[g]Source: p Fischinger, Associate Director, National Cancer Institute, National Institutes of Health, Bethesda, MD, personal communication, Nov 6, 1984
[h]Source: y duBuy, Financial Management Section, National Institute of Allergy and Infectious Diseases, National Institutes Of Health, Bethesda, MD, personal communication, Nov" 8, 1964
[i] Includes an increase of $5,347,oOO over previous estimates for AIDS

PHS agencies' needs for funds for AIDS activities in fiscal year 1985 have necessitated some redistribution of funds from other activities. At NIAID, between $5 million and $5.5 million has been identified as having to come from other activities, and at NCI, the figure is $4,570,000. CDC has said that it will not need to identify additional funds from other activity areas (119). Depending on the number of antibody-positive blood donors identified in its multicenter study of blood donors, NHLBI may have to request or identify additional funds from other activities (175).

In ADAMHA's opinion, all of the AIDS funds appropriated as part of the regular budget process have come from the agency's other activities. In other words, ADAMHA would have received the same total dollar amount for its budget regardless of how the funds were designated to be spent. Only supplemental appropriations and funds from the Cranston Amendment to the fiscal year 1985 appropriations for AIDS constituted additional money for AIDS activities ***(139).***

No additional funds have ever been requested for the AIDS activities at HRSA, although the agency has been expected to participate in the PHS response to AIDS. HRSA's Division of Maternal and Child Health provides information on AIDS to recipients of the Maternal and Child Health Block Grant (which the Administration proposed transferring to OASH in DHHS ***(168)) and to He-*** mophilia Treatment Centers, which are funded through the Division of Maternal and Child Health, and recently helped organize a conference on pediatric AIDS. HRSA expects to be required to take a greater role in the AIDS situation as the number of pediatrics AIDS cases increases. An increased role for HRSA might require additional funds for the agency, and HRSA is optimistic that money could be obtained if the case were made to PHS. To date, HRSA has been told that the

PHS priority for AIDS refers to research into the biomedical aspects of AIDS, and PHS maintains that HRSA has had sufficient funding to complete the AIDS tasks assigned to it (22).

Funding for the PHS Agencies as a Whole

DHHS has encouraged PHS agencies involved in AIDS research to take money and personnel from other activities to avoid asking Congress for additional funds. However, cutbacks and threatened cutbacks in funding and, in particular, in personnel levels have restricted the ability of affected agencies to redirect resources to AIDS-related activities. Tables 5, 7, 9, 10, and *12* compare funding levels suggested in the President's budgets for the years 1983, 1984, and 1985 for CDC, FDA, NIH, ADAMHA, and HRSA, respectively. Tables *6, 8,* and 11 show actual overall agency and AIDS budgets for CDC, FDA, and ADAMHA.

Table 5.—Centers for Disease Control: Initial U.S. Budget Request Compared to Estimated Budget Authority for Previous Year, Fiscal Years 1983 to 1985[a] (thousands of dollars)

	1985R[b]	1984EC	1984R	1983E	1983R	1982E
CDC budget:						
Excluding preventive health block grant[d]	$280,364	$286,310	$270,023	$243,372	$217,192	$202,010
Including preventive health block grant[d]	$369,864	$374,504	$356,352	$329,701	$298,792	$283,610
Percentage increase or decrease over previous year:						
Excluding block grant	−2.1%	—	10.9%	—	7.5%	
Including block grant	−1.2%	—	8.1%	—	5.4%	
CDC FTEs[e]	3,923	4,178	3,975	4,058	3,983	4,268
Infectious diseases budget:[f]	$ 46,161	$ 49,885	34,417	$ 34,882	N.A.[g]	N.A.
Percentage increase or decrease over previous year	−7.5%	—	−1.3%	—	—	

Notes:
[a]Source: Budget of the U.S. Government, Fiscal Years 1983 to 1985.
[b]R = Budget request.
[c]E = Estimated budget authority.
[d]The President's budget proposed that preventive health block grant funds be transferred from CDC to the office of the Assistant Secretary for Health (OASH). CDC budgets both including and excluding the preventive health block grant are shown here because excluding administration of the block grant would affect CDC's size and activity. The preventive health block grant was not transferred to OASH in either fiscal year 1964 or 1985.
[e]FTEs = Full-time equivalents.
[f]The CDC AIDS Activity is located in the CDC Center fOr Infectious Diseases.
[g]N.A. = Not available.

Table 6.—Centers for Disease Control: Overall Agency Budgets and AIDS Budgets, Fiscal Years 1979 to 1985[a] (thousands of dollars)

	1985	1984	1983	1982	1981	1980	1979
Overall CDC budget:	***$410,530***	***$380,489***	***$353,476***	***$302,242***	***$288,228***	***$296,125***	***$263,972***
Percentage increase or decrease over previous year	7.9%	7.6%	17.0%	4.9%	−2.7%	12.2 %/0	—
CDC FTEs[b]	4,401[c]	4,198	4,070	4,317	4,245[c]	4,052[c]	4,048
AIDS budget:							
Budget	$ 23,200[d]	$ 13,750[e]	$ 4,225[f]	$ 500[g]	$ 200	—	—
Plus funds redirected from other activities	—	—	$ 1,977[h]	$ 1,550[h]	—	—	—
Total	$ 23,200	$ 13,750	$ 6,202	$ 2,050	$ 200	—	—
FTEs	155[c i]	80[c]	45	—	—	—	—

Notes:
[a]Source: Except where otherwise noted, B. Shepard, Centers for Disease Control, Atlanta GA, PerSOnal communication, Oct. 16, 1984.
[b]FTEs = Full-time equivalents.
[c]Source: E, N. Brandt, Jr., Assistant Secretary for Health, Public Health Service, U S. Department of Health and Human Services, Washington, DC, letter to Office of Technology Assessment, U.S. Congress, Dec. 20, 1964.
[d]Includes $4,500,000 for CDC virology building.
[e]Includes $1,750,000 in supplemental appropriations.
[f]Includes $2,225,000 in supplemental appropriations.
[g]Supplemental appropriation.
[h]Redirected from surveillance of hepatitis, studies of chlamydial infections and pelvic inflammatory diseases, purchases of laboratory supplies and equipment, studies of influenza risk factors and vaccines.
[i]Estimated.

Table 7.—Food and Drug Administration: Initial U.S. Budget Request Compared to Estimated Budget Authority for Previous Year, Fiscal Years 1983 to 1985° (thousands of dollars)

	1985Rb	1984EC	1984R	1983E	1983R	1982E
FDA budget	***$394,004***	***$382,574***	***$385,933***	***$349,130***	***$356,163***	***$328,032***
Percentage increase over previous year	3%	—	10.5%	—	8.6%	—
FDA FTEs[d]	7,094	7,191	7,163	7,164	7,180	7,192

Notes:
[a]Source: Budgets of the U.S. Government, Fiscal Years 1983 to 1985.
[b]R = Budget request.
[c]E = Estimated budget authority.
dFTEs = Full-time equivalents.

Table 8.—Food and Drug Administration: Overall Agency Budgets and AIDS Budgets, Fiscal Years 1979 to 1985[a] (thousands of dollars)

	1985	1984	1983	1982	1981	1980	1979
Overall FDA budget	$409,700[b]	$394,817	***$361,645***	***$338,268***	***$327,927***	***$320,852***	***$295,154***
Percentage increase over previous year	3.8%	9.2%	6.9%	3.20/0	2.2%	8.7%	—
FDA FTEs[c]	7,068[b]	7,090	7,090	7,159	7,777	7,623[d]	7,561[d]
AIDS budget	$ 8,825[b]	$ ***798***	$ ***350***	$ ***150***	—	—	—
FTEs	20[b]	8[e]	7	—	—	—	—

Notes:
[a]Sources: J. Biviano, Budget Analyst, Food and Drug Administration, Rockville, MD, personal communication, Aug. 28, 1984; and C. L. Wilburn, Food and Drug Administration, Rockville, MD, personal communication, Nov. 5, 1984.
[b]Estimate based on Continuing resolution. Twenty FTEs are in question and $8.3 million will have to be requested by the President in order to be obligated.
[c]FTEs = Full-time equivalents.
[d]Actual positions; accounting conversion had not been made to FTEs.
[e]Redirected from other activities (hepatitis, herpes, pertussis, cytomegalovirus, and chickenpox).

