THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS): UPDATE ON THE DISEASE AND ON NCI RESEARCH ACTIVITIES

Background

Since late 1978, a new disease of unknown cause and great virulence has appeared. This disease has affected more than 600 people; almost half have died, and the ultimate fatality rate may reach 70-80%. The disease has been reported from 27 states, and while the great majority of the patients have been American, 34 cases in 9 other countries (many with American contacts) have been reported. The rate of attack is increasing: In 1981, an average of one new case was reported each day, but in June 1982, about 3 new cases were reported each day. Almost half of the patients have been from New York City, and 22% from Los Angeles or San Francisco.

One-third of the AIDS patients have developed Kaposi's sarcoma, a hitherto rare form of cancer, and other types of cancer (e.g., Burkitt's lymphoma) are becoming apparent as well. A second major way in which the disease manifests itself is through infection by any of several types of organism. The most common infection is caused by Pneumocystis carinii, a protozoan which produces a severe pneumonia. The underlying problem in this disease, however, is a defective immune system which leaves the patients unable to resist infections and cancer. Thus, AIDS is a serious public health hazard, but may offer a profound insight into the normal functions of the immune system and the origins of cancer.

Most investigators now believe that AIDS is caused by an infectious agent, in all likelihood a virus. The agent may be a new virus, a new variant of an existing virus, or a virus which has long existed in a very confined population and only recently been introduced into a much larger population. The spread of AIDS resembles that of the hepatitis B virus ("serum hepatitis"), but there is no evidence that hepatitis viruses are in fact the cause of AIDS.

Seventy-five percent of AIDS patients are young (25-45), white, urban homosexual or bisexual men, who are very active sexually. Homosexuals with AIDS have averaged about 1,100 sexual partners during their lifetime, but homosexual men without any manifestations of AIDS average about 500.

The second largest group of AIDS patients (about 14%) are mainly black or Hispanic heterosexual men from New York or New Jersey who are users of intravenous drugs, e.g., heroin. As with sexually hyperactive homosexual men, drug users are known to have a high incidence of hepatitis B infections, with the virus spread via sexual contact or by contaminated needles.

Hepatitis B is also transmitted through transfusion of whole blood or blood products. Within the past few months, three men with hemophilia have developed AIDS; the appearance of AIDS in this third group is a cause for particular concern because it suggests that the disease was acquired from an infectious agent which contaminated the blood product (a clotting

factor) which hemophiliacs require to prevent bleeding. However, there is no evidence associating ordinary blood transfusions with AIDS. Since the clotting factor administered to hemophiliacs is prepared from the blood of many thousands of individual donors, the risk of exposure of a hemophiliac to a possible infectious agent in the blood would be very much greater than that of patients who receive transfusions of whole blood from one or a few donors.

The fourth identifiable group of AIDS patients, about 6% of the total, are recent Haitian immigrants to the United States. These patients deny homosexual experience, and almost all deny the use of intravenous drugs. AIDS appears to occur in Haiti as well, with 12 cases of KS reported in Port-au-Prince, an extraordinary number for such a small country. Haiti is a favorite vacation spot for many American homosexual men; thus, there is the possibility that these men have carried the disease to or from Haiti. Since there is much chronic illness, malnutrition, and early death in Haiti and poor medical record keeping, it will be difficult to learn whether AIDS, and its putative viral cause, were present in Haiti before the first cases appeared in this country.

A small number of AIDS patients are neither homosexual men, heterosexual male drug users, hemophiliacs, nor Haitian men. Within this group of "others" are 32 women (5% of the total). While some of these women are drug users and some are Haitian, more than half are neither, nor are they homosexual.

