Chapter 1
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The **basic cause of acquired immunodeficiency syndrome** (AIDS) **is almost certainly a newly discovered virus, human T-cell lymphotropic virus, type III, or** "HTLV-III." Researchers who have isolated viruses similar to HTLV-III have given their isolates other descriptive names, such as "lymphadenopathy-associated virus" (LAV) or "AIDS-related virus" (ARV), but these isolates and HTLV-III are essentially the same.

The AIDS virus preferentially infects and destroys certain white blood cells called "T lymphocytes" that are essential for the functioning of the body's immune system. When the immune system is severely depressed or destroyed by HTLV-III, other infectious agents such as bacteria or other types of viruses that usually do not cause disease in persons with normal immune functions may have the opportunity to cause disease ("opportunistic infections") because of the body's weakened defenses. Different types of cancer may also occur with severe depression of the immune system by HTLV-III infection. The cause of these cancers is not certain, but it may be a combination of depressed immune functions and infection with other viruses, or perhaps involve infection by the HTLV-III virus itself.

As more has been learned about the ability of HTLV-III to cause disease, it has become apparent that a broad spectrum of clinical responses can occur. Some people have been infected and shown few or no immunologic abnormalities and no evidence of illness, others have had severe effects on their immune systems and developed fulminant and 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 exposed to HTLV-III remain well while others progress to different stages of clinical illness. **Since AIDS is a newly discovered disease and the time between exposure and the onset of clinical disease can take several years, it is too soon to tell what percentage of persons exposed to the virus will develop AIDS. It is also too soon to tell whether persons exhibiting milder manifestations of disease (e.g., fever, some depression of immune functions, enlarged lymph nodes) will eventually develop AIDS, continue to exhibit signs and symptoms of mild disease, or get well.**

Prior to the discovery of the etiologic (causative) agent for AIDS, efforts to devise preventive and treatment strategies had to depend on empirical observations of AIDS's epidemiology and effects on the body. **The discovery of HTLV-III now provides a theoretical foundation which greatly expands the range of possible strategies to prevent, diagnose, and treat AIDS.** It is important to recognize, however, that the discovery of HTLV-III only begins the next phase of efforts to control AIDS, Thus, it remains to be seen whether the new knowledge that is gained can be used to develop effective drugs and vaccines within a few years. Meanwhile, the number of persons infected with the virus and the number of AIDS cases continue to grow rapidly.

The activities of the U.S. Public Health *Service* (PHS) have laid down most of the foundation for addressing the AIDS epidemic. 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 antibodies; and research on AIDS treatment, vaccine development, and the many remaining questions about the natural history of the disease is progressing. Furthermore, PHS investigators at present are extensively involved in collaborations with non-Federal researchers, both nationally and internationally. **It has not always been clear, however, that the amount of support for AIDS activ-**

ities has been equivalent to the effort that individual researchers and PHS agencies believe is necessary. Furthermore, there are issues that extend beyond the biological nature of AIDS which warrant more attention from the Federal Government—prevention of AIDS through education, **confidentiality and informed consent for research and blood donation, and support for the clinical** and financial needs of AIDS patients.

THE BIOLOGY OF AIDS

When the code contained in the DNA (deoxyribonucleic acid) of a cell's genes is to be "translated" to produce a product such as a protein, an RNA (ribonucleic acid) copy of the relevant piece of DNA is "transcribed," and the RNA copy then travels to the cell's production site, where it serves as a template for protein production. Collectively, this process is termed "gene expression. "

HTLV-III belongs to a group of viruses called "retroviruses," which are so named because they can reverse the process of gene expression when they infect cells. Retroviruses contain RNA, not DNA, but reproduce by incorporation into the DNA of the cells they infect. In order to be incorporated into a host cell's DNA, the retroviral RNA must be transcribed into its DNA counterpart. An enzyme that the retrovirus produces, called "reverse transcriptase, " accomplishes this process. When the retrovirus is ready to reproduce, it initiates the normal process of gene expression whereby DNA is transcribed into RNA but at a greatly accelerated rate, spewing out copies of the retrovirus in its original RNA form.

HTLV-III attacks what is commonly referred to as the "helper/inducer" subset of T lymphocytes, or, more accurately, the "T4" subset. T lymphocytes are classified into various subsets. One method of classification distinguishes between T cells that function to "help" and T cells that function to "suppress" immune functions as the immune system is activated and then is fine-tuned when the body is invaded by foreign materials. T lymphocytes can also be classified by the different molecules on their cell surfaces through the use of monoclinal antibodies that recognize each type of surface molecule as a separate and unique antigen. One such classification system separates T lymphocytes into those that have "T4" and those that have "T8" molecules on their surface (named after the monoclinal antibodies used to distinguish between these two types of surface molecules or antigens). Functional and surface molecule methods of classification result in overlapping categories. Commonly, however, even though both the "T4" and "T8" subsets contain cells that help and cells that suppress immune responses, the "T4" subset is referred to as the "helper/inducer" subset of T lymphocytes, and the "T8" subset, as the "suppressor" subset.

