

## ONE STEP BEHIND A KILLER

Medicine's best and brightest have not yet solved the puzzle of Acquired Immune Deficiency Syndrome. But that's not for want of trying.

*by Susan West*

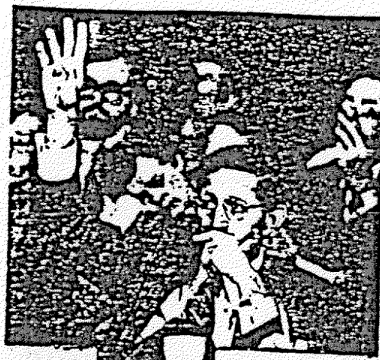
**J**im Curran is making one last phone call. His voice cracks, and he's talking slower than usual. He rubs his eyes and sips coffee when he listens. His white shirt is rumpled. He's been in his office at the Centers for Disease Control since 5:30 this morning.

Curran hangs up and glances at his watch. He shuts the door, sits down, and slouches to a comfortable position. He leans his head on his hand and checks his watch again. And he begins to talk about the epidemic.

*Jim Curran, Centers for Disease Control*



*R. Modersbach*  
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Louis Aledort, National Hemophilia Foundation



Roger Enlow, National Gay Task Force



Donald Francis, Centers for Disease Control

"Very depressing," one CDC doctor said of a January 4 meeting in Atlanta on how to prevent AIDS. "We spent most of the time trying to convince the blood banks it's transmissible. We think there's no doubt, but the blood bank people say give us more proof. We intend to do just that."

The epidemic he describes is strange. It has struck 891 people as of January 15, and it has killed 333 of them. Almost three-fourths of the people who first got the disease are dead. Some researchers believe no one survives it. Since it was detected in 1981, the number of cases has doubled every six months. So far, it has hit young homosexual men, users of intravenous drugs and their sexual partners, Haitians, hemophiliacs, and children. Its name is Acquired Immune Deficiency Syndrome: "acquired" to indicate its victims didn't inherit it, "immune deficiency" because the one thing they have in common is a breakdown of their immune systems, and "syndrome" to cover the grab bag of rare but ravaging diseases that take advantage of their bodies' collapsed defenses.

It's the syndrome part that kills them. At first they feel as though they might have the flu, as if they've been to one party too many. But six to 18 months later they still feel that way; they don't know it, but they have lost their ability to fight off disease. Then about a third of them develop Kaposi's sarcoma, a cancer of the skin or internal organs. The rest come down with an unusual pneumonia caused by a protozoan, *Pneumocystis carinii*. Or any of an arm-long list of so-called opportunistic infections—including rare cancers and diseases caused by fungi, herpes and other viruses, bacteria, and protozoans—that don't affect people whose immune systems are working properly. With treatment the victims may overcome one of these only to succumb to another because their natural defenses never seem to rally.

Everything about AIDS looks as though it is contagious. Scientists think it is passed by "intimate contact"—shared drug needles, for example, or sexual intercourse. Which points to something carried by the bloodstream. Which has a lot of health officials worried about the millions of people who give and receive blood.

The problem is, no one knows a cure. No one even knows the cause.

That's why Jim Curran is tired. He's been working on this thing for almost two years. He is the head of

the AIDS task force at the Centers for Disease Control in Atlanta. The CDC is the federal agency that handles both short-term health threats such as bacterial contamination in fast-food hamburgers and long-term ones such as dioxin in forgotten landfills. The task force isn't the only bunch of scientists trying to crack AIDS; they weren't even the first to know about it. But the CDC is designed for this business of tracking down new diseases.

Curran has finished talking when the phone rings. It is his wife. He picks up his jacket and starts to the hallway. He almost makes it, but someone calls after him, "Jim? Could you, um, would you mind looking at this? It has to be in tomorrow morning." Curran hesitates, so near escape. He sighs, turns back toward his office, and signals the man to follow.