Table 9.—National Institutes of Health: Initial U.S. Budget Request Compared to Estimated Budget Authority for Previous Year, Fiscal Years 1983 to 1985[a] (thousands of dollars)

	1985R[b]	1984E	1984R	1983E	1983R	1982E
NCI budget	$1,101,069	$1,077,303	$989,263	$983,576	$955,449	$986,617
Percentage increase or decrease over previous year	2.2%		0.6%		-3.2%	
NCI FTEs[d]	2,292	2,387	2,259	2,289	2,370	2,504
NIAID budget	$ 325,379	$ 314,117	$281,405	$273,581	$246,043	$235,895
Percentage increase over previous year	3.6%		2.9%		4.3%	
NIAID FTEs	730	762	768	772	814	837
NHLBI budget	$ 718,852	$ 703,197	$628,028	$622,745	$577,143	$559,637
Percentage increase over previous year	2.2%		0.80/0		3.1 %	
DBDR[e]	$ 104,890	$ 102,466	$87,930	$87,572	$78,339	$ 77,563
NHLBI FTEs	913	954	888	900	934	936
NIDR budget	$ 91,096	$ 88,163	$80,583	$78,860	$74,462	$71,983
Percentage increase over previous year	3.30/0		2.2%		3.40/0	
NIDR FTEs	347	362	341	348	369	385
NINCDS budget	$ 344,601	$ 335,205	$301,022	$295,719	$274,505	$265,901
Percentage increase over previous year	2.8%		1.8%		3.20/0	
NINCDS FTEs	705	735	720	730	733	763
NEI budget	$ 157,873	$ 154,683	$143,276	$141,561	$131,550	$127,374
Percentage increase over previous year	2.1 %		1.2%		3.3%0	
NEI FTEs	205	213	224	218	222	227
DRR budget	$ 245,728	$ 242,636	$228,542	$213,804	$191,024	$184,177
Percentage increase over previous year	1.3%		6.9%		3.70/0	
DRR FTEs	96	100	98	99	99	96

Notes:
[a]Source: Budgets of the U.S. Government, Fiscal Years 1983 to 1985.
[b]R = Budget request.
[c]E = Estimated budget authority.
[d]FTEs = Full-time equivalents.
[e]DBDR = Division of Blood Diseases and Resources.

Table 10.—Alcohol, Drug Abuse, and Mental Health Administration: Initial U.S. Budget Request Compared to Estimated Budget Authority for Previous Year, Fiscal Years 1983 to 1985[a] (thousands of dollars)

	1985R[b]	1984E[c]	1984R	1983E	1983R	1982E
ADAMHA budget:						
Including service block grant[d]	$844,955	$846,206	$792,854	$777,556	$737,177	$751,007
Excluding service block grant[d]	$372,655	$384,206	$357,826	$338,556	$305,177	$322,912
Percentage increase or decrease over previous year:						
Including service block grant	-0.1%	—	2.0%	—	- 1.80/0	—
Excluding service block grant	-3.0%	-	5.7%	—	-5.50/0	—
ADAMHA FTEs[e]	1,608	1,707	1,698	1,758	1,694	1,757
NIMH[f] budget	***$226,318***	***$250,547***	***$220,348***	***$225,985***	***$195,783***	***$224,553***
Percentage increase or decrease over previous year	-9.7%	-	-2.50/o	—	-12.80/o	—
NIDA[g] budget	$ 79,270	$ 70,301	$ 71,689	$ 61,202	$ 60,334	$ 57,846
Percentage increase or decrease over previous year	12.8%	=	17.1%	=	4.3%	=

Notes:
[a]Source: Budgets of the U.S. Government, Fiscal Years 1983 to 1985.
[b]R = Budget request.
[c]E = Estimated budget authority.
[d]The budget proposed transfer of service block grant to the Office of the Assistant Secretary for Health, but the transfers were not approved by Congress.
[e]FTEs = Full-time equivalents.
[f]NIMH = National Institute of Mental Health,
[g]NIDA = National Institute on Drug Abuse.

Table 11.—Alcohol, Drug Abuse, and Mental Health Administration: Overall Agency Budgets and AIDS Budgets, Fiscal Years 1982 to 1985[a] (thousands of dollars)

	1985	1984	1983	1982
Overall ADAMHA budget	***$434,093***	***$384,411***	***$340,866***	***$332,423***
(NIMH)	(283,626)	(251,035)	(227,342)	(229,319)
(NIDA)	(81,410)	(71,098)	(61,854)	(56,564)
Percentage increase or decrease over previous year:	12.9%	12.80/o	2.50/o	—
(NIMH)	(12.90/o)	(10.4%)	(-0.90/0)	—
(NIDA)	(14.5%)	(14.9%)	(9.3%)	—
ADAMHA FTEs[b]	N.A.[c]	1,659	1,660	1,624
AIDS budget	***$ 2,812***	***$ 2,791***	***$ 516***	—
(NIMH)	(1,787)	(1,205)	(202)	—
(NIDA)	(1 ,025)	(1,586)	(314)	—

Notes:
[a]Sources: E. N. Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, Washington, DC, letter to Office of Technology Assessment, U.S Congress, Dec. 20, 1984; and U.S. Department of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, "ADAMHA AIDS Research," xerox copy dated Dec. 14, 1984.
[b]FTEs = Full-time equivalents.
[c]N.A. = Not available,

Table 12.—Health Resources and Services Administration: Initial U.S. Budget Request Compared to Estimated Budget Authority for Previous Year, Fiscal Years 1983 to 1985[a] (thousands of dollars)

	1985R[b]	1984E[c]	1984R	1983E	1983R	1982E
HRSA budget:						
Excluding block grants[d]	$ 245,419	$ 459,031	$ 292,444	$ 481,208		
Including block grants[d]	$1,187,119	$1,380,151	$1,127,816	$1,315,226	$1,724,1;	$1,401,9;
Percentage increase or decrease over previous year:						
Excluding block grants	-46.50/o	—	-39.20/o	—	—	—
Including block grants.	-14.0"/0	—	- 14.20/o	—	23.00/o	—
HRSA FTEs[e]	2,704	3,746	3,731	4,627	3,787	4,874

Notes:
[a]Source: Budgets of the U.S. Government, Fiscal Years 1983 to 1985.
[b]R = Budget request.
[c]E = Estimated budget authority,
[d]The presidents budgets for fiscal years 1984 and 1985 proposed that several block grants be transferred to the Office of the Assistant Secretary for Health (OASH). HRSA budgets both including and excluding the block grants are shown here because excluding administration of the grants would have affected HRSA'S size and activity including AIDS activities. For example the proposed transfers included the Maternal and Child Health Block Grant, the program through which HRSA informs grant recipients of information about AIDS, The block grants were not transferred to OASH in either fiscal year 1984 or 1985.
[e]FTEs = Full-time equivalents,

As shown in table 5, for fiscal year 1985, the President requested a reduction in overall funds and personnel ceilings for CDC relative to estimated budget authority for the previous year. A reduction in funding from previous levels for the CDC Infectious Diseases Activity, of which the AIDS Activity is a part, was also requested in both 1984 and 1985, when, as shown in table 6, CDC's actual AIDS expenditures have been increasing at a growing rate over the years. CDC was especially affected by budget cutbacks in the period when it was starting to become heavily involved in AIDS activities. As shown in table 6, the agency's overall budget was reduced by almost $8 million, or 2.7 percent, from 1980 to 1981, The 1982 appropriation brought CDC's budget back to approximately the 1980 level, In 1983, although the overall agency budget increased a substantial amount, the number of FTEs at CDC declined to 4,070 from 4,317.

Levels of funding have similarly varied over the years for other PHS agencies involved in AIDS activities. As shown in table 7, the President's budget suggested 8.6- and 10.5-percent increases in funding for FDA in fiscal years 1983 and 1984, but only a 3-percent increase in funding for fiscal year 1985. FDA is responsible for evaluating the blood test for AIDS and the safety and efficacy of blood products and vaccines.

As shown in table 9, presenting figures for NIH, the President's budget for 1983 suggested a 3.2-percent decrease in funding for NCI. Only minimal increases in funding were suggested for NCI and most of the other NIH institutes in fiscal years 1984 and 1985. If inflation is taken into account, these minimal increases would represent decreases in funding. (A 14-percent increase in funding for the seven NIH institutes involved in AIDS activities was approved by Congress for fiscal year 1985: actual appropriations for the institutes involved were $1,183,806,000 for NCI; $370,965,000 for NIAID; $805,269,000 for NHLBI; $396,885,000 for NINCDS; $181,678,000 for NEI; $100,688,000 for NIDR; and $304,025,000 for DRR).

