AIDS Trends: Projections from Limited Data

Some aspects of AIDS epidemiology are now well understood; others remain puzzling because of the long latency period after infection

By now, the statistics are familiar. Since acquired immune deficiency syndrome (AIDS) was first recognized in 1981, more than 14,000 people in the United States have been diagnosed with the disease, and the number of cases is roughly doubling each year.

There is almost universal agreement among epidemiologists that this grim trend in the total incidence of AIDS will not be broken soon. But there is far less agreement over how widely the disease is likely to spread, especially beyond what are currently defined as the high-risk groups.

The uncertainty stems from inevitable deficiencies in the data from which extrapolations are being made. It also reflects lack of knowledge of how effectively the retrovirus that is widely believed to be the prime cause of AIDS is transmitted sexually from women to men. And it reflects the lack of firm answers to what in many respects is the most troubling question of all: what proportion of people infected with the virus will go on to develop disease symptoms? (See box, p. 1019.)

The disease pattern that has emerged over the past 4 years indicates that the victims have belonged almost exclusively to certain high-risk groups. Some 73 percent are homosexual or bisexual men, 17 percent are heterosexual drug users, 3 percent were infected from blood transfusions or from coagulation products used to combat hemophilia, and 1 percent—predominantly women—apparently acquired the disease through heterosexual contact with an infected partner. The remaining 6 percent do not fit into any of the other risk groups. Whether this pattern will hold true in the future is, however, a matter of debate.

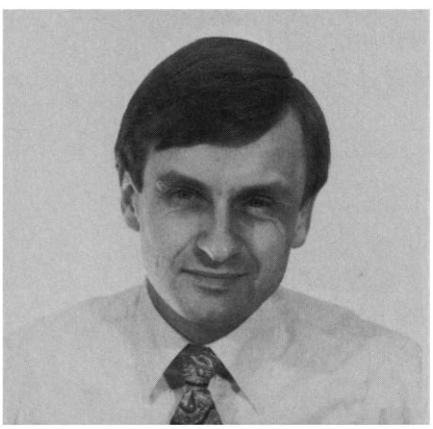
The central difficulty in predicting the likely course of the AIDS epidemic is the long latency period between infection and the onset of symptoms. The patterns of disease that are now showing up reflect patterns of infection several years ago; they do not necessarily provide a firm indication of what the epidemic will look like several years from now, however. The long latency period, during which infected individuals are probably capable of transmitting the virus, also greatly complicates efforts to control the epidemic. "Our society doesn't deal very well with long-incubation diseases," notes James Curran, who heads AIDS studies at the Centers for Disease Control (CDC).

The War on AIDS

This is the fourth article in a series about research on AIDS. Forthcoming articles will examine AIDS in Africa and the programs to develop therapies and vaccines.*

A clearer picture of the likely spread of the disease will only emerge by tracking the spread of the virus rather than AIDS itself: a much more difficult task. It was, in fact, an impossible task until a few months ago, because there was no way to detect infection in people who had not come down with symptoms.

The development of a simple test to detect antibodies to the virus in blood samples has changed all this. Although the test does not actually detect the virus itself, it is generally accepted that those who have antibodies in their blood have not only been exposed to the virus but also have the viral genes integrated in some of their cells; they are assumed to be infected and infectious.



James Curran

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The test is a powerful epidemiological tool, but its development is too recent to fill several important information gaps, perhaps the biggest of which is lack of long-term data. Only when groups of people are followed for several years will it be possible to form a complete picture not only of the spread of the virus but also of the disease process in infected individuals.

What long-term data there are come mostly from a handful of studies in which blood samples were taken from people several years ago as part of other investigations and stored. Researchers have gone back to check these samples for antibodies to the AIDS virus,† and they are following up by taking new blood samples from the same people. This gives a window of several years through which to view the process of the disease and monitor the spread of infection. These studies have provided a very slim database, however, for they involve at most a few hundred people. (See box on p. 1020.)