"We first heard about it in March or April 1981," Curran says. "People were seeing gay patients with *Pneumocystis carinii* pneumonia and a breakdown of their immune systems. Some of the patients were in the New York area, others in Los Angeles. Michael Gottlieb from the University of California at Los Angeles and Wayne Shandera, a CDC officer there, summarized their five cases for the CDC's 'Morbidity and Mortality Weekly Report'. Before it was published, the report came to all the sections. I was the head of the venereal diseases section. It hit us that these were gay men, which meant it could have been sexually transmitted. In May we went to a venereal disease control seminar in San Diego. While we were there, Harold Jaffe from our division found out about a few cases of Kaposi's sarcoma and pneumocystis in San Francisco gays. Meanwhile Alvin Friedman-Kien from New York University called CDC in Atlanta and said there were cases of Kaposi's in New York as well. Gottlieb and Shandera's article came out on Friday, June 5; we came back from San Diego and had a meeting about it the next day."

The study of epidemics, and the dogma by which the CDC lives, is called epidemiology. Epidemiolo-



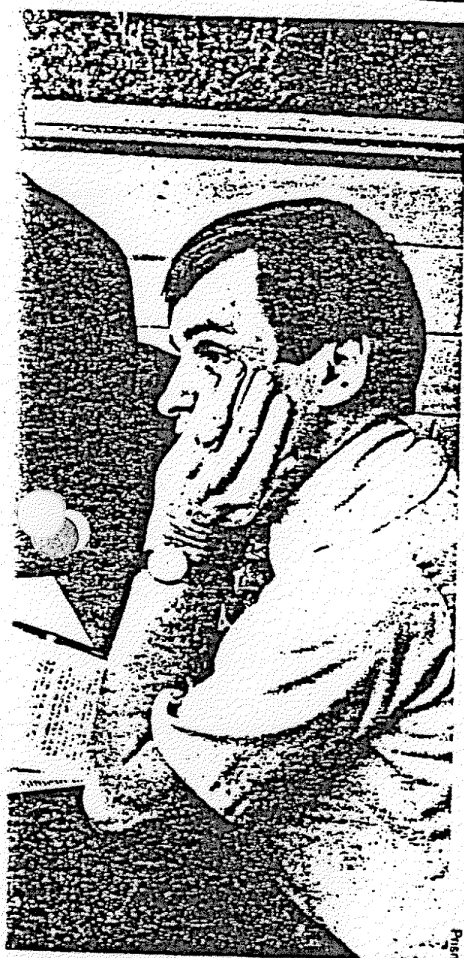
gists beat the streets looking for the who, what, where, and when of a disease. Their discoveries help laboratory scientists look for a why. And the laboratory's findings may send the epidemiologists back to the streets. Every new turn in an investigation reveals a fork in the road; every branch of a fork may have a dozen small lanes; down any one of them may be the answer. So as soon as the CDC decided this outbreak was new and real, several things were set into motion, things that are automatically triggered whenever a new problem comes to the agency.

"We decided what we needed first was a rapid surveillance system—what diseases are we looking for and where are they," explains Harold Jaffe, second in command on the task force. "It's the same if there's diarrhea after the church picnic—you have to have a defini-

*CDC doctors John Bennett, Bruce Evatt, and James Curran discuss AIDS. "In retrospect it will look easy, and we'll wonder why it took so long to figure out," says Evatt. "We are caught trying to design an experiment to solve a riddle."*

tion and how many cases. We decided to look for Kaposi's sarcoma and/or one of a group of life-threatening opportunistic infections in gay men from 15 to 60 years old with no known cause of immunosuppression.

"We decided to look actively for cases in several cities. We intentionally picked cities that have large homosexual populations and some that don't. We used Los Angeles, Miami, and Atlanta for high populations, Rochester and Albany as medium areas, and Oklahoma City as low. We told our people to get in touch with major hospitals in the area—to talk to pathologists, der-



matologists, infectious disease specialists—to see if they had any cases. We also went back through the request file for pentamidine, a drug commonly used for pneumocystis, to see if the occurrence of pneumocystis had risen. We contacted cancer tumor registries to see if there were any cases of Kaposi's in young men. More informally, we made inquiries in 10 other cities. This all happened in June and July 1981.

"We learned that the first case was probably in 1978, and the reason we noticed the disease in the spring of 1981 was because the number of cases had gotten big enough. The first cases in 1978 and 1979 were in New York City, and they were Kaposi's.

"We decided that next we needed uncontrolled interviewing of the cases, a fishing expedition. The logical question was, What is happening to homosexual men that

is not happening to anybody else? We needed a lot of information."