The Administration's pattern for ADAMHA overall, as shown in table 10, has been to suggest more decreases than increases, although increases in funding have been suggested for NIDA. As shown in table 11, appropriations for ADAMHA have increased since 1982. Except for fiscal year 1983, as shown in table 12, the Administration has also suggested substantial decreases in funding for HRSA. (HRSA's actual fiscal year 1985 appropriation was $1,427,694,000,)

Of greater impact than suggestions for holding funding levels about even or decreasing them have been budget requests by the Administration for decreases in PHS agencies' FTE personnel ceilings. The Administration has consistently suggested decreases in personnel ceilings for CDC, FDA, NCI, NIAID, NHLBI, NIDR, NINCDS, ADAMHA, and HRSA. Small increases were suggested for NEI in the 1984 budget and for DRR in the 1983 budget. Decreases in personnel have actually occurred at several of the agencies at critical times. No additional personnel resources have been allocated to NIAID for any of its AIDS activities (etiology, natural history, immunology, treatment, and prevention research) (166).

How AIDS and Other Activities Have Been and Will Probably Be Affected by Funding Patterns

The effect of funding patterns for AIDS has varied over time and by agency. Initially, the lack of resources impeded the funding of extramural research (NCI and NIAID), prospective studies of high-risk individuals (NIH and CDC), and animal studies (CDC) (146). As the Nation's public health monitor, CDC is required to conduct surveillance of a number of diseases and public health outbreaks. FDA's mission is to develop criteria to help it evaluate the safety and efficacy of the products it regulates. Thus, neither agency was easily able to redirect funds and staff into the area of AIDS without sacrificing other important work. The mission of NIH agencies is basic research, much of which may be advanced by involvement in the AIDS problem. Thus, in NIH laboratories, redirection of staff to work on AIDS have not detracted from other activities as much as have redirection of staff at CDC and FDA. This situation at NIH, especially for NCI and NIAID, may change in 1985.

In 1981, 1982, and 1983, CDC redirected funds and personnel from a number of activities (e. g.,

surveillance of hepatitis, studies of chlamydial infections and pelvic inflammatory diseases, studies of influenza risk factors and vaccines, and purchases of laboratory supplies and equipment) to support AIDS activities. In more recent fiscal years, including fiscal year 1985, Congress has appropriated amounts greater than those initially requested by the Administration for AIDS, so the redistribution of CDC funds from other activities has not been necessary (119). Personnel ceilings at CDC remain a problem. Three or four additional staff are needed for a study of blood recipients, but they cannot be promised until the fiscal year 1985 budget is settled. Congress has recommended a personnel "floor" of 4,400 for CDC. In the appropriations, 155 FTEs were specified for AIDS. As of November 1984, only 80 had been received, and CDC will not find out about the remainder until OMB completes its budget process (119). CDC's coordinator of AIDS activities was not optimistic about getting additional FTEs (38). The way budgets have been processed has consistently impeded the making of plans at CDC (51).

FDA (see tables 7 and 8) has had largely the same problem as CDC. In the past, personnel and funds have been redirected from work on interleukin-2 for herpes, chicken pox, and other related viruses; improvement of current vaccines for pertussis; and research associated with hepatitis vaccines (177). Currently, even though it is well into fiscal year 1985, FDA's appropriation is under a continuing resolution. Additional problems are caused by the facts that **$8.3 million of the money designated for AIDS by Congress must be requested by the President before it is obligated; and a reduction in overall agency FTEs was recommended by the Administration and approved by Congress.**

As noted, NIAID and NCI historically have had fewer problems with the redistribution of funds from other activities than have CDC and FDA. In addition, because they are part of a larger agency, NCI and NIAID have been able jointly to fund extramural research projects and lend each other laboratory and other personnel. Currently, NIAID continues to have problems obtaining staff to conduct statistical analyses for its five-city study of high-risk gay men, and NIAID did not receive a fiscal year 1985 appropriation adequate to meet the needs it articulated in the Assistant Secretary for Health's memo to the Secretary of DHHS requesting a budget amendment.

NIAID plans to spend ***$23,262,000*** in fiscal year 1985 on its AIDS activities, ***$4,570,000*** of which will be redirected from other activities (see tables 4 and 13). This redistribution was necessary to fund continuation costs of activities supported as a result of the fiscal year 1984 supplemental appropriation of $4,150,000. As shown in table 13, the redistribution of funds from other activities means that new grants covering the gamut of NIAID activities will not be funded; certain non-AIDS projects that had been planned will not be started. In addition, certain new AIDS projects that had been requested will be foregone or postponed ***(142).*** These include the following (41):

Table 13.—National Institute of Allergy and infectious Diseases: Redistribution Needed To Fund Fiscal Year 1985 AIDS Activities[a] (thousands of dollars)

Amount	Source
$2,258	18 competing research project grants (covering the gamut of infectious diseases and immunology) will not be funded
$1,542	Congressionally requested major new clinical trials on: • ribavirin therapy of viral respiratory diseases • candidate vaccines for Group B streptococcal infections
$ 770	Intramural research on vaccine development other than for AIDS: • hepatitis • rotavirus diarrhea • pertussis
Total $4.570	

Note:
[a]Source: Y. duBuy, Financial Management Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, personal communication, Nov. 6, 1964,

. extramural studies of the development of new vaccines and antiviral drugs for HTLV-III infection;
- extramural studies to develop animal model systems for testing vaccines and antiviral drugs for HTLV-III infection;

- intramural clinical protocols of treatment regimens directed at HTLV-III virus as well as immune defects resulting from viral infections;
- investigations of immune derangements in addicted parents and children;
- epidemiological cohort study of HTLV-III infections in health care workers; and
- support for additional AIDS outreach programs directed at health care workers.

NCI will also have to change its funding patterns in fiscal year 1985, and anticipates some problems as a consequence of changes in personnel ceilings. NCI did not receive any funds under the Cranston Amendment (see table 4), to the chagrin of two of its Boards of Scientific Counselors (Boards of the Division of Cancer Etiology and the Division of Cancer Treatment) (163,176). In order to fund AIDS activities in 1985, NCI will take funds from its research projects grants center, cancer centers, cooperative clinical research, career program development, and clinical education (see table 14). NCI also foresees significant problems at the end of the current contract year when it will be unable to fund continuing costs for anticipated subcontracts at the Frederick (Maryland) Cancer Facility begun with funding from the fiscal year 1984 supplemental appropriation. The subcontracts will be a key element in vaccine development research and it is unlikely that the research can be completed in 1 year (162).

Table 14.—National Cancer Institute: Estimated Redistribution Needed To Fund Fiscal Year 1985 AIDS Activities[a] (thousands of dollars)

	Amount	Source
	$2,550 to $2,800	Research project grants pool
	850 to 930	Cancer centers
	850 to 930	Cooperative clinical research
	550 to 610	Career program development
	200 to 230	Clinical education
Total	$5,000 to $5,500	

Note:
[a]Sources: p, Fischinger, Associate Director, National Cancer institute, National Institutes of Health, Bethesda, MD, personal communications, Nov. 6, 1964. and Jan. 3, 1985; and E. N. Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S Department of Health and Human Services, Washington, DC, letter of Office of Technology Assessment, US Congress, Dec. 20, 1964

In addition to funding problems, a number of factors have come together to make NCI vulnerable to personnel cutbacks. Prior to a year and a half ago, a category of personnel called "special experts" could be hired without being counted against NIH's personnel ***ceilings.*** When the policy was first changed and the experts began to be counted against the NIH personnel ceiling, it did not have much impact on NCI, because most of the institutes at NIH were under ceiling, so the NIH in the aggregate was within the agency limitation. Personnel slots can be "loaned" across agencies at NIH. Now, however, the other institutes are up to strength and are subject to an NIH hiring freeze which sets positions at ***13,507*** FTEs. NIAID had loaned NCI nine positions and now needs them back. As a consequence, NCI is currently under a restriction to hire only one person for every two who leave the institute (162). NIAID foresees that it may have the same restriction (166). According to OASH, however, NIAID will be able to hire three persons for every five who leave, the restrictions on NCI are in effect only until NIH receives its final ceiling for 1985, and the NIH Director has discretion to grant exceptions to the restriction for high-priority needs (22). These changes reduce the prospects of hiring appropriate personnel for specific project initiatives in 1985. Thus, for example, NIH expects to have to make cutbacks in its Clinical Center nursing staff, which means that fewer patients will be available for clinical trials and treatment.