In spite of these inadequacies in the data, many aspects of the disease are now understood with some clarity.

The clearest finding is that, in the words of acting assistant secretary for health James O. Mason, "This is a very difficult disease to catch." Transmission appears to require direct insertion of the virus into the bloodstream, for example through use of contaminated hypodermic needles, blood transfusions, or some sexual practices. There is no evidence that it is being spread in any other way.

Indeed, there is good evidence that the virus is *not* spread by even prolonged, close exposure to AIDS patients. For example, studies by researchers at CDC have found no antibodies to the virus in the blood of family members of patients, other than sexual partners or children of infected mothers. Similarly, there has been only one documented case of infection among health care workers as a result of treating AIDS patients—and that occurred in a British nurse who accidentally injected herself with contaminated blood.

In contrast, it is clear that the virus is transmitted efficiently among some segments of the high-risk groups, where rates of infection have reached very high levels. For example, 73 percent of a group of homosexual and bisexual men being studied in San Francisco have antibodies to the AIDS virus, and 53 percent

*Previous articles in the series were published in *Science*, 25 October, p. 418; 1 November, p. 518; and 8 November, p. 640.

†In this article, the term AIDS virus is used for the virus variously known as human T-lymphotropic virus III (HTLV-III), lymphadenopathy/AIDS virus (LAV), and AIDS-associated retrovirus (ARV).

A Disease in Many Guises

Perhaps the biggest area of uncertainty in the epidemiology of AIDS is what is likely to happen to the 1 million or so people who have been exposed to the AIDS virus and are carrying antibodies to it in their blood. It may be years before that question can be answered with any confidence, given the long lead time between infection and the onset of symptoms, but it lies at the heart of estimates of how many people are likely to come down with AIDS in the next few years.

One problem is that there have been very few studies in which infected individuals have been followed for any length of time. Those studies, moreover, involve only a few dozen people. "We have not had an adequate time window to understand the full outcome" of infection, says Nancy Gutenson, an epidemiologist at the Harvard School of Public Health.

A second complication is that a broad range of syndromes, which do not fit the current definition of AIDS, are now showing up among people infected with the virus. The disease process thus appears to be much more complex than was originally believed, and many physicians are now suggesting that the definition of AIDS should be broadened.

The few long-term studies that have been done indicate that a substantial fraction of those infected with the AIDS virus will remain free of symptoms for at least several years. Among 31 men known to have been exposed to the virus before 1980 in San Francisco, for example, about two-thirds remained symptom-free 5 years later (see box on page 1020). Others will develop AIDS-related conditions, such as swollen lymph nodes, and apparently remain stable for some time. And a third group will experience a steady degeneration of the immune system, leading to full-blown AIDS.

What distinguishes these groups, and what factors determine the outcome of infection with the AIDS virus is a complex medical puzzle. There are a few clues and plenty of theories.

Most researchers are agreed that a person producing antibodies to the AIDS virus has been infected and is probably infectious. The virus is assumed to have entered the bloodstream and integrated its genes into the DNA of some cells. This assumption is borne out by the fact that several researchers have isolated virus from cells of people who have a positive antibody test but appear to be entirely free of symptoms. Indeed, the virus is generally easier to isolate before AIDS itself appears, which suggests that people may be more infectious during early stages of infection. (The virus has also been isolated from some patients who have disease symptoms but have not produced antibodies, a fact that suggests there is not always an immune response to infection, and raises the possibility that a small fraction of contaminated blood donations are slipping through the screening test.)

The primary targets of the virus are T4 cells, lymphocytes that play a central role in orchestrating the body's response to infections. Once the viral genes are integrated into the cells' own DNA, they can apparently remain dormant for an indefinite period without causing any ill effects. Problems arise when the viral genes are activated and new virus particles are formed, which then infect fresh T4 cells. For reasons that are currently poorly understood, the process of viral reproduction kills the infected cell. Eventually, the body's T4 cells are seriously depleted, the immune system collapses, and a variety of infections appear. The victim has AIDS.