So Jaffe and other CDC doctors went to San Francisco and New York and talked to about 30 patients who were still alive out of the nearly 100 known cases. They covered everything—sexual behavior, drug use, hygiene, nutrition, medical history. Before they finished their survey, the epidemiologists had come to the first fork in the road. It was called nitrites.

Amyl and butyl nitrites are stimulants, volatile liquids sniffed from ampules or little bottles. Most often they're called poppers, with names such as Locker Room for their distinctive smell or Rush for the dizzying sensation they produce. Poppers are almost exclusively used by gays. Knowing this, physicians who treat gays had already suggested that a bad batch of nitrites, or simply prolonged use of the drug, might be the culprit. The CDC's fishing expedition supported this idea—more than 90 percent of the cases used nitrites. Poppers, the scientists thought, just might be the easy answer.

The epidemiologists hit the streets again. Within a few weeks, 416 homosexual and heterosexual men in Atlanta, San Francisco, and New York were asked if they used nitrites, how much and how often. The CDC scientists set up card tables on the streets of gay districts and interviewed passersby; they made announcements in gay bathhouses, they bought samples for analysis. "People would tell us, 'They have the best stuff at such and such bar,'" said one scientist. "We went to all these book stores, bars, you name it. Sometimes I felt like I was in a Fellini movie—walking into Spanish Harlem, buying drugs, going to bathhouses."

This "quick and dirty study," as Curran and Jaffe call it, confirmed that few heterosexual men use nitrites. It also indicated that using nitrites accompanies other aspects of life-style, such as having a large number of sexual partners, that could expose someone to disease. So it didn't really show whether poppers cause AIDS.

The task force decided they needed a more sophisticated way to

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sort out what might lead to AIDS. They designed a controlled study, selecting patients and healthy people who were like those patients in every other respect. In October and November 1981, armed with a 20-page, 90-minute questionnaire, they talked to 50 patients and 120 healthy gay men.

Jaffe and his coworkers found they had tapped into a fast-lane subset of the gay culture. Gay men with AIDS were more likely than healthy gay men to use marijuana and cocaine, to have many anonymous sexual partners in bathhouses, bars, and public restrooms, and to engage in sexual practices that cause abrasions and expose the men to small amounts of blood and feces. Both groups, however, used poppers, casting doubt on that hypothesis. But most important, the scientists found, was that the patients had many more sexual partners than the controls, an average of 60 and 25 per year respectively. And the patients more often had a history of sexually transmitted diseases, such as syphilis, parasitic diseases, and hepatitis.

Meanwhile, AIDS was spreading. Since the early fall of 1981, Gerald Friedland at Montefiore Hospital in the Bronx had been treating a handful of cases of pneumocystis and opportunistic infections in heterosexual men and women who were intravenous drug users. The New York and New Jersey state health departments reported that a small group of prisoners had similar symptoms. Physicians in other countries found a smattering of cases. And doctors began telling the CDC about a new phenomenon: a wasting syndrome, called lymphadenopathy, which includes swollen lymph glands, fatigue, severe and sudden weight loss, fever, chills, and night sweats.

