

### The Epidemiology of AIDS

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**M**ORE THAN 1,640 CASES OF ACQUIRED IMMUNE deficiency syndrome (AIDS), a severe disease syndrome involving opportunistic infections and a rare cancer, have been reported to the Centers for Disease Control (CDC) since June 1981. Of these patients with AIDS in the United States, more than 640 have died. The fatality rate is expected to increase with time.

By now, AIDS has become quite well known through scientific publications and the mass media. But its cause is not known. Its method of transmission is not known. And the ultimate measure of its toll in deaths is not known.

The epidemiologic picture of the disease in 1983 strongly suggests that it is caused by an infectious agent or agents. Investigators base the theory of an infectious agent on the following observations: the epidemic is a new one; it appears to have started in limited geographic areas and is now occurring in other areas; clusters of AIDS cases have been identified; and AIDS has appeared almost simultaneously in different and distinct population groups with little in common.

Patients have been found in 38 States, but most patients live on the East or West Coast of the United States—New York, California, New Jersey, or Florida. New York City has more cases of AIDS diagnosed and reported in residents than any other city in the United States.

Early manifestations of AIDS include unexplained weight loss, night sweats, general lymphadenopathy, fatigue, and general malaise. However, the basic disorder appears to be a defective immune system which is no longer able to protect the body against infection and at least one type of cancer.

The first reported cases of the new syndrome were recorded in the Morbidity and Mortality Weekly Report (MMWR) of June 5, 1981. Five young men, all active homosexuals, had been treated in Los An-

geles hospitals for *Pneumocystis carinii* pneumonia (PCP) infection. Two of these five patients had died. All had evidence of other infections and a defective immune system.

Those cases posed the first troubling questions that have since developed into a major national and international public health and scientific challenge. Since *Pneumocystis* pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients, the occurrence of the infection in five previously healthy persons was unusual. Because all the patients were homosexual, there was a suggested association between some aspect of a homosexual lifestyle, or disease acquired through sexual contact, and the infection in the original patients.

#### Puzzles in the Distribution of Cases

At about the same time, Kaposi's sarcoma, an uncommon malignancy in the United States, was diagnosed in 26 homosexual men—20 in New York City and 6 in California. The 26 patients ranged in age from 26 to 51 years. Eight of the patients died—all within 24 months after diagnosis of the unusual cancer.

CDC began systematic surveillance for cases of these diseases in June 1981. A task force was established within the Agency in July 1981 to characterize the disease, to determine the frequency of its occurrence in the population, and to determine who was at risk of becoming ill, and why. The initial search was for laboratory-proven Kaposi's sarcoma (KS) or proven life-threatening opportunistic infections (or both) in previously healthy people between the ages of 15 and 60.

The task force began its search by contacting physicians, other medical specialists, major hospitals, and tumor registries in New York State, California, and Georgia. Of particular value in the surveillance was the review of requests for pentamidine, a drug used to treat *Pneumocystis carinii* pneumonia. Later, a more passive surveillance system was begun, based on phone and mail reports from individual physicians and health departments and on a continuing review of requests for pentamidine; this surveillance continues.

According to the investigation reports of the CDC Task Force, the AIDS epidemic is a new phenomenon. This conclusion is based on opinions of clini-

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cians who treat patients, on the increasing numbers of reported cases, and on the number of requests to CDC for pentamidine isethionate used to treat *Pneumocystis carinii* infections.

In September 1981, CDC began a case-control study. Interviews were conducted with homosexual AIDS patients and with healthy male homosexual controls who were located through private physicians or VD clinics. Fifty patients with AIDS and 120 homosexual men without AIDS were interviewed.

A subset of homosexual men was identified. It included men who were more likely to have many anonymous sexual partners, to have a history of a variety of sexually transmitted diseases, and to engage in sexual practices which increase the risk of exposure to small amounts of blood and feces. The most important variable was that the patients had more sexual partners than the controls—an average of 60 per year for patients compared with 25 per year for controls.

Later in 1981, there were reports from New York of several cases of *Pneumocystis* pneumonia and other opportunistic infections in heterosexual men and women who abused intravenous (IV) drugs. The New York and New Jersey State health departments reported similar symptoms in a small number of prisoners. About the same time, reports were received from Miami, as well as Brooklyn, N.Y., of AIDS in several Haitian patients who had recently moved to the United States.

