

# AIDS — No Relief in Sight

Researchers seek the cause of an immune deficiency disease outbreak

By SUSAN LAWRENCE

The search for an explanation of the mysterious outbreak of immune suppression first seen in promiscuous homosexual men in New York and California has yet to turn up any answers. As it spreads to other areas and other groups of people and a massive interdisciplinary research effort gears up, however, investigators are teasing out bits and pieces of new information. At the same time, they are struggling for funding and hoping that what is being called a serious epidemic does not become explosive.

The condition is now dubbed acquired immune deficiency syndrome—AIDS. The frequency of AIDS, as monitored by the Centers for Disease Control, the federal agency charged with overseeing communicable disease outbreaks, has mounted inexorably over the past two years. By mid-September, 585 biopsy-confirmed AIDS cases had been reported to CDC, 31 in one recent week. Over 200 of these patients have a formerly rare cancer, Kaposi's sarcoma. Over 300 have developed a rare form of pneumonia caused by the parasite *Pneumocystis carinii*. About 70 have suffered other devastating fungal, viral, or protozoal infections. At least 40 percent of the reported patients have died, including 78 percent of the cases reported in 1980 and 66 percent of those reported in the first half of 1981. "We think the true mortality for the syndrome is about 75 to 80 percent," a CDC official says. No patients are known to have recovered normal immunological function.

Determining the cause of AIDS is even more difficult than solving the mysteries of toxic shock syndrome or Legionnaire's disease, researchers point out. The symptoms of toxic shock pointed to a bacterium, so the search for a cause could be targeted. The Legionnaire's disease outbreak was localized, affecting a group of people who had gathered in one spot for a known length of time. AIDS, on the other hand, was originally seen in a handful of men in New York City, Los Angeles and San Francisco whose only known similarity was promiscuous homosexual activity.

About half the AIDS cases now on record are from New York and 20 percent are from

California. Thirteen cases have been reported from Haiti; others are from 27 states, Canada, Copenhagen and other European cities. Although two-thirds of the cases have occurred in homosexual men, the rest have developed in heterosexual men and women, primarily intravenous drug abusers and Haitian refugees. Three heterosexual hemophiliacs who regularly receive blood products have developed AIDS. A fourth case in a hemophiliac is suspected in Canada. As a result, many researchers are inclined to suspect a blood-borne virus as the culprit.

To date, however, no studies of samples from AIDS patients have produced strong evidence of such a virus. Researchers are still not sure whether they are looking for a known virus that has somehow become more dangerous, or whether some new viral strain or previously unrecognized organism might be at fault. Some are reporting evidence of genetic susceptibility in affected individuals. Others have suggested that a toxic agent, such as the recreational drugs amyl and butyl nitrite, or sperm itself—which has known immunosuppressive activity—might injure the immune system. Some suspect that AIDS might be an autoimmune disorder, in which patients generate antibodies to their own tissues for reasons as yet unknown. A virus, however, is considered a leading candidate by many investigators.

At this point, several hundred people around the country are studying pieces of the AIDS mystery as clinicians struggle to save patients with Kaposi's sarcoma, disseminated herpes simplex, disseminated candidiasis, *Pneumocystis carinii* pneumonia, disseminated *Mycobacterium avium intracellulare* infection, cytomegalovirus infection, cryptococcosis, *Cryptosporidium* coccidiosis, central nervous system toxoplasmosis, and more.

The CDC task force is spearheading research efforts and the National Institutes of Health recently set up an AIDS task force. The New York City Health Department, now headed by former CDC director David Sencer, has also established a working group of investigators and clinicians. New York's gay community has formed Gay Men's Health Crisis, Inc., which has donated about \$50,000 so far to AIDS research.