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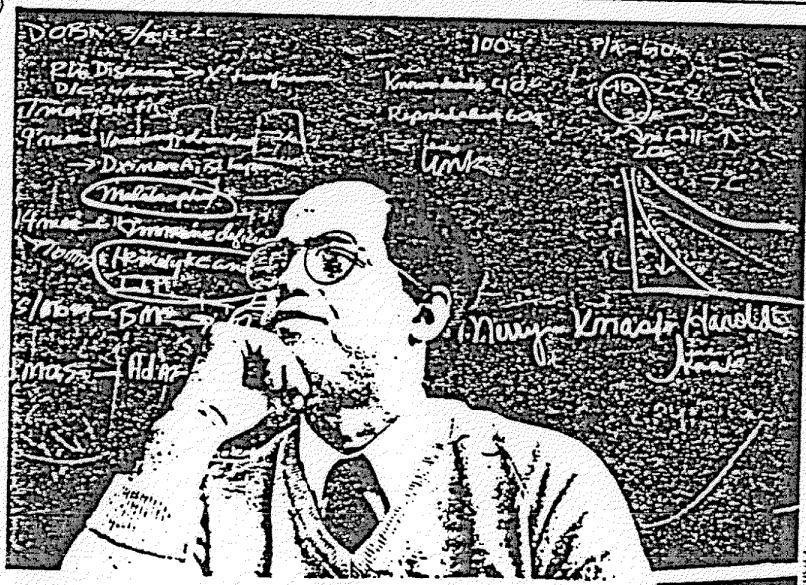
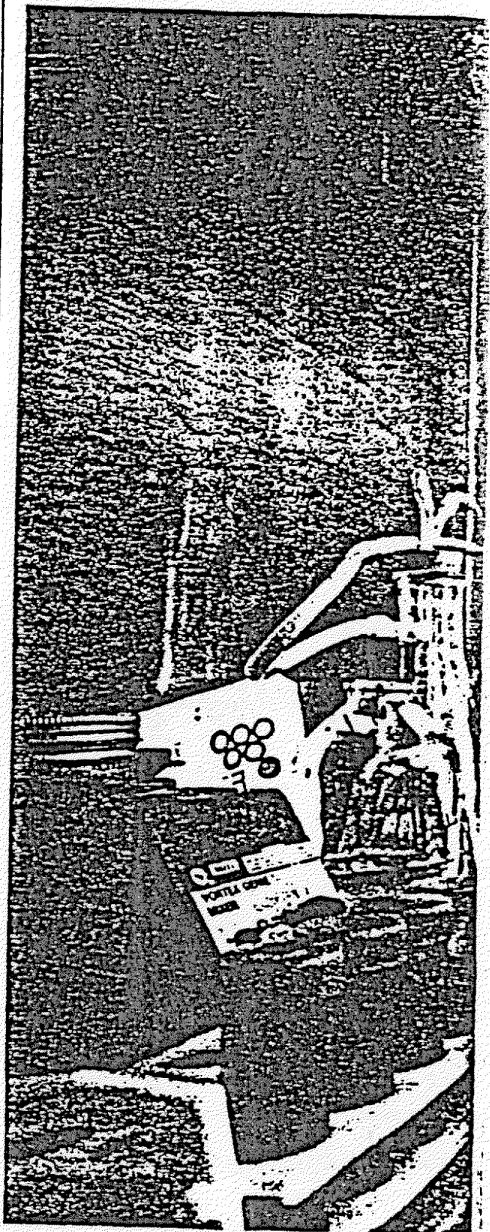
The patients had none of the illnesses that normally cause such symptoms; the doctors suggested lymphadenopathy might be an early stage of AIDS. The task force dispatched more epidemiologists.

Then the Haitians turned up. Early in the fall of 1981, physicians at Jackson Memorial Hospital in Miami told the CDC that a review of autopsy reports had revealed four Haitians who had died of opportunistic infections; a few months later they reported several new Haitian patients. Doctors in Brooklyn also began to see Haitians with AIDS. This was puzzling. Promiscuous gays and drug users might have similar habits that could expose them to disease, but they had little in common with Haitians. There were a lot of reasons Haitians were hard to figure.

"It was a tough picture culturally," recalls Harry Haverkos, the CDC epidemiologist sent to investigate the Haitian cases in Miami. "I found an anthropologist because I

didn't know enough about the culture. I remember talking to one brother of a case. He kept talking about voodoo and chopping off chicken heads. He said his brother died from spirits. He told me, 'Our witch doctors made it look like your disease but it wasn't.' Get that, 'your disease'. There was the fear of being deported. I walk in and say I'm from the federal government and I want to talk to you, and immediately they figure it's the Immigration and Naturalization Service. Also there were problems with language. Their word for gay is transvestite, so you're really asking if they are a transvestite, and you have to assume that if they are, they're probably gay too. You have to find out the number of sexual partners, but you have to define what you mean by sex and draw pictures. Their perception of time and events is different; they don't quantify things. You ask when their birthday is and they tell you Christmas, or maybe Christmas one time and New Year's the next."

It was a tough picture politically too. What few reports came to the CDC from Haiti—either from native physicians or U.S. physicians who visited there—indicated that both Kaposi's and pneumocystis had been found among islanders. The disease had appeared in Haiti about the same time it had among gays. Haiti is supposedly a favorite



vacation spot for gays; had some gay man picked it up there or introduced it to the island? No one wanted to say. The CDC concentrated on figuring out what was different about Haitians that might expose them to this disease.

