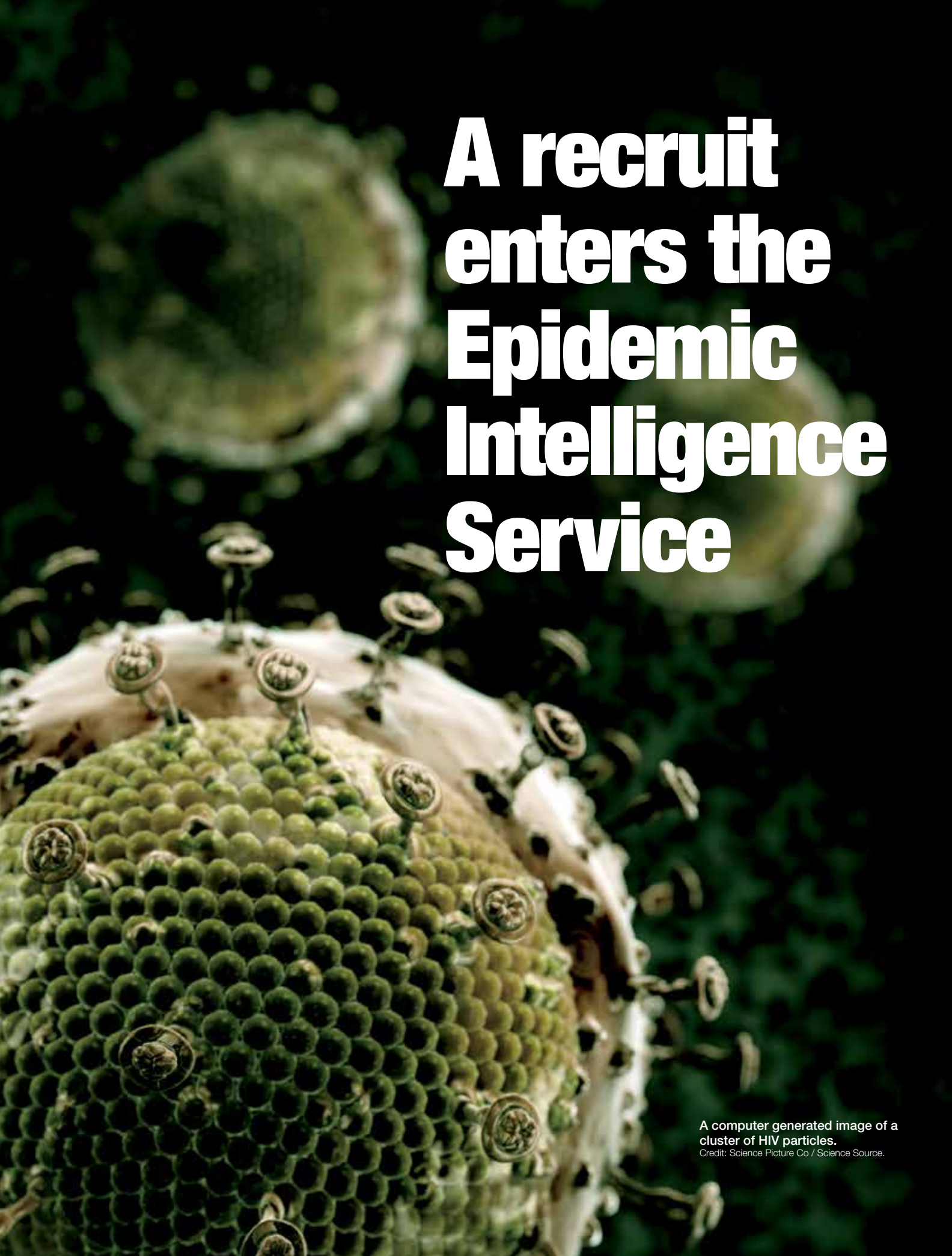
A recruit enters the Epidemic Intelligence Service



A computer generated image of a cluster of HIV particles.
Credit: Science Picture Co / Science Source.