Measures To Increase the Number of Extramural Research Projects

One of the early criticisms of NIH was its inattention to extramural research on AIDS. Critics charged that not enough extramural research was being funded and that what was being funded was taking an unconscionably long time to go through the system. In order to deal with the problem of long delays in funding, NIH initiated mail ballots and other procedures to expedite extramural grant reviews. Subsequently, the award rate at the three NIH institutes most heavily involved in AIDS activities (NCI, NHLBI, and NIAID) was greatly accelerated. For 1983, as shown in table 15, the award rate, or the number of approved ***grants ac***tually funded, in all areas at all three institutes was around 35 percent; for AIDS, the award rates were 67 percent for NCI, 100 percent for NHLBI,

Table 15.—National Institutes of Health Award Rates and Paylines for All Extramural Research Compared to AIDS Extramural Research, Fiscal Year 1983[a]

	NCI	NHLBI	NIAID
All extramural research:			
Number of grants approved for funding	2,610	2,114	1,406
Number of grants actually funded	886	748	522
Award rate	34 %/0	35%	37%
Payline (priority score at which approximately 90%/0 of grants were funded)	181	195	166
AIDS extramural research only:			
Number of grants approved for funding	45	2	17
Number of grants actually funded	30	2	17
Award rate	670/o	100%	100 %/0
Number of grants funded at priority score ranges:[b]			
100-180	8	—	12
181-200	5	1	2
201-250	7	—	2
251-300	10	1	1

Notes:
[a]Source: N. D, Mansfield, Division of Financial Management, National Institutes of Health, Bethesda, MD, letter to Office of "technology Assessment, U.S. Congress, Oct. 22, 1984.
[b]The lower the score, the higher the priority.

and 100 percent for NIAID. For NCI, this meant that a number of extramural grants receiving rather poor priority score ranges were funded (the lower the score, the higher the priority for funding). ADAMHA also expedited its review process and funded projects beyond usual priority scores (151). However, while the use of lower standards for AIDS research by all of the agencies mentioned undoubtedly increased the number of grants funded, it is believed that it also resulted in the funding of some studies of poor quality ***(56).***

Resources for Research on Cofactors and Treatment and for Public Education

In addition to the issue of whether sufficient resources are being allocated to AIDS activities by DHHS and Congress, there remains the question of how resources are being allocated to the various AIDS activities. In particular, doubts have been raised about the adequacy of resources devoted to the search for factors affecting the development of AIDS, the provision of treatment, and public education. In this section, the proportion of the AIDS budget directed at these activities is summarized.

Cofactor Research

In general, the search for factors affecting the development of AIDS has always accounted for a large proportion of the AIDS budget. Immediately after the discovery of the etiologic agent for AIDS, changes in resource allocations were made. As shown in table ***16,*** which represents funding estimates for PHS AIDS activities as of September 11, 1984, for both fiscal years 1984 and 1985, greater amounts were budgeted for cofactor research and epidemiologic studies (items 1b and 4 in the table) after the discovery of HTLV-III than before it. As shown in table 17, which represents the most current estimates, PHS estimates that of the total PHS resources allocated to AIDS in fiscal year 1984, 12.6 percent was obligated to cofactor research, and 31.9 percent, to epidemiologic studies. In fiscal year 1985, a relatively greater proportion (14.9 percent) of total AIDS resources will be obligated to cofactor research, but a substantially smaller proportion (26 percent) will be obligated to epidemiologic studies. In total dollars, however, almost $5 million more will be obligated to epidemiologic studies in fiscal year 1985 than in 1984, and $6 million more to cofactor research.

It is more difficult to estimate the amounts being spent by PHS for research into psychosocial risk factors. As shown in table 17, research on psychosocial factors (item 8 in the table) constitutes a relatively small amount of total fiscal year 1985 resources for AIDS (2.1 percent of the budget, equal to $1,949,000). Furthermore, this category, as defined by PHS, includes research both on the psychosocial consequences of AIDS and on psychosocial factors which might contribute to its development. Possible psychosocial risk factors for AIDS include life stress, exhaustion, health habits, depression, anxiety, coping mechanisms, a sense of helplessness, and the loss of social support (see, e.g., 8,35,95,110).

Several studies of psychosocial risk factors and consequences of AIDS are being supported by NIMH (see app. D). The investigation of psychosocial factors has also been incorporated into epi-

Table 16.—Changes in Funding for PHS AIDS Activities Anticipated After Discovery of AIDS Etiologic Agent[a, b] (thousands of dollars)

Activity	Fiscal year 1984				Fiscal year 1985 President's budget			
	Appropriate ion (Public Law 98-139) before discovery		Obligation respread after discovery'		Before discovery		After discovery	
1. Etiologic agent and cofactors:								
a. Discovery	21 "/0	$10,697	130/0	$ 6,357	100/o	$ 5,654	50/0	$ 2,797
b. Confirmation and extension of observations on causative agent and discovery of role of confections and cofactors	6	2,949	8	4,010	1	689	6	3,337
2. Development and evaluation of blood tests:								
a. Development	6	2,949	5	2,309	5	2,932	3	1,553
b. Evaluation	1	559	4	1,895	5	3,109	6	3,175
3. Surveillance	6	3,100	6	3,092	6	3,260	6	3,260
4. Epidemiological studies (to determine natural history of AIDS)	27	13,756	32	16,279	38	21,231	40	22,651
5. Development of evaluation of vaccine (including animal model)	3	1,477	3	1,477	4	2,237	5	2,554
6. Studies of therapeutic intervention:								
a. AIDS	7	3,414	7	3,414	8	4,471	8	4,337
b. Opportunistic infections	10	5,183	10	5,212	9	5,149	9	5,247
7. Immunologic studies	6	3,023	6	3,023	6	3,238	6	3,238
8. Psychosocial factors	1	709	1	709	2	1,009	2	1,009
9. Simian AIDS	4	1,808	4	1,808	3	1,791	3	1,612
10. Prevention of transfusion-related AIDS	0	22	0	22	1	550	1	550
11. Bioethics and biosafety	0	168	0	207	0	260	0	260
12. Information dissemination/public affairs	2	964	2	964	2	973	2	973
PHS total	1000/0	$50,778	1000/o	$50,778	100%	$56,553	1000/,	$56,553

Notes
[a] Figures are approximate and represent calculations before passage of the supplemental appropriation for fiscal year 1984 and the appropriation for fiscal year 1985
[b] Source: u s Department of Health and Human Services, "AIDS Public Health Service Total," xerox copy provided by W H Little, Office of the Assistant Secretary for Health, sheets dated July 27, 1964, and Sept 11, 1964.
[c] After th, discovery of HTLV-III as th, probable et iologic agent for AIDS, the remaining $29, 106,000 available for obligat ions for Various activities was redistributed or "respread" among the activities

Table 17.—Funding for PHS AIDS Activities by Type of Activity, Fiscal Years 1984 and 1985[a] (thousands of dollars)

Activity	Fiscal year 1984 obligation as of 9130/84		Fiscal year 1985 appropriation	
1. Etiologic agent and cofactors:				
a. Discovery	8.20/o	$5,058	—	—
b. Confirmation and extension of observations on causative agent and discovery of role of confections and cofactors	12.6	7,732	14.90/0	$13,804
2. Development & evaluation of blood tests:				
a. Development	1.7	1,070	1.9	1,754
b. Evaluation	1.7	1,066	4.9	4,569
3. Surveillance	4.5	2,772	4.7	4,400
4. Epidemiological studies (to determine natural history of AIDS)	31.9	19,600	26.0	24,119
5. Development and evaluation of vaccine (including animal model)	4.7	2,879	12.7	11,776
6. Studies of therapeutic intervention:				
a. AIDS	6.3	3,852	8.8	8,158
b. Opportunistic infections	8.1	4,957	6.0	5,554
7. Immunologic studies	11.0	6,753	10.1	9,444
8. Psychosocial factors	1.8	1,105	2.1	1,949
9. Simian AIDS	4.2	2,589	2.7	2,546
10. Prevention of transfusion-related AIDS	0.9	522	0.9	882
11. Bioethics and biosafety	0.1	82	0.2	144
12. Information dissemination/public affairs	2.3	1,423	4.1	3,827
PHS total	100%	$61,460	100%	$92,926[b]

Notes
[a] Source: E N Brandt, Jr , Assistant Secretary fo, Health, Public Health Service, US. Department of Health and Human Services, Washington, DC, letter to Off ice Of Technology Assessment, U.S. Congress, Dec 20, 1964
[b] Excluding $45 million for CDC virology lab.

demiologic studies being conducted under the aegis of other agencies. Thus, for example, NIAID's prospective study of 5,000 apparently healthy gay men in five cities has incorporated some psychosocial items (depression, life satisfaction, self--esteem, social support, sense of control) into its basic questionnaire, and grantees are free to develop additional questions. However, most of the research on risk factors concentrates on factors other than the psychosocial: cytomegalovirus, Epstein-Barr virus, herpes virus, hepatitis, the iatrogenic effect of steroids and other medicines, alcohol and other recreational drug use, smoking, sexual practices, ethnicity, and particular underlying diseases (165).