In mid-August, the National Cancer Institute announced plans to award about

\$1 million for epidemiologic studies of risk factors for KS, AIDS, or precursors; *in vitro* and *in vivo* laboratory studies in immunology, microbiology, virology and toxicology; and treatment and prevention projects. Investigators at a September conference on AIDS at Memorial Sloan-Kettering Cancer Institute were pleased by the NCI announcement, but pointed out that \$1 million is nowhere near enough to fund AIDS research. Basic immunological studies cost \$1,000 or more per person, and the CDC's James Curran noted that its estimate for immunological studies in animals is about \$25,000 per animal per year. The CDC has so far spent over \$1 million on AIDS, and the Department of Health and Human Services is expected to make more money available for AIDS soon.

Hospital costs for patients with KS or opportunistic infections are enormous, and the experimental treatments being attempted—interferon, transfer factor, anti-cancer drugs and experimental antileprosy drugs, bone marrow transplantation and plasmapheresis, to name a few—are tremendously expensive.

At the Sloan-Kettering meeting, which was sponsored by the American Society for Microbiology, Curran urged members of the audience to "exhort and motivate your colleagues in any way we can.... The most important things can be done over the next year in the laboratory, and there is a finite number of people in the world who can do them."

Much is peculiar about AIDS. It appears to be following the pattern of other infectious disease outbreaks, but it does not seem to be virulently contagious. "If it is an organism, it is not something that is passed from one partner to another readily, because we have too many couples where the other partner shows no disease. So it's not something that is highly contagious. We have over 500 cases and not one in medical personnel [who have no other risk factors]," New York internist Joyce Wallace pointed out at the ASM meeting. Wallace has launched a study of female prostitutes in New York City to determine whether they, too, are coming down with AIDS.

Physicians taking care of patients with AIDS have yet to agree on a firm case definition for the condition, although members of the NYCDH working group have been attempting to develop one. Most think Kaposi's sarcoma and opportunistic infections develop some time after an individual's immune system is attacked and shut down, but no one yet knows how to diagnose AIDS before later developments occur. The deficiency appears to be one of cell-mediated immunity, affecting the function of the lymphocytes known as T cells and leaving patients unable to protect themselves from viral, fungal or protozoal infections as a result.

To some clinicians, AIDS patients present a familiar pattern. Their infections and immune status resemble those of pa-

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tients with cancers and those who have received organ transplants whose immunities have been deliberately suppressed by drugs, as Jonathan Gold of Sloan-Kettering noted in New York. What is baffling, though, is the fact that so far, no one has been able to find out why. Under suspicion is the herpesvirus family, which includes cytomegalovirus and Epstein-Barr virus, although how known viruses might suddenly begin causing a new kind of disease is not known.

The recognition of generalized, unexplained, persistent lymph gland swelling among homosexual men is now producing concern since such swelling might indicate an early stage of AIDS. Furthermore, researchers who have begun studying apparently healthy homosexual men for signs of immunological abnormality have found that by some measurements, impaired immunological response is extremely common. Michael Lange of St. Luke-Roosevelt Medical Center in New York reported at the ASM meeting on a study of 81 homosexual men with no evidence of underlying health problems and 20 heterosexual controls who have been observed since November 1981. Fifty of the homosexuals gave no history of symptoms, while 31 said they had had such complaints as amebiasis, lymphadenopathy, fever, diarrhea, weight loss, or thrush (local candidiasis). Lange and colleagues found 80 percent of the homosexuals had depressed helper/suppressor T lymphocyte ratios and low total counts of helper cells — “detectable immune abnormalities, which suggest that AIDS may be a larger public health problem than we have thought,” he said. Those findings were reported in the Sept. 16 *NEW ENGLAND JOURNAL OF MEDICINE* by Lange and colleagues. At the ASM meeting, Susanna Cunningham-Rundles of Memorial Sloan-Kettering reported similar findings.

Complicating the research problems AIDS raises is the lack of agreement among immunologists and other investigators on the significance of available laboratory studies of immunological function. Some believe that such *in vitro* studies of T cell function as ratios of helper and suppressor cells do not provide enough information on the actual functional status of the immune system, and work is underway to perform more refined measurements.