> *Since its founding in 1951 by Alexander Langmuir as a service/training program, the Epidemic Intelligence Service, working out of the CDC in Atlanta, Georgia, has sent out more than three thousand officers to combat every imaginable human (and sometimes animal) ailment.*
>
> *These young people—doctors, veterinarians, dentists, statisticians, nurses, microbiologists, academic epidemiologists, sociologists, anthropologists, and now even lawyers—call themselves "shoe leather epidemiologists." EIS officers have ventured over the globe in search of diseases, sometimes in airplanes or jeeps, on bicycles, aboard fragile boats, on dogsleds, atop elephants and camels.*
>
> —Mark Pendergrast, 2010[1pxi]

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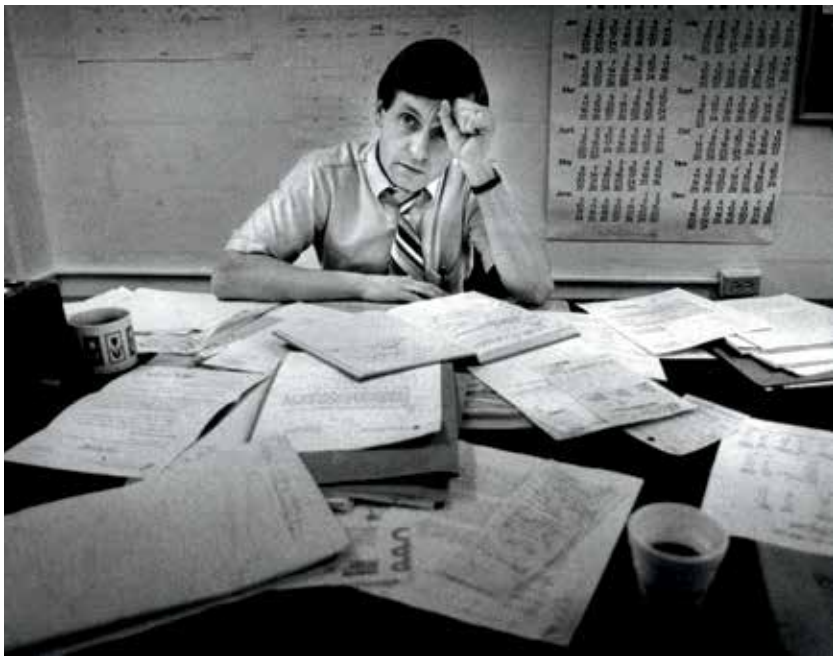
Monday, July 6, 1981. Every new Epidemic Intelligence Service (EIS) officer reports to CDC headquarters in Atlanta to attend a mandatory three-week course consisting of a series of lectures, interactive case studies, a primer on biostatistics, and participation in a field study. My EIS class consisted of sixty-five new officers: fifty-five physicians, four nurses, three academic epidemiologists, two veterinarians, and an anthropologist. Nine of the physicians were international trainees.

Each year, incoming EIS officers conduct a household survey on an assigned topic to get "hands-on"—or "shoe-leather"—experience collecting data on a contemporary public health topic. Performing the survey introduced us to "field" epidemiology and taught us about systematic or probability sampling. Our field study on July 15 was a household survey of injuries and violence in Atlanta. Our class designed a questionnaire and assigned groups of two officers to randomly selected house addresses to conduct the survey.

In the classroom, we studied the well-known 1940 Oswego, New York, church supper outbreak of gastroenteritis. Out of eighty people attending the picnic, seventy-five were interviewed, and forty-six had significant diarrheal disease within twenty-four hours. The source of the outbreak was identified as vanilla ice cream contaminated by one of its preparers. The exercise introduced us to the steps in the investigation of an outbreak:

1. Identify potential investigation team and resources and prepare for field work (e.g., administration, clearance, travel, contacts, designation of lead investigator).
2. Establish the existence of an epidemic.
3. Verify the diagnosis.
4. Construct a working case definition.
5. Find cases systematically, develop line listing of cases.
6. Perform descriptive epidemiology (i.e., orient the data by time, place, and person).
7. Develop hypotheses that explain the specific exposures that may cause disease.
8. Evaluate these hypotheses by appropriate statistical methods using data collected.
9. As necessary, reconsider/refine hypotheses and execute additional studies.
10. Implement control and prevention measures as early as possible.
11. Communicate findings.
12. Maintain surveillance to monitor trends and evaluate control/prevention measures.

Before my first class on Monday, I checked into the



Dr. James Curran in 1985.

A Seattle man with AIDS has purple marks on his face from Kaposi's sarcoma, 1987.

Epidemiology component of Parasitology, my assignment as an EIS officer. My supervisor, Dr. Dennis Juranek, a veterinarian and staff parasitologist, asked me to meet with Dr. James Curran of the Venereal Diseases division on Tuesday to discuss a new project.