Before 1979, Kaposi's sarcoma (KS) was very rare in the United States, although not uncommon in equatorial Africa. When KS did occur in the USA, it was found primarily in elderly men of Mediterranean origin or in individuals whose immune systems had been suppressed by cancer chemotherapy or by drugs used to prevent the rejection of transplanted organs. As a large number of KS cases began to develop in young homosexual men, it became apparent that this was one of the first human cancers to occur in epidemic form (Burkitt's lymphoma, which also occurs in equatorial Africa, is another one). Not only has the incidence of KS in this country increased dramatically, but the course of the sarcoma in AIDS patients is very different from that previously seen in elderly men. The latter patients usually have characteristic indolent skin lesions on their legs which respond well to chemotherapy or radiation and are rarely lethal. However, in AIDS patients, the lesions are usually located on the upper part of the trunk and head, on mucous membranes, and in the visceral organs as well. New lesions develop rapidly, the disease appears to be very aggressive, and most of the patients respond poorly to chemotherapy - partly because of the apparent resistance of the tumor *per se* and partly because the chemotherapy further compromises the patient's immune system, making life-threatening infections even more likely.

The infections seen in AIDS patients are typical of those which occur in immunosuppressed individuals, i.e., they are "opportunistic". About 60% of the AIDS patients, including some who also have KS, have developed *Pneumocystis carinni* pneumonia (PCP). Heterosexual male patients and women have more commonly developed PCP than KS, and as the number of non-homosexual patients has increased, PCP has become more prevalent

among AIDS patients than the cancer. Moreover, a wide variety of other organisms, including viruses, fungi, protozoans, and the bacteria which cause tuberculosis, have also been seen. Indeed, some patients have been infected with organisms that have hitherto only infected animals. Once an opportunistic infection has occurred in an AIDS patient, the patient's course has been inexorably downhill. While individual infections can be controlled with antimicrobial drugs temporarily, they eventually recur or another life-threatening infection develops.

The organisms involved in these infections are almost all of the types that are ordinarily resisted by the cellular immune system, and it is evident that the underlying defect in AIDS patients is one which affects cell-mediated immunity. The patient's humoral immunity is not impaired: AIDS patients have normal or even elevated concentrations of antibodies in their blood. However, these patients have half or less than half of the normal number of peripheral blood lymphocytes. The antibody-secreting B lymphocytes do not appear to be affected, but T lymphocytes, the cells associated with cell-mediated immunity, are low in number and abnormal in composition. In particular, the "helper" T cell subpopulation is greatly depleted and may even be absent, whereas the "suppressor" T cell subpopulation is normal in most patients. Helper T cells aid other types of immune cells to perform their functions, and suppressor T cells inhibit the functioning of these other immune cells. The loss of the helper cell population, while the suppressor cell population remains intact, can thus produce a profound suppression of cellular immunity (although paradoxically, some AIDS patients have demonstrated auto-immune phenomena). In addition to the T cell abnormality, 40% of AIDS patients have a reduced population of natural killer cells, which have also been implicated in cancer cell surveillance. The loss of these components of the cell-mediated immune system may thus allow opportunistic infections to occur, as well as for small numbers of transformed cells, ordinarily destroyed by the immune system, to develop into life-threatening tumors (similar to the probable situation with immunosuppressed kidney transplant recipients who develop KS).

The reversal of the ratio of T helper to T suppressor lymphocytes characteristic of AIDS patients has been found, albeit to a lesser degree, in 80% of seemingly healthy homosexual men in New York. Moreover, a large number of homosexual men in New York City have been reported to have enlarged lymph nodes, fever, weight loss, fatigue, and other symptoms of a chronic, influenza-like syndrome. It is possible that both the symptom-free people with immune abnormalities detected only in the laboratory, as well as the patients with chronic lymphadenopathy, will eventually develop a more severe AIDS with KS and/or opportunistic infections. If so, a very large number of people, in the tens of thousands, may be at risk (200,000 homosexual men live in New York City alone). No patient with lymphadenopathy, PCP, or KS has yet been seen to recover, although some healthy homosexual men - only with the laboratory abnormality - were found to improve with time.