In early 1982, the first report of a hemophilia A patient with PCP came from Miami. The clinical and immunologic features of this and subsequent cases were similar to those recently observed among certain homosexual males, heterosexuals who abuse IV drugs, and Haitians who recently entered the United States. The July 16, 1982, issue of the MMWR reported that "the occurrence among the three hemophiliac cases suggests the possible transmission of an agent through blood products." In most instances,

these patients have been the first AIDS cases in their cities, States, or regions. They have had no common medications (other than blood products), occupations, habits, or types of pets, or any uniform antecedent history of personal or family illnesses with immunologic relevance.

In July 1982, representatives of CDC, the Food and Drug Administration, the National Hemophilia Foundation, and other organizations met to plan studies to evaluate the risks to hemophiliacs. CDC and the National Hemophilia Foundation also initiated collaborative surveillance. A Public Health Service Advisory Committee was formed to consider the implication of these findings.

By December 1982, all three of the initial AIDS patients with hemophilia had died, and four additional heterosexual hemophilia patients had developed one or more opportunistic infections accompanied by evidence of cellular immune deficiency. Data from inquiries about the patients' sexual activities, drug usage, travel, and residence failed to suggest that their disease could have been acquired through contact with each other, with homosexuals, with illicit drug abusers, or with Haitian immigrants. All had received Factor VIII concentrates, a single lot of which may be prepared from the blood of as many as 20,000 donors, and all but one had received other blood components. As of June 29, 1983, CDC had received reports of AIDS in a total of 13 hemophilia patients, and at least 8 had died.

The total of 1,756 AIDS cases reported by late June 1983 includes U.S. residents and 115 persons from 18 other countries. Almost 80 percent of reported AIDS cases in the United States are concentrated in six metropolitan areas. These include New York City, San Francisco, Miami, Newark, Houston, and Los Angeles. The distribution is not only a reflection of the population size of those areas; the number of cases per million persons in residence in New York City and San Francisco is roughly 10 times greater than that of the entire country.

### **Definition of an AIDS Case**

The current definition of AIDS used in CDC's surveillance activities requires the presence of a disease at least moderately indicative of defective cell-mediated immunity in a person who has no known underlying cause for such a defect or any other reason for diminished resistance to disease. The diseases include KS, PCP, or other serious opportunistic infections. Diagnoses are considered to fit the case definition only if based on findings from sufficiently reliable methods, generally histological

or microbiological examinations. However, some patients with less well defined manifestations of AIDS may be excluded from this surveillance definition. The manifestations may range from absence of symptoms, despite laboratory evidence of immune deficiency, to nonspecific symptoms (fever, weight loss, and generalized or persistent lymphadenopathy) to specific diseases that are insufficiently predictive of cellular immunodeficiency to be included in monitoring for incidence. Such diseases would include tuberculosis, oral candidiasis, herpes zoster, or malignant neoplasms that cause, as well as result from, immune deficiency.

There is no specific laboratory test for AIDS that is reliable, inexpensive, and widely available. As of May 2, 1983, the distribution of reported AIDS in high-risk groups was as follows: homosexual or bisexual men—75.7 percent, intravenous drug abusers with no history of male homosexual activity—14.5 percent, Haitians with no history of homosexuality or intravenous drug abuse—5 percent, persons with hemophilia A who were not Haitians, homosexuals, or intravenous drug abusers—0.9 percent, and persons in none of the other groups—3.9 percent.

The incidence of AIDS, by date of diagnosis, has roughly doubled every 6 months since the second half of 1979. In September 1982, more than two cases were being diagnosed every day; by late June 1983, an average of five to six reports were received by CDC each day.

The ultimate case-fatality ratio for patients with AIDS cannot be accurately determined yet, because death from complications of this syndrome may not occur for a number of years after the onset of illness. Of the 1,756 cases reported to CDC by late June 1983, 1,641 were from the United States. Of that number, 644 (39.2 percent) have been fatal. Of the 127 cases diagnosed 2 or more years ago, 103 (81 percent) of the victims are now dead.

The overall fatality rate for persons with cases of PCP without KS (43 percent) is more than twice that for persons with cases of KS without PCP (21

percent), while the rate for those with cases of both PCP and KS (55.5 percent) is even higher. The eventual AIDS case-fatality ratio several years after diagnosis may be far greater. Of the 51 patients diagnosed in 1979–80, 44 (86 percent) are now dead.

