

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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THE 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

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reported by June 29, 1983, from 38 States and the District of Columbia and 115 cases from 18 foreign countries. Of the cases in the United States, 644 deaths (39.2 percent) have occurred. Of the 590 persons with AIDS cases diagnosed more than 1 year ago, 367 (63.9 percent) have died, and of the 127 persons with cases diagnosed 2 or more years ago, 103 (81.1 percent) have died. In late June 1983, new cases were being reported at an average rate of between five and six a day, according to surveillance information from the Centers for Disease Control.

Current epidemiologic evidence identifies several groups in the United States at increased risk for developing AIDS. Most cases (71 percent) have been reported among sexually active homosexual or bisexual men, primarily young (25-45 years) and urban. The second largest group (17.1 percent) of AIDS patients are heterosexual persons who are abusers of intravenous drugs such as heroin. (As with sexually active homosexual men, drug abusers are known to have a high incidence of hepatitis B infections, the virus being spread through sexual contact or by contaminated needles.) A third group of AIDS patients (5.2 percent) is made up of Haitians, especially those who have entered the country in recent years. Other groups of AIDS patients are persons with hemophilia and no history of homosexuality, intravenous drug use, or Haitian background (0.8 percent) and those with no apparent characteristics of other risk groups (3.9 percent) (CDC surveillance data, May 18, 1983).

AIDS is characterized by a variety of symptoms and disorders, but the underlying pathology is a severe and apparently irreversible suppression of the cellular immune system that makes its victims subject to tumors, primarily Kaposi's sarcoma (KS), and opportunistic infections, frequently *Pneumocystis carinii* pneumonia (PCP), and to invasion by a variety of other organisms, including viruses, fungi, protozoans, and atypical mycobacteria. Some pa-

tients have been infected by organisms that hitherto were regarded as primarily animal pathogens (4).

The organisms involved in the opportunistic infections associated with AIDS are almost all of types ordinarily resisted by the cellular immune system. Humoral immunity is relatively intact; AIDS patients have normal or even elevated concentrations of antibodies in their blood. However, their ability to respond to a new antigenic stimulus with immunoglobulin synthesis is reduced. Moreover, these patients have half, or less than half, of the normal number of peripheral blood lymphocytes. 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 their distribution among subpopulations is abnormal. 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 in performing 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 percent of AIDS patients have a reduced population of natural killer cells which have also been implicated in cancer cell surveillance. The loss of those components of the cell-mediated immune system may thus allow opportunistic infections to occur, and 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 Kaposi's sarcoma).

One-third of AIDS patients have developed Kaposi's sarcoma, a hitherto rare tumor, and cancers, such as Burkitt's lymphoma, are becoming apparent as well (5). Before 1979, KS was very rare in the United States, although not uncommon in equatorial Africa. When KS did occur in the United States, 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 rejection of transplanted organs. The incidence of KS in this country increased dramatically, and the course of the sarcoma in AIDS patients is very different from that previously seen in elderly men (6). The latter 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 extremely aggressive, and most patients respond poorly to chemotherapy—partly because of the apparent resistance of the tumor itself and partly because 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 that occur in persons immunosuppressed by other mechanisms. About 60 percent of AIDS patients, including some who also have KS, have developed PCP. Once an opportunistic infection has occurred in an AIDS patient, the course has been inexorably downhill. While individual infections can be controlled temporarily with antimicrobial drugs, they eventually recur or a different life-threatening infection develops.

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 (7). This association suggests a genetic predisposition (if not to the syndrome in its entirety, at least to the sarcoma) that may make high-risk individuals easier to identify.

Most investigators now believe that AIDS is caused by an infectious agent, probably a virus. There is speculation that the agent may be a new virus arising from a mutation; a virus from another species that has adapted to and spread among human beings; or a virus that has long existed in a circumscribed human population where, for some reason, it did not come to medical attention. The spread of AIDS parallels that of hepatitis B infection, although there is no evidence that hepatitis viruses are the cause of AIDS. It is believed to be transmitted through intimate contact and/or by blood or blood products.