When I met with Dr. Curran, he told me that he and others had been working on a number of new diseases among gay men in New York and California. CDC's pathologists had already confirmed the diagnoses of Kaposi's sarcoma (KS) and *Pneumocystis carinii* pneumonia (PCP) in several patients from biopsy materials. They had confirmed (steps 2 and 3) that those few cases represented an epidemic. Curran asked me if I had heard anything about it. I told him I knew nothing about KS, but that I had seen a few patients with PCP (including one gay male) in Pittsburgh during my infectious diseases fellowship. I told him about my work on open lung biopsies among organ transplant recipients and cancer patients, and mentioned that I had read the June 5 *Morbidity and Mortality Weekly Report* (*MMWR*) detailing five cases of PCP among gay men in Los Angeles.[3] Curran said that he would interview a few of my classmates before making a final decision about staffing a new team. If I was selected to join the task force, I had to be willing to work with gay men and make a commitment of at least six months.

On Wednesday, Curran called and offered me a position with the new investigation team. I accepted. My job was to set up a surveillance system for those new diseases, steps 4, 5, and 6. Early in the second week of class, he called again to ask how I was coming along with my project; I was unprepared and he was unhappy with me. He told me I had to develop and present a case definition and plan to my EIS classmates by the end of the third week of class, when we would all disperse on our field assignments. Later that day he called yet again, this time with welcome news: he had arranged for me to skip classes so I would have the necessary time to complete the assignment.

I reported to Curran's office first thing Monday. He told me to develop a case definition. He suggested that I review the case reports collected in the spring, read about the diseases being reported, review files on requests for the drug pentamidine, and talk with Dr. Kathy Shands, who had developed a surveillance system for toxic shock syndrome (TSS) two years earlier.

From my class notes, I knew that surveillance was "information for action," the ongoing systematic collection, analysis, and interpretation of outcome-specific data essential to the planning, implementation, and evaluation of public health practice. I spent Monday and Tuesday in the CDC library reading about KS and other opportunistic infections (OIs), including PCP, toxoplasmosis, disseminated herpes virus infections, tuberculosis, and cryptococcosis.

By the end of the week I proposed the following three-part definition:

1. Biopsy-proven Kaposi's sarcoma and/or culture or biopsy-confirmed life-threatening OIs at least moderately predictive of immunosuppression.

2. Persons between the ages of fifteen and sixty years.

3. No prior evidence of underlying immunosuppression, i.e., cancer diagnosis, organ transplant recipients, or use of steroids or other immunosuppressant agents.

We defined OIs as those in which at least 50 percent of cases reported in the medical literature had occurred in immunocompromised patients. For PCP, essentially every adult case occurred in an immunosuppressed person. A former EIS officer assigned to Parasitology had reviewed all cases of PCP reported to CDC between 1967 and 1970, and 191 of the 194 cases he reviewed were clearly linked to immunosuppression. The three outliers were infants.[4]

Other OIs were not as clear cut. By my calculations, cryptococcal meningitis occurred in immunocompromised patients in 50 percent of the reports, and in healthy hosts 50 percent of the time, so it barely met the criterion for inclusion. Tuberculosis, on the other hand, occurred predominantly in otherwise healthy individuals and less so (about 15 to 20 percent) in immunocompromised patients, so it was excluded. The initial list of OIs included PCP, esophageal candidiasis, cryptococcal meningitis, disseminated infection with *Mycobacteria,* and extensive mucocutaneous *Herpes simplex* virus infections.

I had never heard of KS, much less seen a case during my clinical training, so I had to do more digging. I learned that dermatologists from New York City and California reported twenty-six cases of KS among young gay men between January 1979 and June 1981, including five fatalities.[5] Prior to 1980, approximately 300 new cases of biopsy-proven KS occurred annually in the United States, predominantly among men aged sixty or older and renal transplant recipients. In elderly patients, KS appeared as persistent skin lesions and rarely proved fatal. Those twenty-six gay men had skin lesions of KS by biopsy, but their disease followed a more fulminant course, with spread to the lungs, stomach, and intestines. Seven gay men with KS also had PCP—especially striking since concomitant KS and PCP had never been reported before!