As shown in table 18, all of the PHS agencies, except FDA and HRSA, are involved in the investigation of confections and cofactors (item 1b) and in epidemiologic studies to determine the natural history of AIDS (item 4). Further details on the proportion of resources being devoted to the various AIDS activities by each agency, including cofactors and epidemiologic research, are provided in appendixes C and D.

Treatment

Tables 17 and 18, and appendix C, indicate the relative proportion of PHS resources being devoted to research on treatment. As shown in table 17 (item ***6),*** the most recent calculations indicate that 14.8 percent ($13,712,000) of the AIDS budget for fiscal year 1985 was to be used for studies of therapeutic intervention (8.8 percent for AIDS and 6 percent for opportunistic infections). These include studies of the drugs suramin, ribavirin, pentamidine, and dapsone; the use of polyamine inhibitors to control cytomegalovirus infections; and the use of interferon and interleukin-2. They do not include the study of psychosocial factors related to treatment, which are included in the 2.1 percent of the budget allocated to psychosocial factors (item 2 in table 17). The PHS emphasis has been on studies of biological treatment. In addition, except for the treatment given to AIDS patients at the NIH Clinical Center and the benefits patients gain from certain PHS activities (e.g., public education efforts directed at health care workers, the funding of researchers in extramural hospitals), no PHS funds have been allocated to the treatment of AIDS patients per se. The NIH Clinical Center is a research hospital to which patients are admitted on the basis of ongoing protocols, not need for treatment. The role of Federal agencies other than PHS in obtaining money for treatment for individual patients is discussed in the "Related Issues" section below.

Public Education and Prevention

In the past, relatively little money was allocated to public education about AIDS. Between 1984 and 1985, however, the amount allocated for such activities in the PHS agencies more than doubled, from $1.4 million to $3.8 million, most of it for CDC (item 12 in tables 17 and 18).

The AIDS budget of the Office of Public Affairs in OASH, where much of the public education has taken place, is scheduled to decrease to $120,000 in fiscal year 1985, from $200,000 in fiscal year 1984. PHS's public education activities are discussed further in the "Related Issues" section below.

PHS View and OTA Conclusions

In general, PHS believes that OTA's review of resources for AIDS is overly critical, especially with respect to fiscal year 1985. In his response to the first draft of this report, Assistant Secretary for Health Brandt said that OTA failed to give adequate credit to PHS for the "massive effort" it has mounted in response to the AIDS problem. "Although it is true that each of the PHS agencies has had to make readjustments and reallocations of its resources, " the Assistant Secretary wrote; "we have nevertheless been successful in mounting a coordinated attack in the fight against AIDS. I assure you that adequate funds have been appropriated for fiscal year 1985 to permit the PHS agencies to carry out all of the AIDS requirements which have been presented to me" (22). More specifically, PHS agencies whose comments were transmitted by the Assistant Secretary stated that other activities will not suffer from a reallocation of resources to AIDS activities in fiscal year 1985, that the fiscal year 1985 mix of AIDS activities is appropriate to meet require-

Table 18.—Funding for PHS AIDS Activities by Type of Activity and Agency, Fiscal Years 1984 and 1985[a] (thousands of dollars)

Activity	Fiscal year 1984 obligation as of 9/30/84	Fiscal year 1985 appropriation
1. Etiologic agent and cofactors:		
a. Discovery		
CDC	$3,330	—
NIH:		
NCI	1,373	—
NINCDS	355	—
Total	5,058	—
b. Confirmation and extension of observations on causative agent and discovery of role of coinfections and cofactors:		
ADAM HA	1,036	$ 685
CDC	1,403	3,210
NIH:		
DRR	71	95
NCI	3,929	8,058
NEI	25	150
NHLBI	483	422
NIAID	785	1,184
Total	7,732	13,804
2 Development and evaluation of blood tests:		
a. Development:		
CDC	650	1,244
NIH:		
DRR	7	9
NCI	111	203
NHLBI	302	298
Total	1,070	1,754
b. Evaluation		
CDC	471	1,018
FDA	—	3,270
NIH:		
NHLBI	555	195
NINCDS	40	86
Total	1,066	4,569
3. Surveillance:		
CDC	2,732	4,335
NIH:		
NCI	40	65
Total	2,772	4,400
4. Epidemiological studies (to determine natural history of AIDS):		
ADAMHA	688	648
CDC	2,710	4,068
NIH:		
DRR	1	—
NCI	4,098	5,177
NEI	19	135
NHLBI	3,513	7,044
NIAID	8,449	6,788
NINCDS	122	259
Total	19,600	24,119
5. Development and evaluation of vaccine (including animal model):		
CDC	500	516
FDA	—	4,660
NIH:		
NCI	1,582	4,955
NIAID	706	1,458
NINCDS	91	187
Total	2,879	11,776
6. Studies of therapeutic intervention:		
a. AIDS		
FDA	798	895
NIH:		
DRR	132	222
NCI	1,759	2,817
NHLBI	—	800
NIAID	1,113	3,117
NIDR	—	206
NINCDS	50	101
Total	3,852	8,158
b, Opportunistic infections:		
CDC	250	186
NIH:		
DRR	274	244
NCI	170	298
NEI	16	15
NIAID	4,124	4,725
NIDR	81	—
NINCDS	42	86
Total	4,957	5,554
7. Immunologic studies:		
CDC	300	32
NIH:		
DRR	121	167
NCI	2,612	3,695
NIAID	3,720	5,345
NIDR	—	205
Total	6,753	9,444
8. Psychosocial factors:		
ADAMHA	1,067	1,479
NIH:		
DRR	4	5
NIAID	34	34
NINCDS	—	431
Total	1,105	1,949
9. Simian AIDS:		
NIH:		
DRR	746	989
NCI	850	1,403
NIAID	183	154
NINCDS,	810	—
Total	2,589	2,546
10. Prevention of transfusion-related AIDS:		
CDC	500	707
NIH:		
NCI	22	50
NHLBI	—	125
Total	522	882
11. Bioethics and biosafety:		
CDC	54	124
NIH:		
NCI	10	20
NHLBI	18	—
Total	82	144
12. Information dissemination/public affairs:		
CDC	850	3,260
NIH:		
NCI	71	110
NIAID	502	457
Total,	1,423	3,827
PHS Total	$61,460	$92,926[b]

Notes:
[a]Source: E, N, Brandt, Jr., Assistant Secretary for Health, Public Health Service, U.S. Department of Health and Human Services, Washington, DC, letter to Office of Technology Assessment, U.S. Congress, Dec. 20, 1984.
[b]Excluding $4.5 million for CDC virology lab. Includes $8.3 million for FDA which has not yet been obligated.

ments, and that planning for AIDS activities has been impeded by the rapidly changing problem of AIDS and related investigations rather than by inadequate resources, although "perhaps planning could have been improved if resource availability had been known at the onset. "

PHS agencies also commented on the five "open issues" that OTA identified in the introduction to this section. With respect to the first issue, the extent to which progress in other disease areas has suffered as a result of diversions to AIDS activities, the comment from PHS was that "other disease areas have not necessarily suffered as a result of the increased emphasis being planned on AIDS" and that "what we learn from AIDS will have significant importance in other areas, with far-reaching benefits for our research on numerous disease conditions. " Further, the NIH will be able to fund 1,500 more new and competing research grants (for a total of 6,500) with its fiscal year 1985 appropriation, providing "momentum across the entire research base."[1]

Commenting on the second issue, the wisdom of limiting the priority status of AIDS primarily to biological research, Assistant Secretary Brandt stated that "the effort has never been exclusively limited to this priority." He pointed out that only about half of ADAMHA's AIDS activities in fiscal year 1985 will be for biomedical research and that the AIDS activities of CDC primarily support nonbiomedical research activities (i.e., laboratory investigations, surveillance, epidemiologic studies, technology transfer, information dissemination, and programs on disease prevention and control). He also stated, however, that "a concerted effort in public education or in areas such as psychosocial factors cannot take place until we have discovered, through biomedical research, the answers we must have to the numerous questions involving this puzzling disease. "

As for the manner in which limited resources can be allocated among agencies, the response from PHS was that because Congress appropriates funds by agency, PHS does not have the ability to reprogram funds between its agencies. Nevertheless, the Assistant Secretary noted, PHS has consistently placed a high priority on AIDS. NIH, for example, has allocated approximately $9 million of its fiscal year 1985 appropriation increases to expand AIDS activities.