NIH Research Directed at AIDS

NIH research into this new and puzzling malady was triggered by an early 1981 alert from a grantee in California. By mid-year, the first of a growing number of AIDS patients (60 patients at various times as of May 1, 1983) had been admitted to the Magnuson Clinical Center on the NIH campus in

Bethesda, Md. Before the end of 1981, the National Cancer Institute (NCI) had sponsored a workshop on AIDS for health professionals, and studies on various aspects of the syndrome and its victims had been launched by NCI, the National Eye Institute (NEI), and the National Institute of Allergy and Infectious Diseases (NIAID). Intramural and extramural investigations have intensified and expanded steadily since that time.

The scope of the AIDS research effort by NIH is indicated by the growth in expenditures: \$3 million in fiscal 1982, approximately \$9.5 million to be spent in FY 1983, and an estimated \$12.5 million in FY 1984 (see table).

Extramural activity. The National Cancer Institute issued a Request for Applications (RFA) in August 1982 that will lead to joint funding by NCI and NIAID of projects at a level of about \$2.8 million this year. A second RFA, developed by NCI and NIAID specifically to search for an infectious agent in the syndrome, was issued in May 1983 and will be funded in FY 1984 at an expected level of \$2 million.

A project entitled "Etiologic Studies of Acquired Immunodeficiency Syndrome" has been initiated by

Expenditures (in thousands of dollars) by the Public Health Service for research on the acquired immune deficiency syndrome, FYs 1982-84

Agency	1982, actual	1983, estimate	1984, revised request
Total, National Institutes of Health	\$3,355 ¹	\$ 9,582	\$12,461
National Cancer Institute ...	2,400	4,400	4,700
National Heart, Lung, and Blood Institute	5	346	846
National Institute of Dental Research	25	25	30
National Institute of Neurological and Communicative Disorders and Stroke .	31	72	76
National Institute of Allergy and Infectious Diseases ..	297	4,050	6,050
National Eye Institute	33	45	58
Division of Research Resources	564	644	701
Centers for Disease Control ..	2,000	4,600	4,300
Food and Drug Administration .	150	350	400
Alcohol, Drug Abuse, and Mental Health Administration	500
Total, Public Health Service	\$5,505	\$14,532	\$17,691

¹ \$4.5 million already spent or awarded.

² The Administration has requested authority from Congress to re-program an additional \$12 million for AIDS research from other Department of Health and Human Services funds.

NCI through its system of Clinical Cooperative Research Awards. These awards will make it possible for investigators in a number of institutions to conduct major clinical research into the causes and prevention of AIDS. NCI has also given high priority to grant-supported studies of KS and similar malignant tumors related to AIDS. In addition, NCI has used a series of existing contracts to provide laboratory and technical support for studies of patients who have, or are at risk of having, AIDS. Studies carried out under this mechanism can be pinpointed at locations around the country that offer the greatest likelihood of producing new clues to the cause of various cancers.

The National Institute of Allergy and Infectious Diseases is supporting research in three areas related to AIDS: on cellular immunology and regulation of the immune system, on deficiencies in the immune system, and on cytomegalovirus, one of the viruses possibly related to the development of AIDS.

Additional NIAID-supported studies are aimed at investigating the involvement of other infectious agents in AIDS. Finally, NIAID-supported Sexually Transmitted Disease Centers at the Universities of Washington and North Carolina have engaged in studies of homosexual men since 1981, including an evaluation of the immune response to those exposed to cytomegalovirus.

The National Heart, Lung, and Blood Institute (NHLBI) initiated a study in which blood plasma and other body fluids from AIDS patients are being administered to chimpanzees; the animals will be examined later for development of immune dysfunction, AIDS, or AIDS-like disease. Evidence linked to the transmission of a causative agent will be sought.

NHLBI is also conducting a study in which groups of patients receiving large amounts of blood products by transfusion are being examined for dysfunction in a particular part of the immune system. This study is being carried out in cooperation with the CDC. The Institute also plans to initiate studies of "surrogate tests" for AIDS, which may lead to a method for screening blood before transfusion.