The central question is what kicks the viral genes into action? A widely held theory is that further challenges to the immune system, such as a second infection with the AIDS virus or another organism, may be the trigger. Another possibility is that the disease may proceed more swiftly in those whose immune system is already impaired, for example through use of drugs or from other infections. The bottom line, however, is that "we really don't know why the virus lies dormant and gets activated at certain times. But we don't know that about many agents, such as genital herpes," says Samuel Broder, associate director for clinical studies at the National Cancer Institute.

What is happening to the immune system during the course of infection is, however, only part of the story. It is now clear that the virus also attacks other cells. Researchers at the National Cancer Institute isolated virus from the brains of some AIDS victims last year, and it has recently been isolated from cerebrospinal fluid by scientists at the University of California at San Francisco. This indicates infection of the central nervous system, although it has not yet been determined with certainty which cells are involved.

The virus's apparent lack of fastidiousness about the cells it infects raises some interesting questions about which molecules on the cell surface constitute the "receptor" that enables the virus to slip into the cell. It also greatly complicates the disease picture. For example, infection of the central nervous system can result in serious neurological problems, which can appear in the absence of severe immune system impairment. Broder notes, for example, that patients who do not fulfill the criteria of AIDS itself are showing up with cortical atrophy, meningitis, and motor problems. There have also been reports of Guillain-Barré syndrome, indicating the possibility of peripheral nerve damage.

In addition, several types of cancers are appearing among infected individuals. Jerome Groopman of Harvard University and New England Deaconess Hospital says he has seen six cases of Hodgkin's disease in the past 6 months in people infected with the AIDS virus; and Burkitt's lymphomas are showing up in a "bizarre" form. In addition, there have been several cases of squamous cell carcinoma of the head and neck—a cancer usually seen in older people who have been heavy smokers or drinkers, it is now showing up in young men in their twenties. Groopman and others surmise that these cancers may not be directly caused by the AIDS virus, but may result from impairment of the immune system, including opportunistic infections by other agents.

"The disease is much broader than we had once thought," notes William Haseltine of Harvard University's Dana-Farber Cancer Institute. "We will really know only after about 20 years what the impact of this virus is," he suggests.—**C.N.**

The Epidemic's Unsung Heroes

For the past 18 months, some 500 homosexual and bisexual men in San Francisco have been taking part in perhaps the most comprehensive and important study of the epidemiology of AIDS in the United States. Every few weeks, they subject themselves to a battery of tests and a barrage of questions from researchers seeking information on how the AIDS virus is spreading and what causes the disease to develop in some, but not all, infected individuals. "These men are the unsung heroes of this epidemic," says Dean Echenberg, director of San Francisco's Bureau of Communicable Diseases.

They did not originally set out to participate in an AIDS study at all. They are part of a group of 6875 gay men who sought treatment at the San Francisco City Clinic in the late 1970's for sexually transmitted diseases, and volunteered to take part in a major survey of hepatitis B infection. The survey, conducted by the Centers for Disease Control (CDC) in conjunction with the San Francisco health department, involved the donation of serum samples, which were tested and subsequently frozen and stored at CDC's Atlanta headquarters. In 1983 and 1984, says Echenberg, "We realized that a very high proportion of these men were getting AIDS," and an effort was made to enroll a random sample of the original group in an AIDS study.

According to William Darrow, a CDC sociologist who is participating in the study, 492 agreed to take part and gave permission for their early blood samples to be tested for antibodies to the AIDS virus. The results were startling. Some 4.5 percent of the samples drawn in 1978 tested positive. By 1980, the proportion infected had risen to 24 percent, and by mid-1985, 73 percent of the group had antibodies to the AIDS virus, according to analyses of recently drawn blood samples. Clearly, the virus had spread widely well before AIDS itself was recognized as a new disease.