In 1872, Moricz Kaposi, a Hungarian-born dermatologist at the University of Vienna, described three fatal cases of hemangiosarcoma in elderly men. Since then the disease has borne his name. In the early 1900s, KS was described in sub-Saharan Africa in adults, mainly young men, and in children—the male to female ratio of cases in Africa was five to one. Italian oncologist Gaetano Giraldo, studying KS in Uganda, linked the sarcoma to cytomegalovirus (CMV) infection, using electron microscopy and blood tests. Another form of KS was reported among organ transplant recipients in the United States in the 1960s.[4]

Step 5 is to find cases systematically and develop a line listing. I discussed the passive surveillance system for TSS with Dr. Shands. In retrospect, she regretted that she had not conducted active surveillance. After TSS was linked to a specific brand of tampons (Rely tampons) and the link was reported widely in the press, physicians stopped reporting cases. It appeared that TSS had disappeared. Fortunately, active surveillance was conducted in Minnesota and Wisconsin, and showed that cases continued to occur.

Passive surveillance refers to data supplied to the health department by the source of the data, often based on a known set of rules or regulations stipulating reportable conditions. A review of death certificates, for example, constitutes passive surveillance. Shands had conducted passive surveillance: she developed a case definition for TSS, published a series of cases occurring in menstruating women in *MMWR*, and asked individuals to call her if they knew of any additional cases matching her definition. She received calls, as anticipated, from physicians and nurses, but also from patients, their relatives, and their neighbors. Given these criteria, undercounting of cases occurs often with passive surveillance systems.

Active surveillance, on the other hand, is initiated by the data collector and involves proactive solicitation of reports, typically from selected health care providers, generally in addition to requests for passive reporting. Active surveillance systems are more costly, both economically and in time and effort expended. The data generated, however, are usually more reliable. During the TSS investigation, epidemiologists in the Wisconsin and Minnesota state health departments identified chiefs of medicine at selected large hospitals and called them regularly to solicit information on potential new cases. These chiefs continued to report new TSS cases, even

Dr. Moricz Kaposi.
National Library of Medicine/Science Photo Library

Physicians meeting with AIDS patient, 1987. © Roger Ressmeyer/CORBIS

after Rely tampons were taken off the market. Indeed, it was subsequently determined that TSS was caused by an exotoxin F subsequent to staphylococcus infection and not specifically by the Rely tampon, although the design of the tampon increased the risk of infection.

My conversation with Dr. Shands convinced me that we needed an active system to supplement passive reporting. I proposed that each EIS officer assigned to a field position identify the largest hospitals in their cities and call on chiefs of infectious diseases, oncology, medicine, and dermatology to tell them about our cases of PCP and KS, and find out if they had heard of any similar cases at their institutions. They would be contacted at regular intervals, and any cases would be reported to me. Curran approved this plan.

We selected six EIS officers from my class and six cities in which to conduct active surveillance: two cities considered by reputation to have a high percentage of gay men—New York City and Los Angeles; two cities with a moderate percentage of gay men—Albany and Rochester, New York; and two cities with a low percentage of gay men—Tallahassee, Florida, and Oklahoma City. Curran contacted another twelve EIS officers, assigned them to other cities, and encouraged them to look for new cases. He also sent a letter to all state health departments asking them to report any potential cases to CDC and giving my telephone number as the point of contact (passive surveillance).

I developed a two-page case report form that included the patient's name, age, self-reported sexual orientation, diagnosis, how the diagnosis was made (biopsy or culture), and contact information for the reporting physician. EIS officers completed the forms when referring physicians reported cases. We avoided collecting information from patients or family members, partly because that approach had created problems during the TSS investigation and partly because our case definition required a more advanced understanding of pathology and microbiology. I made the report form as easy to complete as possible—mainly a series of check boxes—to keep the phone calls with clinicians as short as possible.[4]

I continued reviewing the case reports that others at CDC had collected, including the five cases reported by Dr. Michael Gottlieb in the June 5 *MMWR*. One of Dr. Gottlieb's patients had had a prior lymphoma and was excluded. The four other men were previously healthy gay men who had PCP, extensive mucosal candidiasis, and multiple viral infections, including CMV; one had KS. Three of the four patients had prolonged and unexplained febrile episodes. An immunologist at UCLA, Gottlieb had conducted extensive immunologic studies on his patients. The underlying defect, he suggested, was a low or inverted ratio of T-helper lymphocytes to T-suppressor lymphocytes.[6]

While I was setting up active and passive surveillance, Dr. Curran charged Dr. Harold Jaffe with listing hypotheses of causation and designing a study to test them (steps 7 and 8). Dr. Jaffe listed his leading hypotheses:

1. Cytomegalovirus
2. An environmental toxin, most likely nitrite inhalants
3. Immune overload caused by exposure to multiple infectious agents
4. A "new" infection agent, most likely related to herpes or hepatitis viruses

Cytomegalovirus was on the top of everyone's list. Gottlieb had found evidence of CMV infection in his initial five cases. Giraldo, working with KS patients in Africa, had found evidence of herpes virus infection in KS tissues, and suggested CMV as the causative agent. But why would CMV be causing an epidemic now? Could it be a new or mutated strain now circulating among gay men? And what was its relationship to immunosuppression: was it causing immunosuppression or taking advantage of another immunosuppressive cause—was CMV the chicken or the egg?

Inhalants containing alkyl nitrites, commonly known as "poppers," were discussed as a possible toxic cause of

immunosuppression. Gottlieb noted that all five of his patients had used them. CDC had conducted a survey of 420 men attending venereal disease clinics in New York, San Francisco, and Atlanta, and found that 85 percent of gay men interviewed reported using poppers at least once in the last five years, compared to just 15 percent of heterosexual men. Curran hoped that poppers or some contaminant of those drugs would be implicated as the causative agent because the solution would then be straightforward.

Nitrite inhalants are commonly abused substances in the United States and Europe—used primarily by gay men, adolescents, and young adults to enhance sexual activity by prolonging penile erection. Alkyl nitrites (e.g., amyl, butyl, and isopropyl nitrite) are colorless or yellow liquids at room temperature and highly volatile. They have a fruity odor (often described as unpleasant) and have been nicknamed "poppers" because of the sound made when the glass capsules containing amyl nitrite are crushed. The vasodilatory effect following inhalation of amyl nitrite vapor was described in 1859 and led to the first report of its clinical application to provide relief for angina pectoris in 1867. The substance was initially marketed by prescription in the United States in 1937 and remained a prescription drug until 1960, when it became available over the counter. Beginning in the 1960s, the nitrates (e.g., nitroglycerine, sublingual tablets, dermally applied ointments, and later, transdermal nitrate patches) replaced amyl nitrite as the preferred treatment for angina pectoris. In the late 1960s, pharmacists and drug manufacturers noted widespread purchases of amyl nitrite by apparently healthy young men. Those over-the-counter purchases became the impetus for the FDA to reinstate the prescription requirement in 1968. Soon thereafter, an underground market for amyl nitrite and other nitrite congeners emerged. Those products were initially sold as "room odorizers," and are still being sold, now illegally in the United States, under that guise.

Finally, a novel infectious agent or some hybrid or mutation of a known organism was considered as the possible immuno-suppressive agent. A new herpes virus, particularly a new CMV, generated much discussion, although other viruses were also considered. The prevalence of the OI clusters among gay men and drug addicts suggested that hepatitis B-like viruses should be considered and sought.

In step 8 the study is finally conducted. For most outbreaks, the investigator must decide between a case-control and cohort study. The former is more efficient when the disease is rare, usually defined as occurring in less than 20 percent of the population studied. By October 1981, fewer than 100 cases were recognized in the United States. In addition to the condition's rarity, the vast number of exposures requiring investigation favored a case-control design. If a cohort study were performed, who would be selected as a participant? How long would they be followed? How many would be lost to follow-up? And how much would it all cost?

Case-control studies, however, have their own drawbacks. They are often beset by selection, interviewer, and recall biases. How does one determine an appropriate control group? The investigator must always be concerned about information bias and the obscuring effect of confounding variables. Having weighed the pros and cons of each study design, Jaffe chose to conduct a case-control study.[7]

As a starting point, he defined a case as a gay male with KS and/or PCP, fifteen to sixty years of age, and with no prior evidence of immune suppression. He decided to recruit all patients meeting his case definition in New York City, San Francisco, Los Angeles, and Atlanta.