Other components of NIH are also active in AIDS research. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is conducting research into neurological aspects of AIDS, and the Division of Research Resources (DRR) is seeking to develop animal models for AIDS. In a DRR research symposium held last March, scientists explored the outbreaks of AIDS-like infections among monkeys at two primate research centers. It is possible that these naturally

occurring epidemics among research animals may provide clues to development of an animal model for AIDS.

Intramural activity. Concurrent with the external research assault on AIDS, NIH's intramural laboratory and clinical scientists mounted a multidisciplinary attack on the syndrome. The continuing internal collaboration at the Bethesda location involves at least 25 investigators and their teams in a dozen laboratories, including those working directly with patients in the Clinical Center and the newly activated Ambulatory Care Research Facility. The investigations draw upon the National Cancer Institute; the Bureau of Biologics of FDA; the National Institute of Dental Research; the National Institute of Neurological and Communicative Disorders and Stroke; the National Institute of Allergy and Infectious Diseases; the National Eye Institute; the National Heart, Lung, and Blood Institute; and the microbiology and critical care departments of the Clinical Center.

The range of intramural investigations underway at NIH is indicated by the following:

- *At the National Cancer Institute.* Researchers in the Laboratory of Pathology are examining tissue specimens taken from AIDS patients during surgery to examine the immunological characteristics of certain AIDS-related lymphomas. The Field Studies and Statistics Program is conducting epidemiologic studies of immunological profiles of healthy homosexual men in New York, Washington, D.C., and Denmark, and profiles of hemophiliacs without symptoms, as well as persons with AIDS or members of population groups at risk of developing AIDS. Division of Cancer Treatment investigators are using alpha-lymphoblastoid interferon in combination with chemotherapy to treat KS in AIDS patients. These researchers have also participated in the development of an NIAID study using gamma interferon to treat AIDS patients. Also under study is the possible role of retroviruses in AIDS. (Retroviruses are RNA viruses, the proviruses of which become incorporated into the genetic material of the cell; many of the cells are oncogenic.) NCI has organized a task force on AIDS, and Dr. Robert Gallo, who first isolated the human T-cell leukemia virus (8), is heading the effort to determine the role of this virus in AIDS (9-12). This task force will also coordinate laboratory and clinical studies of AIDS patients within the Institute.

- *At the National Institute of Dental Research.* The roles of viruses and interferon in disorders of the

human immune system are being studied. The studies indicate that AIDS patients examined have abnormalities in their interferon systems. These abnormalities are seen as a defect in the ability of the lymphocytes to produce interferon (usually of the gamma type), or as a significant increase in circulating interferon (usually of the alpha type).

- *At the National Institute of Neurological and Communicative Disorders and Stroke.* The Infectious Diseases Branch is conducting clinical and laboratory research on AIDS. The Institute is collaborating with the California Regional Primate Research Center on the examination of tissue obtained from rhesus monkeys who have simian acquired immune deficiency syndrome (SAIDS)—a disorder which may be similar to AIDS. Scientists are looking for the presence of new viruses that might be the cause of SAIDS and for known viruses such as cytomegalovirus (CMV) that can occur in animals with SAIDS. NINCDS researchers are also examining the transmissibility of SAIDS by inoculation of unaffected rhesus monkeys with material taken from animals with SAIDS.

- *At the National Institute of Allergy and Infectious Diseases.* Intramural scientists are searching for an infectious agent or agents that might trigger AIDS and are conducting immunological studies. Several scientists are examining the immunoregulatory defect that occurs in these patients. In addition, in the Laboratory of Immunoregulation, scientists are determining the precise mechanisms of immune dysfunction. These investigators are conducting studies aimed at reconstitution of the defective immune system by performing bone marrow transplants, lymphocyte transfusions, and interferon therapy.

In the Laboratory of Clinical Investigation, an evaluation of the roles of herpes infections and of Epstein-Barr virus in relation to AIDS is under way. The Laboratory of Infectious Diseases is investigating the role of hepatitis in AIDS because virtually all AIDS patients have had hepatitis. NIAID scientists are also evaluating AIDS patients for parvoviruses, a group of DNA viruses.

A major commitment to isolate the agent of AIDS and to develop therapy for patients has been made by NIAID. Most AIDS patients are studied and receive treatment in the NIAID service of the Clinical Center where specimens for research are collected and a gamma interferon clinical trial is underway. Much of the experimentation is being conducted in the hepatitis B chimpanzee facilities of the Institute.