What makes this group so important in the effort to unravel the epidemiology and natural history of the AIDS epidemic is the fact that, because serum samples are available from at least 5 years ago, there is a relatively large window through which to view the spread of the virus and follow the progress of the disease itself. Most other studies involve groups of individuals who have been followed for much shorter periods.

So far, the San Francisco cohort, as it is widely known, has provided some important preliminary information on the number of people infected in relation to the number who have actually been diagnosed with AIDS. In 1980, the ratio was about 825 to 1, but by 1984 it had shrunk to about 30 to 1. This is in large part the basis for CDC's much-publicized guess that the ratio nationwide is between 50 and 100 to 1, which translates to between 700,000 and 1.4 million people who have been infected with the AIDS virus.

The cohort has also provided some clues about the rate of development of AIDS among those infected. Thirty-one of the cohort members had antibodies to the virus by 1980, but by 1985 only two of them had developed full-blown AIDS. Another eight had AIDS-related conditions such as swollen lymph nodes. In other words, 5 years after being infected, one-third were showing symptoms of infection and two-thirds remained healthy.

According to Echenberg, studies of the San Francisco cohort are being expanded and an attempt is being made to recruit more members from the original hepatitis study, especially those likely to have been infected early in the epidemic. Researchers from the University of California at San Francisco are studying cohort members in an investigation of psychological and sociological aspects of the disease. A project involving researchers from the University of California at Berkeley is aimed at understanding the transmission of the virus to sexual partners of cohort members, including heterosexual partners of bisexual men. Another study will attempt to determine whether there are any common factors involved in the progression of the disease from infection to full-blown AIDS. And yet another project will investigate the extent to which those with positive antibody tests, but no sign of disease, are shedding virus. Says Echenberg, "These men are putting up with a lot of tests and questions. Their contribution is going to be important for the rest of the world."—**C.N.**

of a group of 66 homosexual men in New York City, who are being followed by epidemiologists from the National Cancer Institute, were found to be infected as early as June 1982.

These extraordinarily high rates of infection probably reflect the fact that the groups were drawn from people presenting themselves for treatment for a variety of illnesses, including sexually transmitted diseases, and thus are likely to represent a highly sexually active segment of the homosexual population. Lower, but still significant, rates of infection have been found in other groups of homosexual men. For example, Michael Marmor and his colleagues at New York University Medical Center have found an infection rate of about 45 percent in a group of randomly selected homosexual men in New York City.

Lower rates are expected to be found among homosexuals in areas away from the foci of the disease, but much more extensive monitoring is needed to determine the extent to which the virus has spread in this risk group. Five major studies, each involving about 1000 randomly selected homosexual men, are being funded by the National Institute of Allergy and Infectious Diseases to help provide some answers. They will not be completed until late 1987, however.

The second major risk group, intravenous drug users, currently shows a highly localized pattern of infection, with an epicenter in New York City and its immediate surrounding area. Some 80 percent of the drug-related AIDS cases have come from this region. The virus apparently entered this population early and spread rapidly.

Studies by Donald Des Jarlais of New York's Division of Substance Abuse Services indicate that as early as 1979 between 25 and 30 percent of 49 blood samples donated by drug users as part of a study of methadone safety had antibodies to the AIDS virus. By 1980, 40 percent were infected, and in 1985 between 55 and 60 percent of new serum samples had antibodies to the virus. Collaborative studies of drug users in San Francisco and Chicago show rates of infection of around 10 percent, Des Jarlais says.

The highest infection rates of all—more than 70 percent, according to several studies—are found among hemophiliacs who used preparations of factor VIII derived from blood donations. Elaine Eyster of the Milton S. Hershey Medical Center of Pennsylvania State University has found that most of these infections occurred by 1983, before the AIDS virus was even identified. It has since been demonstrated that heat treatment will

inactivate the virus, and factor VIII preparations are now probably safer than whole blood transfusions.