By January 1982, 10 months after the CDC first heard about AIDS, there were 216 cases; 88 people had died. Eighty-four percent of the cases were gay men, nine percent intravenous drug users, and two percent Haitians;



only five percent of all the cases were women. If these people had the same disease, there must be a single cause. Some people still favored poppers or another quirk of life-style. Others suggested a new bug, like a virus, or a mutated old bug that could destroy the immune system. A third idea was "drugs and bugs"—perhaps a virus that was deadly in the presence of nitrates or heroin. Yet another was the "immune overload" theory, that each of these groups is so bar-

raged by years of infections that their immune systems finally give out, paving the way for Kaposi's and the other infections. Promiscuous gays, for instance, are exposed to large amounts of sperm, which can trigger antibodies against sperm, which are believed to attack the body's immune system. Drug addicts are known to have chronically enlarged lymph glands, probably the result of exposure to so many foreign substances. But the Haitians didn't quite figure into

*Epidemiologist Harold Jaffe, opposite page, and immunologist Tom Spira: "The epidemiology and the lab work increase the power one to the other. It's synergistic, truly it is. Sometimes the answer requires perspiration, tedious attention to details. Other times it's the bright answers. We need a combination of both."*

any of these scenarios. They didn't all use needles, they weren't all gay, they hadn't all just come to the U.S., they didn't all have unsanitary living conditions. Some people doubted if these groups even had

the same disease. Curran, Jaffe, and some others leaned toward the infectious organism theory. And in the first few months of 1982, two things turned up that made them look nearly clairvoyant. These were the hemophiliac cases and the "L.A. Cluster."

In January a report drifted in of a Miami hemophiliac who died with pneumocystis. "We weren't sure what to make of it because the patient had received steroids, had had liver disease, and was dead. So we set it aside," says Jaffe. "Then the second one came along in the spring. We became more concerned. Bill Foege, director of the CDC, said if we got two there will be a third. Sure enough he came along right away. By then we were convinced something peculiar was going on."

What was peculiar, and frightening, was that the most likely way the hemophiliacs could have been exposed was through the blood products on which their lives depended. These people lack part of a blood-clotting protein called factor VIII, which they get in injections derived from donor blood. Factor VIII is so fragile that nearly any purification process damages it, including pasteurization, the typical method of cleansing blood products. A single injection may contain factor VIII from 2,500 donors, so that a hemophiliac may be exposed to the blood of 25,000 to 75,000 people every year. Apparently whatever causes the disease had gotten into the factor VIII injections. In July 1982, representatives of the CDC, the Food and Drug Administration, the National Hemophilia Foundation, and other organizations met and planned studies to evaluate the risks to hemophiliacs, to examine factor VIII supplies for contamination, and to figure out ways to make the derivative safer.

The hemophiliac cases won a lot of converts. "People who didn't believe one way or the other started to believe it was transmissible," says

*Dermatologist Marcus Conant, codirector of the University of California at San Francisco's Kaposi's Sarcoma Clinic, examines skin lesions of a Kaposi's patient.*



**GRO-A**

Jaffe. The L.A. Cluster, he says, convinced even more.

In February 1982, Jaffe and David Auerbach, a CDC officer in Los Angeles, began hearing rumors that some of the gay men with AIDS who lived around L.A. might have known each other and had sexual intercourse before becoming ill. Auerbach began to investigate.

"I went out there in April 1982," says Bill Darrow, a CDC sociologist who worked with Auerbach. "We interviewed three to four people each day, one in the morning, one in the afternoon, one in the evening. One day our morning interview was with an Orange County case. He said he had had sexual contact with one person who had Kaposi's sarcoma and gave us the name. It was a man in New York."

"In the afternoon, we spoke to a man who was the lover of a case. We asked him who else his friend had sex with. He said not very many people, but two were out of state. One was the guy from New York." Darrow raises his eyebrows pointedly.

"Then in the evening we went to see another case. He said he would have to look up the names of his contacts; they were scattered around on little scraps of paper stuck in his dictionary and books. So we just asked him if he knew any names without looking them up."