- *At the National Eye Institute.* Clinical Branch scientists are studying ocular lesions that occur in patients with AIDS. These studies have the dual purpose of determining whether there are distinctive ocular signs that might help in recognizing AIDS victims and in obtaining new clues to the role of the immune system in eye disease.

- *At the National Heart, Lung, and Blood Institute.* Scientists are examining plasma specimens in an attempt to transfer a causative agent or agents taken from AIDS patients in the Clinical Center to chimpanzees. The goal is to isolate a transmissible, infectious agent.

Because of the multiple approaches to the mystery of AIDS, mechanisms have been established to coordinate and expedite research and information exchange among agencies involved, within the national scientific community, and throughout internal research efforts. An Inter-Institute Working Group was established in July 1982 to foster exchange of scientific findings among components of NIH and to provide a ready channel to make current data available to CDC, FDA, and other agencies. In addition to participation by each of the NIH Institutes, representatives of CDC and FDA are members of the Working Group. A complementary Working Group coordinates the collection and dissemination of information.

NHLBI has an interagency agreement with CDC for surveillance of certain groups of patients, such as hemophiliacs, who receive large quantities of blood. FDA representatives participate in interagency meetings to formulate plans for future collaborative projects.

The Office of the Scientific Director of NIAID has compiled a comprehensive bibliography of articles in the scientific literature on AIDS and related disorders that is updated periodically. The bibliography, which contains some 300 entries, and future updates are available on request from AIDS Bibliography, NIAID, Building 5, Room 135, NIH, 9000 Rockville Pike, Bethesda, Md. 20205.

Since the problem of AIDS surfaced, NIH has convened three major scientific workshops on the syndrome—by DRR on animal models for AIDS, by NHLBI to gain suggestions for future studies on prevention of transmission of AIDS in blood and blood products, and by NIAID to stimulate research in search of a causative agent. All meetings were open to the press and public. (See the summary of workshops on pages 318–319.)

In addition, NIH scientists regularly attend meet-

ings to exchange information with scientists throughout the country. The NHLBI has taken the lead in research among the Institutes, in cooperation with FDA and CDC, to assure that blood and blood products are safe. A list of suggested research projects to address this problem has been prepared, and the Institute is preparing to solicit proposals.

The Science Base

It must be emphasized that NIH and the scientific community are able to respond to AIDS only because of an enormous public investment in fundamental biomedical research over the years. That research has generated basic knowledge in such areas as immunoregulation, viral agents, opportunistic infections, and blood purification and storage. This science base makes possible a rational attack on the mystery of AIDS and prompts confidence that it ultimately will be solved.

It would have been impossible even to identify and characterize AIDS without the benefit of modern immunological understanding and technologies. Several advances in immunology, such as the following, are vital to the study and possible treatment of AIDS:

- Development of monoclonal antibodies was necessary to identify various lymphocyte subpopulations. The observation that the number of helper T-lymphocytes is decreased in both PCP or opportunistic infections and Kaposi's sarcoma patients was a key to understanding that these are two presentations of the same underlying disease.
- Determination of interactions between lymphocyte subpopulations provided a basis for understanding the pathogenesis of the disease and will provide a theoretical base for development of treatment strategies.
- Identification of histocompatibility antigens will be important to an examination of a genetic basis for increased susceptibility.
- Characterization of congenital immunodeficiency diseases has produced the concept of immunological reconstitution, that is, restoration of missing lymphocyte subpopulations. This has recently been accomplished with several patients with congenital immunodeficiency diseases. This concept may prove important to the treatment of AIDS, since these patients also lack a specific type of lymphocyte.

Other factors that have been suggested as important to AIDS include interferon and lymphokines (general immune system regulators), because normal

regulation appears to be compromised in AIDS patients. Involvement of these factors in regulation of the immune system is being actively studied intramurally and extramurally.

Considerable research support has also been committed to sexually transmitted diseases. This important continuing commitment is expected to provide information necessary to the understanding of AIDS.