The primary defect in AIDS is an acquired, persistent, quantitative, and functional depression of T4 lymphocytes. 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 the HTLV-III virus and the T4 molecule is apparently the way in which the virus gains entry into the cell.

The T4 molecule can be found not only on T4 lymphocytes but also on some other types of white blood cells that perform a scavenging or phagocytic function by engulfing foreign material and consuming debris and foreign bodies. This observation raises the question of whether these other white blood cells may also become infected with HTLV-III. Furthermore, brain cells and T lymphocytes are known to share some common c-en 'surface molecules, and recent evidence has shown that the brain of an AIDS patient can be infected and the virus reproduced there. Infection of the brain would further complicate future treatment prospects because of the general difficulty in getting drugs into the central nervous system.

The availability of various tests for HTLV-III should result in a more precise delineation of the natural history of AIDS. Studies of different populations at risk, their variations in associated

risk factors and in clinical responses upon exposure to HTLV-III, are of immediate relevance to our understanding of how the disease spreads, preventive strategies, and the possibility of early treatment. For example, the human immune system will produce antibodies to whatever antigens are encountered, so the mere presence of antibodies to HTLV-III does not necessarily mean that the types of antibodies that will ***neutralize*** the virus have been produced. By studying persons who are at high risk for AIDS but who have not developed the disease, scientists may discover which of the several antibodies that are produced in response to infection with HTLV-III might neutralize the virus.

Production of antibodies upon exposure to HTLV-III is also the basis for a blood test that will be used initially for screening blood donations and plasma collections. It is now known, however, that some persons can be infected with the virus but have no current symptoms of disease and not produce antibodies. The blood test for antibodies to HTLV-III, therefore, will not replace screening procedures designed to exclude potential blood donors in groups at high risk for AIDS. Because of current technical capabilities, the first-generation blood test relies on detection of antibodies to HTLV-III instead of detection of the virus itself (or its parts). Large quantities of HTLV-III can now be grown and used as the antigen to detect antibodies in tested blood. Methods to mass produce antibodies to detect the presence of viral antigens in tested blood, however, have yet to be developed.

Use of the blood test raises difficult issues pertaining to informed consent and confidentiality, because the meaning of a positive test, other than evidence of exposure to HTLV-III, is uncertain. Does **a** positive result mean that a person who has antibodies to the virus is also infected with it? This question can be answered on a case-by-case basis by a few researchers who have the capability to test for the presence of the virus, but the capacity to perform such tests routinely has yet to be developed. What are the chances that an antibody-positive person will develo$_p$ AIDS? The answer to this question will only come after long-term monitoring of persons who are HTLV-111 antibody-positive.

The discovery of HTLV-III makes possible the tentative confirmation that newer methods of preparing antihemophilic factors from plasma can inactivate the virus. Some plasma protein products, such as albumin, are already heated to temperatures that inactivate most viruses without causing these products to lose their activity. However, the coagulation proteins are not as resilient in preserving their activity when heated. Improvements in heat treatment using buffers to protect the proteins during heating, however, have recently been shown to inactivate some viruses, and with the availability of HTLV-III for testing, these new methods and further improvements on them have been shown to inactivate HTLV-III. (The cellular elements of blood that are used in transfusions—red blood cells and platelets—and fresh plasma, would be destroyed by the temperatures necessary to inactivate HTLV-III.)

The discovery of HTLV-III also makes possible the development of more specific therapeutic approaches to AIDS. Cultures of T lymphocytes mixed with HTLV-III can be used to test drugs that might inhibit infection by HTLV-III. At least three drugs, suramin, ribavirin, and HPA-23, have been shown to inhibit infection by blocking the action of the reverse transcriptase enzyme and are now being tested in limited clinical trials. More importantly, **the life cycle of the virus is now under study, and theories based on the understanding gained will lead to multiple therapeutic approaches.** Thus, for example, the experiments leading to the discovery that the T4 molecule on T4 lymphocytes was an essential component of the cell-surface receptor for HTLV-III raise the possibility of using monoclinal antibodies against the T4 molecule to block the virus's entry into the cell.