He said yes. And he gave us the name, the guy in New York.

"Well. These three men had never met, never had sex, yet they named the same guy in New York. I actually dropped my pen. Auerbach's mouth was just hanging open, and he practically fell off his chair."

Darrow and Auerbach were able to draw connections between nine of the 19 cases in the Los Angeles area; since then, 40 patients in 10 different cities have been connected. Selma Dritz of the San Francisco health department has diagrams detailing other such relationships, drawn like impossible football plays on her blackboard.

The infectious organism hypothesis took over. A virus, or something related, fit all the data: something passed sexually, particularly

through abrasions; something carried by dirty needles; something picked up in unsanitary living conditions; something that could contaminate blood. Even the lymphadenopathy patients fit; they could be part of the "iceberg phenomenon" that occurs in many infectious diseases. As Jaffe says, "Maybe this disease is common, maybe a lot of people are exposed to the organism. But maybe most fight it off, maybe only a thousand people develop a subclinical form of the disease, maybe ten develop lymphadenopathy, maybe one of those develops Kaposi's or pneumocystis." All of this reminded the task force of the ways the viral liver disease, hepatitis B, is transmitted by blood, semen, or even saliva.

In fact, a lot of hospital workers and physicians, who are at a high risk of catching hepatitis B, began to act as though AIDS were hepatitis. They started taking the same precautions with blood, urine, and semen from AIDS patients that they would have taken with that from hepatitis patients. By late summer 1982, some doctors were pulling on two pairs of latex gloves whenever they treated someone who might have AIDS and thinking about the number of times they hadn't washed their hands after seeing such patients.

No one liked the corollary: that the disease could show up in blood and blood products.

But no one wanted to draw the next corollary, that like hepatitis B, this disease could start showing up in other people exposed to blood and blood products, people who got transfusions or who were on dialysis machines. That was a large and alarming step. Said one CDC scientist at the time: "Unless we get a lot of people getting it that way we can't say it's passed by transfusion. It has to be traced to a donor who developed AIDS or to patients who received the same blood and have all gotten it."

If that's what they were looking for, they finally got it late last fall. The task force was checking reports about children who might have AIDS when they heard about a 20-month-old San Francisco boy with peculiar symptoms. "We found out he had been transfused and asked to see the list of 19 donors," says Jaffe. "Lo and behold, one of our cases was there. It was a

GRO-A

A Kaposi's sarcoma patient describes the first signs of his illness—lymph node swelling—to a meeting of San Francisco area physicians and researchers working on AIDS.

It isn't clear if the babies pick it up in the womb or from intimacy with their parents.

guy we interviewed in March 1982." He had not had symptoms when he donated blood. Since then, the CDC has confirmed that two adults have come down with AIDS after receiving blood transfusions, though not from the same source. And five more hemophiliacs, including a seven-year-old and a 10-year-old, are believed to have the disease.

There are, however, about three million Americans, including 20,000 hemophiliacs, who receive blood or one of its derivatives each year. If AIDS were rampant in the nation's blood banks, reasons the CDC, there would be many more cases. "For the average person who needs to get a transfusion it is no concern," says Jaffe. "But all of these recent cases together make us feel strongly that this is an issue that needs to be re-reviewed. We feel something has to be done. We look at it as a potential threat that right now is very small. But we need to look at who donates and the ways to test them to decrease the chance of getting AIDS from a transfusion."

On January 4, people from every governmental health agency and the commercial blood banks met in Atlanta to discuss just that. None of the alternatives are pleasing: Tightening government regulations on commercial blood centers, not allowing gays or Haitians to donate, screening donors for past infections of hepatitis B on the presumption that the people who get hepatitis might get AIDS. None will be chosen without considerable turmoil and probably not for several months.

Right now, the attention is on two new groups of victims. The first is women who are sexual partners of men with AIDS, adding support to the belief that AIDS is passed by

sexual contact. The second group is children.

As of mid-January, 26 children less than five years old appear to have gotten the syndrome; 10 have died. None have Kaposi's, but they have pneumocystis and other infections and the characteristic immune system breakdown. Most of the children have parents who are Haitian, drug users, or who have had homosexual contact. Some of the parents have AIDS; others could be carriers. No one knows if the children pick it up in their mothers' wombs or from the intimate relationship of parent and infant. But more than ever, AIDS appears to be infectious.