Several viruses have been suggested as possible etiologic or adventitious agents in AIDS and the associated Kaposi's sarcoma: cytomegalovirus (CMV), herpes, Epstein-Barr, and hepatitis. Significant research efforts to understand these viruses are being supported and some of these research programs have now focused on a possible association with AIDS.

There is serious concern about possible transmission of AIDS by blood and blood products. Research on inactivation of infectious agents in blood has been a continuing commitment of the Division of Blood Diseases and Resources of NHLBI.

Basic research on recombinant DNA and genetic engineering has resulted in efforts aimed at the production of clotting factors, including Factor VIII, by recombinant DNA. This advance would obviate the danger to hemophiliacs of bloodborne infectious agents.

Conclusion

NIH intends to pursue its high-priority research effort into AIDS until the mystery of the disease is solved. Confidence in ultimate success arises from the advances in biomedical knowledge and the sophisticated technology available today that can be applied to the enigma of AIDS by the world's most talented and able scientists. However, until the etiology of AIDS is understood, it will continue to be a health threat in the United States and throughout the world. An effective means of prevention is not available today because the agent of AIDS and the pathway of its transmission are unknown; clinicians are therefore forced to focus on alleviation of symptoms.

Once the agent of AIDS is isolated, the first step toward control of the epidemic can be taken. A diagnostic test could then confirm the presence of the syndrome in its early stages and make preventive measures possible. At present, the disease cannot be identified until it is relatively advanced.

If the cause of AIDS is a virus, as is now suspected, and the virus is isolated, the uncertain and usually lengthy process of vaccine development would still be necessary before prevention through immunization could be attempted. Given the suspected 6-month to 2-year incubation—and possibly

'An effective means of prevention is not available today because the agent of AIDS and the pathway of its transmission are unknown; clinicians are therefore forced to focus on alleviation of symptoms.'

infectious—period of AIDS, a continued rise in morbidity and mortality for an extended period must be anticipated. As one scientist close to the NIH research effort on AIDS said recently: "Optimism about the ultimate conquest of AIDS is based on the fact that the finest minds and most advanced technology are focused on the problem today. Given the present state of our knowledge and the complexities of the problem, however, one must conclude realistically that the epidemic of AIDS will get worse before it gets better."

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NIH Scientific Workshops on Acquired Immune Deficiency Syndrome

Since the beginning of 1983, components of the National Institutes of Health (NIH) have held three major scientific workshops to share information about acquired immune deficiency syndrome (AIDS) with the scientific community and with the public and to encourage additional research on the problem.

SAIDS Workshop

The Division of Research Resources (DRR), the NIH component that supports seven regional primate research centers around the country, held a workshop on March 2 on a naturally occurring disease in monkeys, termed simian acquired immune deficiency syndrome (SAIDS), reported by two regional primate research centers. Clinical findings in the monkeys bear considerable resemblance to those in human AIDS, and it is hoped that further investigation of the occurrence will provide useful information to those studying human AIDS. Control of SAIDS among the monkeys could be an important step toward understanding of AIDS and would help preserve

the animal colonies, which are a valuable resource for other research projects.

The New England Regional Primate Research Center, a Harvard Medical School facility, reported SAIDS in 15 macaques (*Macaca cyclops* and *Macaca mulatta*), and the California Primate Research Center at Davis experienced four separate outbreaks since 1969 involving approximately 200 monkeys (*M. mulatta* and *Macaca arctoides*). It is not known whether the disorders at the two centers are identical; their etiology is unknown. The disease in monkeys is apparently spread by close contact. The outbreaks reported at the meeting occurred in monkeys living in groups housed in separate corrals. The most recent outbreak in California occurred when 56 new *M. mulatta* (most of them females) were placed in August of 1981 in a corral holding 8 seemingly normal female monkeys who had survived an earlier epidemic in that corral. By May 1983, 32 of the animals, all females and mostly young animals, showed signs of SAIDS, and 27 died. Four of the eight original monkeys were among those stricken with SAIDS.

SAIDS appears to be comparable to human AIDS in that the animals have opportunistic infections, including *Pneumocystis carinii* pneumonia, sarcoma, and lymphomas (a very uncommon finding among monkeys). Preceding the