The development of a vaccine against HTLV-111, using novel as well as established methods, is now under way. The many unknowns associated with HTLV-III make it prudent to develop a vaccine that does not contain the virus's genetic material, so current efforts are focused on finding and using the part ("subunit") of the virus that would elicit the proper antibody to neutralize the virus. Current efforts to develop a "subunit" vaccine include breaking down the virus and testing its various parts; taking the gene that corresponds

to the **particular part of the virus under study and inserting it through recombinant DNA techniques into bacteria, yeast, or mammalian cells so that the subunit can be produced in quantity; inserting the corresponding gene into other, benign viruses (e.g., into vaccinia virus, used** to immunize against smallpox) with the intention of using those viruses as the vaccine; and developing copies of the relevant viral subunit through novel manipulations of antigen-antibody interactions.

Despite these rapid developments in vaccine research, serious obstacles remain. The first is that most of the newer techniques are largely experimental, the first of the vaccines from the most understood recombinant DNA techniques (i.e., a vaccine for hepatitis B) having just become available. Second, there is evidence that the genes which code for the parts of the virus that would be most likely to make an effective vaccine (i.e., the surface membrane or "envelope" of the virus) change frequently, although not drastically. If these genetic mutations are significant enough that their corresponding protein molecules change their antigenic characteristics, it will be difficult to develop an effective vaccine.

In contrast to these promising developments in understanding the biology of AIDS are the ever growing number of AIDS patients and the rapidly enlarging pool of persons who have been exposed to HTLV-III and who may be carriers of the virus. The total number of AIDS cases reported to the Centers for Disease Control (CDC) by the end of 1984 was approximately 7,000, and the number of reported cases has been doubling every year—fewer than 900 cases prior to December 1982, more than ***2,000*** cases in ***1983,*** and almost ***4,000*** cases in 1984. Seventy-three percent of patients diagnosed before January 1983 have died. **Forty thousand new cases are expected to be reported in the United States in the next 2 years.** Furthermore, surveys of high-risk groups (gay men, intravenous drug abusers, hemophiliacs) for the presence of antibodies to HTLV-III in their blood have shown marked increases in positive rates since about **1980, with current positive rates between 65 and 90 percent in some of the tested populations.**

AIDS is not only a problem in the United States. There are at least 500 cases in the rest of the **Americas, 600 in Europe, and several thousand** in central Africa. **In some parts of central Africa, where infection with the HTLV-III virus appears to predate infections in the United States, heterosexual transmission appears to be common and may be the predominant mode of transmission. Heterosexual transmission has occurred in the United States, but is still relatively uncommon and has been primarily from males to their female partners, particularly in the intravenous drug abuser group.** A significant portion of U.S. female intravenous drug abusers practice prostitution, and the possibility of increased female-to-male transmission and risks associated through contacts with prostitutes are under study.

Thus, while significant advances in understanding the biology of the AIDS virus are occurring and may lead to effective therapeutic drugs and a vaccine, the number of persons exposed to the virus and probably carrying it and the number of AIDS cases continue to increase at an accelerated pace.

FEDERAL SUPPORT OF AIDS RESEARCH

The U.S. Department of Health and Human Services (DHHS) has designated AIDS as its number one health priority, and much of what we know about the biology of AIDS is a result of federally sponsored activities. However, the Department's position has been that funds for AIDS activities should be transferred from other PHS activities, and increases in funding specifically for AIDS activities have come at the initiative of Congress, not from DHHS. Personnel ceilings have been a special problem.

Although AIDS funding has been substantial, particularly in fiscal years 1984 and 1985, the history of specific funding for AIDS has been marked by tension among the individual PHS agencies,

DHHS, and Congress. Through the Assistant Secretary for Health, individual PHS agencies have consistently asked DHHS to request particular **sums from Congress; the Department has 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, the Department has maintained that PHS agencies should be able to conduct AIDS research without extra funds. However, threatened cuts in overall funding and personnel levels have restricted the ability of affected agencies to redirect resources. **Of greater impact than holding general funding of PHS agencies about even or decreasing it have been budget requests for decreases in personnel ceilings. At critical times, several of the PHS agencies have actually experienced decreases in personnel.**

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 uncertain distribution of resources has intensified competition among agencies 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.

In addition to the question of whether or not sufficient resources are being allocated to PHS agencies' AIDS activities by DHHS and Congress, there remains the question of whether ***resources*** are being allocated adequately to the various AIDS activities. In particular, doubts have been raised about the adequacy of resources devoted to the search for factors affecting transmissibility, the provision of treatment, and prevention through public education.

In general, the search for factors affecting the development of AIDS has always accounted for a large proportion of the AIDS budget. For both fiscal years 1984 and 1985, greater amounts were budgeted for cofactor research and epidemiologic studies after the discovery of HTLV-III than before its discovery. PHS estimates that 12.6 percent of the resources allocated to AIDS in fiscal year 1984 were 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 substantially less as a percentage of the total (26 percent) will be obligated to epidemiologic studies than in fiscal year 1984. In total dollars, however, almost $5 million more will be obligated to epidemiologic studies in fiscal year 1985 than in fiscal year ***1984,*** and ***$6*** million more to cofactor research.