The occurrence of generalized lymphadenopathy in patients with manifestations of systemic illness—such as weight loss and malaise, but without KS, PCP, or other opportunistic infections—may represent a prodromal phase of AIDS. Many physicians have reported seeing an increase in the number of homosexual men with chronic, unexplained, diffuse lymphadenopathy. Some, but not all, of these men have cellular immune deficiency. A small proportion of these patients have later developed KS or opportunistic infections.

Investigators from New York City have described the occurrence of abnormalities of cellular immune function, usually mild, in apparently healthy homosexual men. The natural history of this “subclinical immunosuppression” is unknown. If AIDS is caused by an infectious agent, its transmission appears most commonly to require intimate, direct contact involving mucosal surfaces, such as sexual contact between homosexual males. Parenteral spread, such as occurs among intravenous drug abusers and possibly hemophilia patients using Factor VIII concentrate, would also seem a route of transmission. Airborne spread and interpersonal spread through casual contact do not seem likely. These patterns resemble the distribution of disease and modes of spread of hepatitis B virus, and hepatitis B virus infections occur very frequently in AIDS patients.

It is possible that AIDS may cause other disease manifestations in homosexual men. For example, thrombocytopenic purpura in homosexual men with cellular immunodeficiency, diffuse undifferentiated non-Hodgkin's lymphoma, and lymphoma of the brain in young homosexual men have been reported.

### Reducing Risks Related to AIDS

Evidence that AIDS is caused by an infectious agent, including the similarity of its epidemiologic course to that of hepatitis B, has made it necessary to develop precautions for clinical and laboratory staffs who might come in contact with such an agent during the course of a day's work. These precautions are similar to those advocated for medical or hospital personnel working with persons who have cases of hepatitis B.

If the theory is correct that AIDS is caused by a virus, health workers having parenteral exposure to

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blood from AIDS patients need to be watched for signs and symptoms of the disease. The rate of occurrence of disease in affected groups will be a function of the transmissibility of the agent within each group, the presence of pre-existing immunity, if any, and the incubation period of the disease. That period now appears to be 12 months or more.

The potential danger from blood products was underscored by the report of an infant who developed severe immunodeficiency and an opportunistic infection. Several months after receiving a transfusion of platelets derived from the blood of a man who showed no symptoms, the child became ill. Subsequently the donor was found to have AIDS. Several other similar observations have raised the possibility that blood may be a vehicle for transmitting AIDS.

The health community developed recommendations designed to prevent the transmission of AIDS through the use of blood products because of evidence that AIDS was apparently occurring for the first time in patients with hemophilia and the preliminary evidence that blood transfusions might be implicated in the transmission of AIDS. The National Gay Task Force, the National Hemophilia Foundation, the American Red Cross, the American Association of Blood Banks, the American Association of Physicians for Human Rights, and others issued statements about the prevention and control of AIDS.

On March 4, 1983, the Public Health Service recommended the following actions to reduce the risk of contracting AIDS.

1. Sexual contact should be avoided with persons known or suspected to have AIDS. Members of high-risk groups should be aware that having multiple sexual partners increases the probability of developing AIDS.

2. As a temporary measure, members of groups at increased risk for AIDS should refrain from donating plasma or blood, or both. This recommendation includes all persons belonging to such groups, even though many individuals are at little risk of AIDS. Centers collecting plasma or blood should inform potential donors of this recommendation. The Food and Drug Administration is preparing new recommendations for manufacturers of plasma derivatives and for establishments that collect plasma or blood. The recommendations are an interim measure to protect recipients of blood products and blood until specific laboratory tests are available.

3. Studies should be conducted to evaluate screen-

ing procedures for their effectiveness in identifying and excluding plasma and blood with a high probability of transmitting AIDS. The procedures should include specific laboratory tests as well as careful histories and physical examinations.

4. Physicians should adhere strictly to medical indications for transfusions, and autologous blood transfusions are encouraged.

5. Work should continue toward development of safer blood products for use by hemophilia patients.

## Questions Raised in the Laboratory

Laboratory work on AIDS has brought to light as many puzzling questions as has the epidemiology of the disease. The first and most apparent link between the varied groups of AIDS patients was the immune defect, apparently not a genetic phenomenon. Patients with AIDS have normal or elevated levels of antibodies and of the cells that produce them. A certain type of white blood cell, helper T-cells ( $T_H$ ), which assist the immune system in battling invaders, are abnormally low in number. Their opposites, suppressor T-cells ( $T_S$ ), are present in normal or increased numbers, and the result is a lower than normal ratio of  $T_H$  to  $T_S$  cells.