Assistant Secretary Brandt's response to the problem of personnel ceilings in PHS agencies was that while personnel resources are always limited and difficult decisions must be made, "careful management" can "minimize the impact on science and other AIDS activities. " The Assistant Secretary further noted, with respect to the problems NCI and NIAID are experiencing, that "there is... a provision for exceptions to be granted by the Director, NIH, to these restrictions for high-priority needs. AIDS is considered a high priority. "

Finally, with regard to the issue of the extent to which PHS agencies will be able to pursue AIDS work adequately in the face of further cutbacks, the PHS response was that "it is difficult to predict any actions to be taken in the future, " but "as long as AIDS continues to be a high priority health problem, PHS will continue to assign it a high priority and allocate the necessary resources for its support. " Assistant Secretary Brandt pointed out that at NIH there has been a 42-percent increase for AIDS from 1984 to 1985, as compared to a 14-percent increase in total appropriations for the seven participating institutes. Greater increases for AIDS research relative to non-AIDS activities, Brandt noted, are apparent at "most" of the other agencies.

OTA concludes that although PHS has indeed undertaken a massive effort and made significant accomplishments, the statement that AIDS is DHHS's number one health priority has not always been supported by financial and personnel resources. The responsibility for this situation, however, appears not to rest with the Office of the Assistant Secretary in PHS, but instead to reflect decisions made at higher levels of the Federal Government. The Administration has not pursued an appropriation for the Public Health Emergency Act, choosing instead to rely on se-

[1] Subsequent to the Assistant Secretary's letter, it was reported that the Office of Management and Budget (OMB) plans to reduce NIH's fiscal year 1985 competing grants from 6,526 to 5,000 by obligating funds for 1,526 grants in fiscal year 1985 but not actually spending the money until fiscal year 1986 (*FDC Reports* ("The Blue Sheet") l:P&R-1, Jan. 9, 1985).

curing appropriations for individual PHS agencies from Congress. Although insufficient and uncertain distribution of resources has not been the sole cause of delays or inadequacies in PHS AIDS research, surveillance, and service provision, it has resulted in at least inadequate planning, increased competitiveness among agencies, inadequate attention to certain areas which are perceived by many to be important (e.g., public education and prevention), and a diversion of attention from other critical health areas.

RELATED ISSUES

This memorandum is primarily focused on the biomedical questions surrounding AIDS and the ways in which PHS has attempted to address these questions. Several related issues that also deserve mentioning, however, are those that involve confidentiality and informed consent, prevention of AIDS through education on the risk factors associated with the disease, and financing for the clinical and supportive services that AIDS patients require.

Confidentiality and Informed Consent

AIDS has been described as a "legal emergency" as well as a medical crisis (49). Much of the concern centers on discrimination experienced by members of high-risk groups, especially gay men and intravenous drug abusers (124). (Private consensual homosexual activity is illegal in 23 States and the District of Columbia (17).) There have been reports of discrimination in housing, employment, health or life insurance coverage, or in the receipt of medical or dental care, not only against AIDS patients but also against those thought to have AIDS.

Two sections of the Public Health Service Act have been used to protect confidentiality in federally sponsored research. Section 242a of the act (*42* U.S.C. section 242a) authorizes the Secretary of DHHS to protect the privacy of individuals participating in research on mental health, including research on the use and effect of alcohol and other psychoactive drugs, by: 1) withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals; and 2) prohibiting persons authorized to protect the privacy of such individuals from being compelled to identify them in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. (Thus, for example, section 242a has been used to protect the confidentiality of participants in NIAID's five-city study of the natural history of AIDS.)

Section 242m(d) of the Public Health Service Act (*42* U.S. C. section *242* m(d)) provides that information may not be used for any purpose other than the purpose for which it was supplied unless consent has been given. Assurances of confidentiality based on this section were issued by CDC in July 1984 to cover the agency's surveillance work, and epidemiologic studies and studies of transfusion-related AIDS are being reviewed by CDC for possible application of section 242m(d) to these areas.

These two sections of the Public Health Service Act apparently cannot cover all AIDS research. Section 242a applies only to mental health research or research into drug or alcohol use. Section 242m(d) is applicable only to the Centers specified in the statute (i. e., the National Center for Health Statistics, the National Center for Health Services Research, and the National Center for Health Care Technology). CDC has applied section 242m(d) to its surveillance activities, because they are similar to the functions and purposes of the activities carried on by the National Center for Health Statistics and because both CDC and the National Center for Health Statistics are funded in the same way (113).

These limitations of existing statutory assurances of confidentiality have led to a proposal by the National Gay Task Force and Lambda Legal Defense and Education Fund to expand section 242m(d) to cover AIDS-related research and surveillance undertaken directly or indirectly by PHS

(113). The need for such a **statute will increase if members of high-risk groups fail to present themselves as research subjects (as some gay organizations have advised), fearing breaches of confidentiality.**

Closely linked to concerns over confidentiality is the issue of informed consent. For example, the National Gay Task Force has stated that if confidentiality is to have any real meaning, researchers must contractually obligate themselves to the research subject not to disclose identifying information, and that this objective can be accomplished by requiring the researcher to use a strong consent form containing such a guarantee (113).

Until assurances of confidentiality can be given for all AIDS-related research, informed consent may require that research subjects be told that such assurances cannot be guaranteed. This was an issue in drafting the consent form for the NHLBI study in which serum samples of ***200,000*** voluntary blood donors are being collected so that they can be tested for the presence of antibodies to HTLV-III. The wording in the informed consent document that was forwarded to the Institutional Review Boards of the blood centers involved in the study and whose use PHS recommended, was as follows: "Only authorized staff of this institution and members of the research team are expected to have access to the information relative to my test; however, officials of the Food and Drug Administration or others authorized by law may require access to this information" (167).

Another informed consent issue that arose in drafting the consent document for the NHLBI blood donor study was the significance of a positive test for the presence of antibodies to HTLV-III. (As stated earlier in this memorandum, aside from indicating exposure to HTLV-III, the implications neither of a positive test nor of a negative test are known.) The document that was sent to the blood centers for their use stated: "The significance of the presence of the antibodies and the reliability of the method used to detect them are not known at this time. If my blood is tested and ***if these antibodies are detected, I will be informed of the results and offered further testing to clarify their meaning"*** (emphasis in original) (167).

One commentator has concluded that the uncertainty surrounding the blood test meant that "neither respect for persons nor beneficence allows us currently to disclose the antibody test results to the subject or others. Research subjects should be promised a detailed explanation of their status when that information is validated" (116). Other commentators, assuming that it would violate the same set of ethical principles (respect for persons and beneficence) for research subjects or blood donors to remain unaware of the information, despite its uncertain implications, have described the disclosure of HTLV-III antibody test results as a question of "how," not "if" (4,37).

Blood banking and commercial plasmapheresis organizations are currently grappling with the social and ethical issues surrounding the imminent availability of the blood test. One concern is that if the test is initially available only at blood banks and plasmapheresis centers, gay men will present themselves as donors in order to learn the results of the tests on their blood. Because of the dangers to the blood supply and the added expenses of screening and not using blood that tests positively for antibodies to HTLV-III, there have been suggestions that the test be made available at a low cost through health centers in high-risk areas.