National Cancer Institute immunologist Gene A. Shearer, for example, thinks determining the specific components of cell-mediated immunity that are missing in affected individuals is important. “We should be doing more functional analyses” to determine whether the defect involves macrophage activity, decreased helper cell activity, or increased suppressor cell activity, he believes. Working with material provided by Susan Zolla-Pazner of New York University, Shearer has begun to study the cytotoxic response of lymphocytes from asymptomatic homosexual men to influenza and is looking at whether

their B lymphocytes produce antibodies to it, he said in a recent interview.

Other researchers are searching for some early marker for AIDS that would allow physicians to make a diagnosis sooner. Depression of cellular ability to produce interferon may prove to be a marker for the syndrome, Carlos Lopez of Sloan-Kettering suggested at the New York meeting. Lopez is also working with Frederick Siegal of Mount Sinai Medical Center in New York on a clinical trial of interferon therapy in men with lymphadenopathy.

Some investigators, however, are not sure such an assay — or treatment of affected individuals with interferon — will be of value. Olivia Preble of the Uniformed Services University of Health Sciences in Bethesda, Md., reported at the ASM meeting on comparisons between sera from homosexual men with Kaposi's sarcoma or unexplained lymphadenopathy with sera from patients with systemic lupus erythematosus, an autoimmune disorder. In both groups, sera produced human leukocyte interferon of an unusual type, suggesting that an autoimmune disorder might underlie Kaposi's sarcoma and lymphadenopathy, Preble reported.

The CDC's James Curran hopes studies now underway may soon produce information on the cause and progress of AIDS. More discussions are scheduled in October, at the ASM's Interscience Conference on Antimicrobial Agents and Chemotherapy in Miami Beach. In the meantime, those caring for people with AIDS and its complications are prey to the feelings summed up by Sloan-Kettering's Donald Armstrong: “I have never felt so out of control. Again and again, I feel a sense of failure ... this is the most frustrating and anxiety-provoking experience I have had.” Hospital personnel worry about contracting AIDS from the patients for whom they are caring. Researchers find themselves at a loss for answers for those who, although not critically ill, have immunological abnormalities or have developed the swollen lymph glands, fever and weight loss that

appears to precede more dramatic illness. The new, mysterious disease is even causing concern over such seemingly unrelated issues as the hepatitis B vaccine and blood donation.

The CDC has pointed out that no cases of AIDS have occurred in people who have received hepatitis B vaccine, and it is thought that the process used to kill the hepatitis virus would also kill any virus causing AIDS, but Armstrong said in New York that candidates for the vaccine should be told of the CDC statement and asked to sign written consent forms before receiving the vaccine.

The question of whether AIDS poses hazards for blood banks has also emerged, particularly in light of the diagnosis of AIDS in three hemophiliacs. Assistant Secretary for Health Edward Brandt convened an HHS meeting at the end of July attended by representatives of the National Hemophilia Foundation and blood banking groups as well as federal agencies. One result is that a review evaluating hospitalizations, illnesses and deaths among the country's 20,000 or so hemophiliacs is now underway and should be completed in October.

Although the CDC has not issued any recommendations calling for restrictions on sexual activity or blood donation, gay physician Dan Williams has advised “promiscuous gay men with a prior history of multiple sexually transmitted diseases not to give blood until more information is available,” while noting that “homosexuality per se is not a risk factor.”

Writing in the *New York Native* newspaper, Williams also advised gay men that “your chances of remaining disease-free will improve the more you limit your number of *different* sexual contacts ... Multiple sexual contacts with anonymous partners is especially risky now, and it should be discouraged for purely medical reasons. It's not immoral, but it is unquestionably *very unhealthy*, both for individuals and for the gay community at large.” □

### Kaposi's sarcoma (KS), pneumocystis pneumonia (PCP) and other opportunistic infections (OI), United States, 1979-1982

Centers for Disease Control, USPHS, Atlanta, Ga.