Herpesviruses comprise one group of viruses that causes persistent infections of various body cells. The herpesviruses that infect circulating and noncirculating lymphocytes—most notably Epstein-Barr virus (EBV) and cytomegalovirus (CMV)—could fulfill some of the criteria required of an agent causing AIDS. CMV has been suggested as a cause of AIDS by several investigators, although in several patients there is inconclusive evidence of previous CMV infection, based on the laboratory data now available. Human T-cell leukemia virus (HTLV) is also transmitted person-to-person, is found to infect individuals in clusters, and is associated with the development of cancer after a long period. This virus infects helper T-cells and apparently alters their function to that of a suppressor cell. The adult T-cell leukemia-lymphoma, which occurs at increased rates in areas where HTLV is endemic, has been described by the Japanese as a new disease. Although HTLV is not widely prevalent in the United States, scientists are examining what role, if any, this or similar agents might have in causing AIDS or illness among patients with AIDS.

Assuming that the infectious agent hypothesis is correct, what will the future hold? A continued increase of cases may be expected among homosexual men. If the hepatitis B virus model is a valid one, the sexual partners of affected heterosexual men and

women may become infected. If blood from infected persons can transmit disease, recipients of other blood products may contract AIDS.

During the past 2 years, an epidemic of devastating illnesses has been taking place in the United States. These diseases include fatal opportunistic infections, Kaposi's sarcoma, and perhaps other cancers and illnesses. These diseases have afflicted young homosexual men predominantly. The reported incidence of AIDS has continued to rise steadily, and only 19 percent of the known patients have survived 2 years or longer after diagnosis.

If AIDS is caused by an infectious agent, it is possible that the agent produces a spectrum of illnesses ranging from subclinical to fatal. In this case it would be similar to legionellosis, the disease identified in 1976 when nearly 200 Legionnaires were stricken with disease during a convention in Philadelphia. When the causative bacterium for that ill-

ness was discovered, it was found that it, or members of the same family, caused disease ranging from the milder Pontiac fever investigated in 1967 to the fulminating pneumonia of legionellosis. It could also cause subclinical illness and leave evidence of its presence in antibodies in patients.

The tragedy of the AIDS epidemic is intensified by the youth of the victims, the lack of proven treatments, and the prolonged, costly, debilitating, and often fatal illnesses that occur. The median age of the victims has been 34 years; 92 percent are below the age of 50. Many productive years of life have been prematurely lost to this epidemic. Many patients have survived one illness, only to suffer a fatal recurrence of infection or to develop a fatal cancer.

The occurrence of this epidemic offers a unique scientific opportunity to understand the human immune system and its relationship to cancer and infection. These opportunities are not being lost.

## **The National Institutes of Health and Research into the Acquired Immune Deficiency Syndrome**

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**T**HE PERNICIOUS DISEASE OF UNKNOWN cause termed acquired immune deficiency syndrome (AIDS), which has reached epidemic proportions in the United States, is under intense scrutiny by the National Institutes of Health (NIH). Although the cause of AIDS remains unknown, several characteristics of the disorder and its victims have been determined and are under exhaustive clinical, laboratory, and epidemiologic study by investigators focusing on neurological, microbiological, pathological, and immunological aspects of the disease. The objectives are to determine the pathogenesis of AIDS, to determine how it is transmitted and, finally, to develop methods of prevention and treatment.

When the AIDS problem was recognized in early 1981, close liaison was established among the Public

Health Service agencies with major responsibility in the area, each emphasizing its primary mission: the Centers for Disease Control (CDC), surveillance and investigation; the Food and Drug Administration (FDA), preventive measures related to blood collection and its use; and NIH, research into fundamental causes and clinical aspects of AIDS.

NIH is uniquely qualified to mount a major research effort into AIDS. Through its extramural research program, which supports thousands of individual investigators and their teams throughout the nation, research relevant to AIDS is being drawn upon for leads. Funding for current research is being supplemented to enable scientists to expand or to emphasize research directed to the AIDS problem, and the review of research proposals has been expedited to allow rapid support for promising studies. In its intramural program, NIH has mobilized basic and clinical researchers to attack the disease from a variety of scientific bases.

### **Characteristics of AIDS**

The picture of AIDS emerged in reports to CDC in the spring of 1981, and the disorder was established as a clinical entity with publication of three papers, from California and New York, in the New England Journal of Medicine in December of that year. Two of the reporting teams had received NIH research support (1-3).

Since June 1981, the point when CDC initiated national surveillance, 1,641 cases of AIDS had been