The questions for blood banks are many. Should registries of HTLV-III antibody-positive donors be maintained? Should donors be listed separately as HTLV-III positive, or should they be aggregated with others deferred for different health reasons? What should recipients of blood products from donors who are HTLV-III antibody positive be told? (See previous box on PHS recommendations for screening blood and plasma donations for recommendations on notification and confidentiality. These recommendations were addressed by an ad hoc group convened jointly by The Hastings Center, a bioethics organization, and the American Blood Commission in January 1985 (5).)

Other concerns about the blood test involve its potential use by employers, the military, the immigration service, health insurers or others. Should a private insurer, for example, be allowed to use a positive test result as evidence for denial of benefits because AIDS was a "pre-existing con-

dition"? Should a positive result be the basis for the dismissal or transfer of a food handler or the transfer of a prisoner to an isolated section of the prison?

A task force convened by The Hastings Center recently reviewed Federal, State, and local statutes as they applied to information gathered for use in AIDS treatment, research, surveillance, and scientific and program audits. One of its conclusions was that "administrative and statutory safeguards should be created at Federal and State levels to prevent both unjustifiable voluntary and involuntary disclosure of personally identifiable data." The task force found that "(t)he strength of State and local protections . . . is unknown, since they have not been challenged in court by Federal authorities" (10). Its report also contains specific recommendations on institutional policies regarding who should have access to what kinds of data; what kinds of patient identifiers would be appropriate; how to balance the tensions between the desire for confidentiality and public health reporting requirements; and what degree of variability in these policies is appropriate across various legal jurisdictions, research institutions, and public health bodies.

The Office of Protection from Research Risks (OPRR) is the NIH agency responsible for overseeing human subjects research. In general, the policy of OPRR is to provide to local Institutional Review Boards guidance on informed consent procedures, rather than to establish central Federal direction, ***or*** models of informed consent forms (98). Officials from OPRR have stated, however, that legislation providing guarantees of confidentiality might begin to be considered.

Prevention Through Education

In spite of the discovery of the probable cause of AIDS, prevention through education remains the primary means of restricting the spread of this disease. Effective treatment and especially prevention of infection through vaccines represent difficult technical objectives yet to be achieved.

PHS has focused its educational efforts on physicians and other health professionals, leaving education of high-risk groups largely up to the leadership of the groups themselves. (Appendix D provides details about PHS public information activities.)

Efforts at direct public education have included the AIDS hotline, the ***Facts About AIDS*** newsletter, partial funding of a public television documentary, NIH radio programs, a videotape about AIDS, periodic announcements by DHHS Secretary Heckler, and the publication of booklets (147,148). The most direct advice on risk reduction has been published by CDC in two sets of interagency prevention recommendations, the latest in anticipation of the blood test to detect antibodies to **HTLV-III (153,159; see box 2-B below for precautions recommended by PHS for individuals likely to have an HTLV-III infection). Reprints of PHS interagency precautions have been distributed to community health centers, other health facilities and drug treatment centers. NIDA has reprinted AIDS materials** and generated materials of its own for distribution to drug abuse treatment and counseling centers.

Efforts directed at health professionals include CDC's conferences for health care professionals and State health agencies. CDC is cosponsoring a major international conference on AIDS in April ***1985*** with nearly a thousand participants expected. PHS has developed videotapes and a booklet (149) directed to health care workers and others who might come in contact with AIDS patients as a consequence of their employment (e.g., court officers, prison officials, morticians). NIMH is developing a booklet on ***Mental Health Implications of AIDS,*** and its Center for Prevention Research cosponsored a meeting on the Psychosocial Aspects of AIDS in December 1984. NIAID has established an outreach program to transmit the latest technical advances in AIDS research to primary care physicians and allied health personnel. State and local health agencies in particular have played a role in distributing information about AIDS, including advice about prevention, to their communities. A DHHS-funded U.S. Conference of Mayors' survey of local, mostly government, groups found that ***40*** percent of the material distributed had been prepared by the Federal Government (143).

Perhaps the most controversial aspect of prevention through public education has been the

Box 2-B.--PHS Recommendations for Individuals Likely To **Have an HTLV-III Infection**

An individual judged most likely to have an HTLV-III infection should be provided the following information and advice:

1. **The prognosis for an individual infected with HTLV-III over the long-term is not known. However, data available from studies conducted among homosexual men indicate that most persons will remain infected.**
2. **Although asymptomatic, these individuals may transmit HTLV-III to others. Regular medical evaluation and follow-up is advised, especially for individuals who develop signs or symptoms suggestive of AIDS.**
3. **Refrain from donating blood, plasma, body organs, other tissue, or sperm.**
4. **There is a risk of infecting others by sexual intercourse, sharing of needles, and possibly, exposure of others to saliva through oral-genital contact or intimate kissing. The efficacy of condoms in preventing infection with HTLV-III is unproven, but the consistent use of them may reduce transmission.**
5. **Toothbrushes, razors, or other implements that could become contaminated with blood should not be shared.**
6. **Women with a seropositive test, or women whose sexual partner is seropositive, are themselves at increased risk of acquiring AIDS. If they become pregnant, their offspring are also at increased risk of acquiring AIDS.**
7. **After accidents resulting in bleeding, contaminated surfaces should be cleaned with household bleach freshly diluted 1:10 in water.**
8. **Devices that have punctured the skin, such as hypodermic and acupuncture needles, should be steam sterilized by autoclave before reuse or safely discarded. Whenever possible, disposable needles and equipment should be used.**
9. **When seeking medical or dental care for intercurrent illness, these persons should inform the individuals responsible for their care of their positive antibody status so that appropriate evaluation can be undertaken and precautions taken to prevent transmission to others.**
10. **Testing for HTLV-III antibody should be made available to individuals who may have been infected as a result of their contact with a seropositive person (e.g., sexual partners, persons with whom needles have been shared, infants born to seropositive mothers). Revised recommendations will be published as additional information becomes available and additional experience is gained with this test.**

Reported by CenterS for Disease Control; Food and Drug Administration; Alcohol, Drug Abuse, and Mental Health Administration; National Institutes of Health; Health Resources and Services Administration.

SOURCE: Us. Department of Health and Human Services, Public Health Service, Centers for Disease Control, "Provisional Inter-Agency Recommendations for Screening Donated Blood and Plasma for Antibody to the Virus Causing Acquired Immunodeficiency Syndrome," *Morbidity and Mortality Weekly Report* 34:1-5, Jan. 11, 19SS.

provision of advice to gay men and intravenous drug abusers. One reason may be that providing advice on preventive practices may be viewed as condoning bisexuality, homosexuality, or intravenous drug abuse. Another has been that not enough was known to support definitive guidelines. Too, there is some concern that gay men may be wary of advice from the Federal Government, believing it to stem from a bias against homosexuals or to be based on insufficient medical knowledge (76). Despite remaining questions, there are preventive measures to which all parties agree. The use of condoms, while not assuredly protective against AIDS transmission, does provide some protection against sexually transmitted diseases. Likewise, the use of disposable or sterilized rather than shared or otherwise contaminated needles for intravenous drug use will almost certainly reduce transmission. These considerations are mentioned very briefly in the PHS brochure aimed at gay and bisexual men (148) and are mentioned more explicitly in the recent PHS

recommendations. Brochures designed by gay organizations (69,112,128) have provided much more explicit and practical advice on the relative safety of various sexual practices.

Rather than funding local groups directly, PHS has funded the U.S. Conference of Mayors to act, among other things, as a distribution channel for PHS-developed materials. The Conference of Mayors' role has been expanded to provide risk reduction and blood test information through gay community groups. Fiscal year 1984 appropriations provided $150,000 to be used for prevention projects of community groups; funding decisions for specific projects will be made in early calendar year ***1985 (75).*** Fiscal year 1985 funding for the Conference is anticipated to be $200,000. In addition, CDC is expanding its support of research to evaluate education efforts (e.g., changes in sex practices and number of partners, changes in drug use) by both private and public groups, a research area which NIMH is also supporting.