Prior to the discovery of AIDS in the three patients with hemophilia, a great deal of attention was given to the possibility that this disease was induced by a drug (e.g., nitrite "poppers"), toxin, cytomegalovirus, or one of the many other types of infectious agents known to occur commonly in sexually hyperactive homosexuals. Another etiologic possibility was an immune

phenomenon, such as an anti-sperm antibody that might cross-react with T-helper cells. Now however, attention is focused on a possible blood-borne viral pathogen which destroys helper T cells, not only because of the hemophiliac experience, but also because of the overall similarity of the epidemiology of this illness to that of hepatitis B and because of the discovery of clusters of AIDS patients (including pairs of "roommates") who have had intimate contact with one another. Hepatitis B commonly infects homosexuals, drug addicts, donor-blood recipents, and, partly because of poor sanitary conditions, most Haitians.

Finally, it may well be that not all people exposed to the agent which causes AIDS will develop the disease, or that the specific manifestations of the syndrome among patients at risk may be genetically determined. For example, there appears to be an unusually high frequency of a certain genetically determined leukocyte antigen (HLA-DR5) among AIDS patients with KS. This association suggests a genetic predisposition, if not to the syndrome in its entirety, than at least to the sarcoma, and may make high-risk individuals easier to identify.

NCI Activities

The NCI has taken an active role with respect to AIDS. The first large meeting of scientists anywhere in the world to discuss this new disease was sponsored by the NCI and held at the NIH in September, 1981. Since that time, the CDC and the NCI have taken the initiative in encouraging recognition of, and research on, AIDS. In FY 82, a series of contracts which provide support for research projects in the Environmental Epidemiology Branch, DCCP, was redirected toward providing laboratory and technical aid for NCI studies of patients with this syndrome; a total of $450,000 was spent in this way. Moreover, a number of large NCI program project grants which explore the possible viral etiology of human cancer, or the relationship of the immune system to cancer in man, were re-focused on research questions generated by AIDS patients. Finally, 10 NCI grants were specifically supplemented in FY 82 to allow an expansion of clinical studies on AIDS patients, including grantees at UCLA, the University of California at San Francisco, Memorial Sloan-Kettering Institute, and NYU. The total NCI grant pool which was supplemented, redirected, or related closely to AIDS in FY 82 is approximately $500,000. Together with the amount spent for epidemiology contract support, NCI funding for AIDS in FY 82 was approximately $1,000,000. The large number of AIDS publications by NCI-supported researchers which have recently appeared confirms the importance of the NCI funds awarded so far.

More than $2,000,000 will be awarded by the NCI to support AIDS-related research in FY 83, including funds set aside for a new Cooperative Agreement. The NCI anticipates making multiple awards as a result of its recent request for Cooperative Agreement applications, the due date for which is October 22, 1982. It is anticipated that a total of $1,000,000 will be awarded to fund the initial year's awards. It is intended that this research will be conducted in the context of a working group, i.e., a group of institutions carrying out various research projects funded as

a result of this Agreement. NCI staff will serve as a resource of information and will work to facilitate the exchange of information and material between involved investigators. The studies to be supported will stress innovative approaches to the AIDS problem, and will include any or all of the following three components:

1. Epidemiologic studies designed to identify risk factors in patients with AIDS or prodromal conditions, along with appropriate control populations.

2. Laboratory research projects in etiology and pathophysiology; these will include studies in such areas as immunology and virology.

3. Innovative treatment and prevention research projects.

The NCI has encouraged applications from institutions or consortia possessing resources and expertise in all three areas.

Finally, the intramural program of the NCI is also extremely interested in AIDS. More than 20 patients have so far been admitted to the Clinical Center and have been jointly treated by investigators of the NCI, NIAID, the Critical Care Medicine Unit, and the Bureau of Biologics. A large number of laboratories throughout the NIH are studying tissue specimens from these patients, and a clinical trial of interferon therapy for Clinical Center AIDS patients with KS is about to begin, following the suggestion from investigators at Memorial Sloan Kettering that KS lesions may be responsive to this agent. Other therapeutic research will be devoted to pharmacologic and biologic methods by which the immune system of AIDS patients might be reconstituted, thus controlling or preventing the infections and cancer.

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