While the epidemiologists were out in the streets, the laboratory researchers were doing their homework. They knew, for instance, that before this epidemic Kaposi's sarcoma and pneumocystis were rare. In the United States, Kaposi's most often shows up in older men of Jewish and Mediterranean descent. It also afflicts males of all ages in Africa, particularly Uganda. It starts as small purplish spots, almost like bruises, usually on the feet and legs. Until the AIDS epidemic, it was not considered particularly deadly. Physicians were used to encountering pneumocystis as well as Kaposi's in kidney transplant patients whose immune systems are temporarily knocked out so they won't reject the kidney or in cancer victims treated by chemotherapy.

The scientists also knew of conditions that could cripple a person's immune system. Common viral illnesses such as influenza and mononucleosis, for example, cause transient immune deficiencies. So do transfusions and malnutrition. They also knew of the link between viruses and cancer: Viruses cause cancer in animals, and a virus has been isolated that is believed to cause a type of human leukemia.

Then they began learning about AIDS. One of the first and most important characteristics they noticed was the peculiar type of immune defect these patients have. Patients with AIDS have normal or elevated amounts of antibodies



and of the cells that make them. But the white blood cells called helper T cells, which assist the antibodies and antibody-making cells, are very low in number. Moreover, their counterparts, which inhibit the antibody system and are called suppressor T cells, are not affected. With more suppressor cells than helper cells, the immune system is held back from attacking foreign organisms.

Much of this evidence reinforced what the epidemiologists were turning up—that something like a virus is causing AIDS. So by the spring of 1982, when the infectious



organism theory took the lead, the laboratories already had a few candidates. A popular nominee is a member of the herpes family called cytomegalovirus or CMV. Most gay men carry one form or another of CMV, which usually causes flu-like symptoms and which has been linked to Kaposi's sarcoma in Africa. Epstein-Barr virus, another herpes relative associated with a cancer of the lymph system, is another possibility, as is the newly discovered human leukemia virus, or a deadly variation of the hepatitis B virus. Or it could be something altogether new.

*James Oleske, pediatric immunologist with the University of Medicine and St. Michael's Medical Center in Newark, New Jersey, comforts a two-year-old girl who is believed to have AIDS. Oleske has treated eight of the 26 children with the disease.*

The labs stepped up their search for a viruslike organism. The researchers put samples of urine, blood, sputum, and semen from AIDS patients in cultures designed to coax even the most stubborn virus to grow. They checked each culture under the electron microscope for signs of foreign organisms. They marked antibodies to

known viruses with fluorescent dyes and set them loose to see if they would latch onto a new but related virus. They isolated well-known viruses and examined them to see if there was anything new and different about them. They fed the cultures growth factors and concentrated them to make it easier to spot a virus. They injected marmoset monkeys and chimpanzees and mice with samples from the patients to see if the animals would get AIDS. After nearly two years, they've found nothing.

There may be a good reason they haven't. It may be that the virus or organism is long gone by the time a doctor realizes a patient has AIDS and the laboratory gets specimens. If scientists could find people soon enough, the culprit might still be there. But this presents a vicious circle. Says CDC immunologist Tom Spira: "It would be nice if we had a test to identify the early stage of the disease, but we can't develop a test until we have found the agent. And to isolate an agent we have to catch patients early enough." Patients with the vague syndrome called lymphadenopathy may represent the beginning of the disease, and Spira and coworkers are keeping track of some of them to see if they develop full-blown AIDS. But even that stage may not be early enough, he says.

"Eventually," says CDC virologist Paul Feorino, "someone will study a particularly susceptible population—get them while they are still healthy, follow them and routinely take specimens, watch to see who develops the disease, then go back and look at all their specimens. But it will take hundreds of people to get one case. And lots of money."

If the epidemiologists can find such a population, if the laboratory researchers can isolate an organism, then maybe they can develop a test to determine who has AIDS and a vaccine to give those who do—if it's an organism for which a vaccine can be made. But that may be too many ifs; too many for the victims of AIDS and too many for Jim Curran to go back to a nine-to-five schedule, anytime soon. □

*Susan West is a Science 83 staff writer.*