About 2. I percent of the AIDS budget for fiscal year 1985, or nearly $2 million, is being spent for research on psychosocial factors related to AIDS. As defined by PHS, this category includes research into the psychosocial consequences of AIDS as well as research into the contribution of these factors to the development of AIDS. Psychosocial risk factors include life stress, exhaustion, health habits, depression, anxiety, coping mechanisms, a sense of helplessness, and the loss of social support.

Approximately 14.8 percent of the AIDS budget for fiscal year 1985 is devoted to research on treatment (8.8 percent for the etiologic agent, and 6 percent for opportunistic infections). Except for treatment given to AIDS patients at the National Institutes of Health's Clinical Center, which is a research hospital, no funds have been allocated to the treatment of patients per se.

In the past, relatively few funds were allocated to public education. Between 1984 and 1985, however, the amount allocated to such activities more than doubled, from ***$1.4*** million to **$3.8 million,** most of it **for** CDC. The AIDS budget in PHS's Office of Public Affairs, which has maintained the AIDS hotline, the Facts ***About AIDS*** newsletter, and developed booklets and a videotape about AIDS, is scheduled to decrease from ***$200,000*** in fiscal year **1984 to $120,000** in fiscal year **1985.**

Whether information about AIDS has been generated and disseminated on an adequate and timely basis has also been a cause of recurrent concern. The involvement of multiple organizations in similar research activities but addressed at different aspects of a common problem is arguably the best scenario for research. However, it means

that researchers are constantly striving to keep abreast of the work of others.

In addressing AIDS, sharing of information has taken place through the informal networks that exist among PHS agencies and among their researchers and has been augmented by coordinating committees, external advisory committees, conferences, and cooperative agreements on funding extramural research and conducting intramural research. Most of these sharing and coordinating activities would have taken place regardless of any directive from PHS central management. In some instances, however, PHS (or departmental level) guidance might have led to better coordination—e.g., PHS might have directed the National Cancer Institute to share virus cultures with CDC. Finally, the announcement by the Secretary of DHHS of the discovery of the etiologic agent for AIDS appears to have been too optimistic regarding the use of a blood test to screen for exposure to HTLV-III and did not take into account the social implications and ethical dilemmas that would have to be addressed when persons who might be carriers of the HTLV-III virus were identified through a blood test.

Two factors which may have impeded the generation and dissemination of information are matters of more generalizable policy concerns. First, in the context of a public health emergency such as AIDS, the Federal grants application and approval process for extramural research works too slowly. Second, although private industry is involved in similar research and development activities, Federal regulations concerning commercial development of drugs, biologics, and devices mean that much of the information generated is not available to other researchers. A systematic examination of these more generalizable concerns is needed.

Thus, OTA finds that while the Federal Government has designated AIDS our country's number one health priority, increases in funding specifically for AIDS activities have come at the initiative of Congress, and PHS agencies have had difficulties in planning their AIDS-related activities because of uncertainties over budget and personnel allocations. Furthermore, in some instances, coordination between PHS researchers and between DHHS policy makers and PHS researchers could have been better managed. Two general questions that need further examination are: 1) how Federal research funding can be accelerated in public health emergencies without compromising the quality of research to be supported, and 2) how access to commercially sponsored research might be improved without infringing on the property rights of commercial enterprises.

RELATED ISSUES

It will be some time before the new knowledge that has been gained about AIDS can be expected to be translated into effective preventive and therapeutic interventions. In the interim, and probably even if biological remedies for the disease become available, prevention of AIDS through education about ways of minimizing exposure to HTLV-III has the greatest potential of limiting the spread of this disease. So far, efforts to prevent AIDS through education have received minimal funding, especially efforts targeted at the groups at highest risk.

The issues of confidentiality and informed consent, first arising in the context of treatment of AIDS patients and participation in AIDS-related research projects, will soon be a major concern as tests for evidence of exposure to or infection by HTLV-III become generally available. Confidentiality safeguards can be improved without sacrificing the surveillance needs of public health officials or data sharing among researchers. Informed consent will bean 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, will develop AIDS, or will remain well. **These developments portend even more widespread and serious implications for our country's public health and social policies.** Decisions will have to be made

soon that attempt to balance the public health concerns surrounding the transmissibility of AIDS from persons who have antibodies against HTLV-111 versus the stigma that may attach to these persons, which could lead to their exclusion from some occupations and perhaps to even greater isolation from the rest of society.

Finally, 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. To date, the Federal response has focused on the biomedical aspects of AIDS, so the primary responsibility for AIDS-related activities has rested with PHS. The potential contribution of PHS agencies to the provision and financing of 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, such as the Health Care Financing Administration.

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