Defining the ideal control group presented a greater challenge. The use of controls who were very similar to the cases could result in overmatching and could obscure important risk factors. On the other hand, the use of controls very different from cases could make comparison difficult, so that differences between cases and controls could not be interpreted. Jaffe decided to recruit multiple controls for each case, ranging from persons relatively similar to the case (friend controls) to persons relatively different from the case (heterosexual male controls). Since obtaining a true random sample of gay men to serve as controls did not appear feasible, he asked health departments, private clinics, private physicians, and individual patients, to help recruit controls. Each control was a man of the same race/ethnicity, age (plus or minus two years), and metropolitan residence as the patient to whom he was matched. Jaffe sought five matched controls per case: one friend control, a gay male identified by the patient as a friend who had never been a sexual partner; two venereal disease clinic controls, homosexual men who were patients of the venereal disease clinic; one private practice gay control, a homosexual patient of a local private practice physician seen for an acute illness and selected randomly from the referring physician's rolodex or log book; and one private practice straight control, an exclusively heterosexual patient of a local private physician selected randomly from the physician's rolodex.

Jaffe developed a questionnaire and decided who would conduct the interviews. One of the greatest strengths of his study was the front-end work he invested in developing the questionnaire, which ensured back-end data that was less likely to be contaminated by information bias. Task force members and other EIS officers—all physicians—conducted the interviews. The same officer who interviewed a case interviewed all the controls matched to that case.

All of us were trained to conduct the interviews in a consistent, non-judgmental fashion. At the training, during which Jaffe mock interviewed Curran, I asked if we should be concerned about participants misrepresenting their sexual activity—exaggerating exploits, perhaps, or minimizing certain behaviors. Curran acknowledged the difficulty in collecting such private information, but was emphatic about the importance of the interview data. He pointed out that we were not

looking for the truth per se, but for differences between cases and controls. Importantly, we would also collect blood samples and mouth and anal swabs from all participants for a more objective investigation of immunologic and infectious markers at our Atlanta lab.[8] Training now complete, we were prepared to enter the field in October.

On Sunday October 4, Curran and I flew to New York City. On Monday morning we met others at the New York City Health Department to get our marching orders. Local health officers cleared Jaffe's protocol through the Health Department's sanctioning process and arranged for us to begin our study. We conducted interviews of cases in hospital rooms, physician offices, or at patients' homes. We interviewed controls at the venereal disease clinics, physician offices, and even in our hotel room. After an interview of about forty-five minutes, we drew blood and collected the swabs. Following standard practice of that era, we did not wear gloves to draw blood.

During my month in New York City, I conducted about sixty interviews. The participants seemed impressed that CDC physicians from Atlanta had traveled to New York to engage face-to-face with them in any and every setting. By attempting to answer all of their questions, we seemed to gain rapport with the subjects and the gay community, demonstrating that CDC was serious about this problem. In turn, I recall being impressed with how open and apparently honest the participants were in describing the most intimate details of their lives.

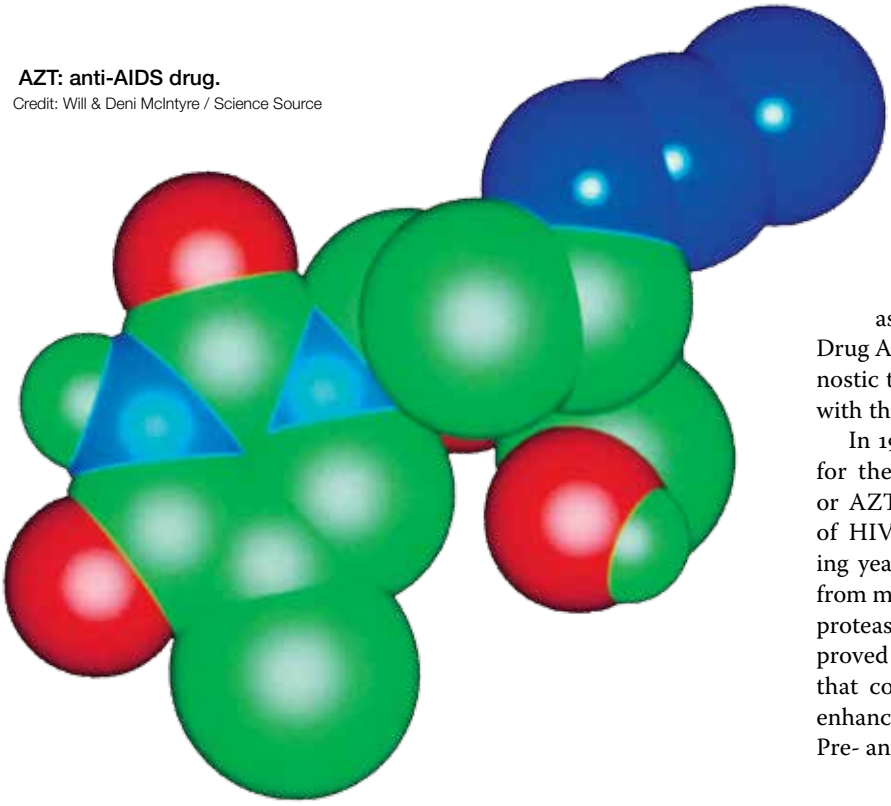
When we returned to Atlanta at the end of October, I transitioned from field work to phone work. I spent up to eight hours each day on the phone talking with physicians, the press, anyone who called the number. I filled out the surveillance form for each patient while on the phone with the reporting physician. This was before speaker phones were invented, and I remember the heat generated by holding a phone to my ear for extended periods of time—I would transfer the phone from ear to ear over and over again.