As noted earlier, about 4 percent of the PHS AIDS budget (exclusive of the Office of Public Affairs in OASH) for fiscal year 1985 was allocated to public education, compared to 2 percent in fiscal year 1984 (see tables ***17*** and **18).** One need found by the U.S. Conference of Mayors' survey of local governments was for training and technical assistance in the community, particularly on safe sex guidelines and the blood test (143). One critic of PHS's budget priorities questions the top priority given to research, sees research and public education working hand-in-hand, with each less effective without the other, and concludes that in the absence of effective interventions and treatment therapies, the only option at this point is prevention of the disease (92). Furthermore, a representative of the National Gay Task Force has stated (88): "The PHS knows how to target its message to specific audiences—using the gay media would be no different but for the fear of being associated too directly with the gay community . . . if the PHS is going to make a conscious decision to leave prevention education to us, they should at least provide some funding. " Finally, one AIDS researcher has observed (99a): "There is an immense job left to do in public education about AIDS risk. This need will certainly become more evident and acute as the disease moves outside of existing risk groups and into the general population in the next 2 years. At that time, continued education will be needed for those in the risk groups about limiting contagion, as well as for the general population in order to prevent hysteria and give the public concrete recommendations as to how to reduce risk of contraction. It would be helpful if Federal funding sources anticipate this trend and plan for such funding. "

Financing of Clinical and Supportive Services

Questions on financing of the clinical and supportive services for AIDS patients and who should be responsible for such financing have arisen repeatedly. It has been estimated that the cost of caring for an average AIDS patient ***from*** diagnosis to death is about ***$60,000*** to ***$70,000 (109,117).***

The Social Security Administration has two programs which provide Federal assistance for those disabled through illness. Both programs apply to those who are unable to work because of a physical or mental disability expected to last at least 12 months or result in death. One program, Disability Insurance (Title II), is for those who have paid into Social Security; the other, Supplemental Security Income, is for those who have not paid enough into Social Security. These tests can usually be met by AIDS patients. However, other factors complicate the process of meeting eligibility requirements for financial assistance and of obtaining coverage for clinical and supportive care. First, there have been criticisms that the use of the relatively conservative surveillance definition of AIDS by CDC has delayed needed financial assistance for patients not meeting this definition of AIDS ***(83).*** Second, Federal and State insurance programs generally reimburse for established and standard treatments, while the most important and promising treatments for opportunistic infections in AIDS are still in the experimental stage (117). Finally, although admission to a hospice might be appropriate or desired by some AIDS patients, recently promulgated reimbursement regulations require that physicians certify that their patients are not expected to live

more than 6 months before the Federal Government will reimburse for care (24).

Additionally, the question remains as to which, if any, government entities—local, State, or Federal—should be responsible for or share in covering the expenses that AIDS patients cannot meet either directly or through their health insurance coverage (123). PHS's potential contribution to services coverage is limited, if not nonexistent. Thus, discussions about possible Federal assistance must include other entities in DHHS, such as the Health Care Financing Administration.

CONCLUSIONS

Accumulating evidence indicates that the recently discovered retrovirus HTLV-III is the basic cause of AIDS. As more has been learned about HTLV-III'S ability to cause disease, it has become apparent that a broad spectrum of immunologic and clinical responses can occur. Some persons have been infected with few or no immunologic abnormalities and no evidence of illness, others have had severe effects on their immune systems and developed fulminant and inevitably fatal AIDS, while others have manifested responses between these two extremes. Associated risk factors are under examination and will help in understanding why some people are able to resist infection while others progress to different stages of clinical illness.

Rapid advances in knowledge about HTLV-III are being made possible because of previous knowledge of the existence of a closely related retrovirus (HTLV-I), recent advances in understanding the functioning of our immune systems, the availability of recombinant DNA technologies, and tests based on immunologic and recombinant DNA principles. The new knowledge about HTLV-III has led to an expanded and increasingly precise cataloging of methods that might be applied against HTLV-III and associated infections and tumors found in AIDS, and some methods, such as drugs that might inhibit infection, are already being tried in limited clinical trials. On the other hand, the discovery of HTLV-111 as the primary cause of AIDS can also be seen **as** only the beginning of focused efforts to control AIDS, and it remains to be seen whether the knowledge that is gained can be used to develop effective vaccines and therapeutic drugs within a few years.

Although DHHS has designated AIDS as its number one health priority, in terms of financial support, this priority has been implemented at PHS and not at the Department level. The Department's position has been that funds for AIDS activities should be transferred from other PHS activities, and increases in funding for AIDS activities have come at the initiative of Congress, not from DHHS. This has also been the case for personnel ceilings, with personnel allocated to AIDS activities within the overall ceilings imposed by OMB on DHHS, which in turn allocates personnel levels to PHS and its agencies.

The question of whether AIDS funds should come out of existing PHS agency budgets or whether such funds should augment agency budgets is related to perceptions about: 1) whether AIDS-related research is part of the overall missions of the PHS agencies involved, and 2) whether the AIDS epidemic is a sufficiently unique and growing public health problem that it requires additional resources. PHS agencies are involved precisely because their basic activities are relevant to AIDS research, which also promises to extend our understandin g of immune mechanisms and the causes of cancer. Such research is attracting many researchers for purposes in addition to finding a solution to the AIDS problem. The issue, therefore, is in deciding: 1) when other activities are being curtailed too much because of fund transfers from those activities to AIDS-related activities; 2) when AIDS-related activities are being delayed because of wrangling over how much funds are to be transferred and from which other activities; and 3) when such fund transfers become inadequate to fund AIDS-related activities. There is probably no way to reach a consensus on when these thresholds have been or will be reached.

Aside from the issue of fund transfers and their ability to meet AIDS-related research needs without substantially retarding research in other priority areas, the allocation of funds and the sources of those funds in themselves are important measures of priority-setting for addressing the AIDS problem. On this point, while PHS has reacted to OTA's assessment by stating that the funds PHS agencies have (including appropriations voted by Congress and resisted by DHHS) are adequate (22), PHS had previously asked for additional funds (20), two NCI advisory bodies have stated that more funds are needed (163,176), and numerous Federal and non-Federal researchers have privately told OTA that additional funds and personnel have been needed.

Another consideration that pertains to the adequacy of resources devoted to AIDS-related research is that research and development are going on internationally and within both the public and private sectors. Thus, an examination of PHS's contribution to AIDS-related research provides an incomplete picture of the extent of activities and resources devoted to addressing the AIDS epidemic. However, PHS's activities are laying down much of the foundation, and PHS investigators have been indispensable and are extensively involved in collaborations with non-Federal researchers both nationally and internationally.

In contrast to AIDS-related research which is international and involves both for-profit and nonprofit investigators, there are other AIDS-related activities that are domestic in nature and which involve public health policy. These activities involve issues which could not be addressed extensively within this memorandum primarily on the biology of AIDS, but which were of sufficient importance to be identified and raised briefly—namely, prevention of AIDS through education, financing of clinical and supportive services for AIDS patients, and assurances of confidentiality and informed consent.

Although significant advances have been made in understanding AIDS, its primary cause, and associated factors, it will be some time before this biomedical knowledge can be expected to be translated into effective preventive and therapeutic interventions. In the interim, and probably even if biological remedies become available, prevention through education on ways of minimizing exposure to HTLV-III has the greatest potential of limiting the spread of AIDS. So far, efforts to prevent AIDS through education have received minimal funding, especially efforts targeted at the groups at highest risk.

Providing and assisting in paying for clinical and supportive services is already a significant problem in those areas of the country with relatively large numbers of AIDS patients. This situation will worsen as the number of AIDS patients increases and if new treatments prolong life but do not restore health. The Federal response to date has focused on the biomedical research aspects of AIDS; thus, PHS has been given the primary responsibility for AIDS-related activities. Increasing demands for Federal support are inevitable, but the potential contribution of PHS agencies to providing and financing service needs is severely limited by the nature of their responsibilities. Thus, if the Federal Government is to respond to the service needs of AIDS patients, Federal activities will have to expand beyond those attributable to PHS and at a minimum involve other organizational units within DHHS. The allocation of responsibility between Federal, State, and local governments will also have to be determined, and legislation defining the Federal responsibility will most likely have to be enacted.

A final related issue identified in this memorandum is that of confidentiality and informed consent, first arising in the context of treatment of AIDS patients and participation in AIDS-related research projects, and soon to be a major concern as tests for evidence of exposure or infection to HTLV-III become generally available. Confidentiality safeguards can be improved without sacrificing the surveillance needs of public health officials and data sharing among researchers. Informed consent will be an especially difficult issue, because the first tests to be applied will detect exposure to HTLV-III through the presence or absence of antibodies. However, persons who test positive will not be able to know whether they are actually carriers of HTLV-III, whether they will develop AIDS, or whether they are not infected and will remain well.