While logging calls about patients with KS and life-threatening OIs, I noticed that clinicians were spontaneously reporting a growing number of gay men with unusual clinical complaints, such as intermittent and prolonged fever, generalized lymphadenopathy, weight loss, and blood dyscrasias that remained unexplained after extensive workups. I filled out case reports for each of those patients and placed them in a separate file cabinet in my office.

In September 1982, CDC coined the term AIDS (acquired immune deficiency syndrome) to capture this constellation of OIs and malignancies.[9] Our case-control study among homosexual men, which identified the two leading risk factors for infections as the lifetime number of sexual partners and meeting partners in bathhouses, suggested a novel sexually transmitted agent.[7,8] As surveillance continued, however, it soon became apparent that AIDS was not confined to homosexual men. Over time, the demographic pattern widened to include injection drug users, heterosexual women, Haitian-Americans, Caribbean islanders, hemophiliacs, blood transfusion recipients, heterosexual men, infants and children, health care workers, women who have sex with women, and transgenders. Patients were reported from Europe, then Africa, South America, Australia, and Asia.

In 1983, a French team led by Luc Montagnier isolated a new retrovirus from the lymph nodes of patients in Paris. Called the human immunodeficiency virus, it is widely known as HIV.[10] Two years later, the U.S. Food and Drug Administration (FDA) approved the first diagnostic test for the virus, an antibody test, designed with the goal of screening donated blood.

In 1987, the FDA approved the first medication for the virus, the antiretroviral azidothymidine, or AZT.[11] Tremendous progress in the treatment of HIV infection has occurred in the intervening years. Twenty-six antiretroviral agents—drugs from multiple classes, such as reverse transcriptase, protease, and integrase inhibitors—have been approved by the FDA. It has been found, moreover, that combination treatments reduce viral loads, enhance CD4 counts, and prolong survival times. Pre- and post-exposure prophylactic regimens have



AZT: anti-AIDS drug.
Credit: Will & Deni McIntyre / Science Source

Luc Montagnier in Paris, France on January 23rd, 1987. Credit: Francois LOCHON

also been tested, demonstrating about 50 percent effectiveness. Nonetheless, concerns regarding those antiviral medications abound: they are toxic and expensive; treatment is lifelong; and improper usage may lead to drug resistance.

In 2002, President George W. Bush developed the President's Emergency Plan for AIDS Relief (PEPFAR) and committed $15 billion over five years to provide antiretroviral therapies to two million infected persons in resource-limited settings, with the goal of preventing seven million infections by 2010. PEPFAR has reportedly prevented more than one million deaths per year in Africa.

Less progress has been realized in changing behaviors to prevent new infections. CDC initially encouraged persons to reduce the numbers of sexual partners, and enlisted health departments to close bathhouses. Behavior change strategies evolved to recommend use of condoms, and avoid needle sharing. Newer approaches include male circumcision, pre-exposure prophylaxis, and preventive antiviral therapy.[12] A vaccine, unfortunately, remains elusive.

Despite these advances in addressing HIV/AIDS, more than 39 million lives have been lost. Furthermore, WHO estimates that 35 million people worldwide are HIV-infected, and 2.1 million new infections occurred in 2013. If we are to control this disease, we must redouble our efforts. We need more strategic use of antiretrovirals for HIV treatment and prevention. We must eliminate new HIV infections in children and expand access to pediatric treatments. We must expand and improve health care coverage for HIV among key populations worldwide, and develop further innovations in prevention.

Regardless of all the challenges ahead, this fact stands out in the fight against HIV/AIDS: today, the life expectancy of an HIV-infected person receiving antiretroviral treatments approaches that of a person without HIV.[12]

Acknowledgment

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