While rates of infection in the high-risk groups are being intensively studied, far less is known about spread of the virus in the general population. Partly for this reason, there is an intense debate among researchers about the likely extent of the epidemic. Many researchers argue that AIDS, like other sexually transmitted diseases, will spread by any type of sexual intercourse and more and more cases will start showing up among heterosexuals.

So far, this has not happened. The disease pattern has undergone "remarkably little change," notes Harold Jaffe, who heads epidemiological studies of AIDS at CDC. In late September, CDC reported that heterosexual transmission had been documented in only 133 diagnosed cases of AIDS out of more than 13,000 that had then been reported. Only 15 of these cases involved transmission from women to men.

Heterosexual transmission is, however, strongly suspected in scores of other cases where no obvious risk factors could be determined. But the number of both documented and suspected cases of heterosexual transmission has not increased in relation to the total during the 4 years since the disease was first recognized.

Some researchers argue that heterosexual transmission is unlikely to play a dominant role in the spread of the disease because the AIDS virus is not like many other sexually transmitted agents. It appears to require direct insertion into the bloodstream to cause infection, and this is more likely to occur during anal intercourse than vaginal intercourse. Moreover, this argument suggests that transmission from women to men would occur very infrequently, a suggestion supported by the very low incidence of documented cases of heterosexually acquired AIDS among men.

Although the pattern of diagnosed cases shows little heterosexual spread of AIDS, far less is known about the spread of the virus itself. According to Jaffe, a small study by CDC in collaboration with the Atlanta Red Cross indicated that blood donors who had antibodies to the AIDS virus belonged almost exclusively to high-risk groups. CDC is about to begin a much larger study of antibody-positive donors in New York City to determine whether they follow the same pattern.

If AIDS is not spreading widely into the heterosexual community in the United States, it will be difficult to equate this with what appears to be happening in Africa. According to many recent reports, AIDS is afflicting Africans in roughly equal numbers, and it has all the hallmarks of a heterosexually transmitted sexual disease. (A separate article on African AIDS will appear later in this series.)

"The potential for heterosexual transmission is pretty clear to me," says William Blattner, an epidemiologist at the National Cancer Institute. "We have underestimated this virus from time to time in the past," he warns.

—COLIN NORMAN

Reagan Vetoes NIH Bill; Override Is Likely

A year ago, Congress passed an NIH bill that mandated the creation of two new institutes at the National Institutes of Health—one for arthritis and another for nursing research. President Reagan killed the bill with a veto. This fall Congress again passed comprehensive reauthorization legislation for NIH (*Science*, 1 November, p. 525). On 8 November, the President vetoed it. The second bill, written with an eye to securing White House approval, provided for the establishment of an arthritis institute but omitted provisions for the controversial nursing institute and settled for a nursing center within NIH instead. But the compromise was not enough to satisfy the Administration, which objected to other features of the legislation as well.

But this time it looks as though Congress may well prevail. Within days of receiving the President's veto message, the House voted overwhelmingly to override the veto. The Senate will take the matter up shortly after Reagan returns from the Summit meeting in Geneva. The bill has strong support in the Senate and chances that it, too, will vote to override are said to be very good.

In his message to Congress, the President attacked the bill (H.R. 2409) as one that would "adversely affect the pursuit of research excellence" by giving legislators far to much say about the day-to-day conduct of biomedical research. In Reagan's view, the bill imposed too many administrative and program requirements on NIH and created unneeded new organizations and committees "which would lead to unnecessary coordination problems and administrative expenses while doing little to assist biomedical research endeavors. . . ." The bill, he said, "is overloaded with objectionable provisions that seriously undermine and threaten the ability of NIH to manage itself. . . ." NIH officials and certain biomedical organizations, including the Association of American Medical Colleges, heartily agreed and the AAMC's executive committee has been letting senators know that it would be happy to see the veto sustained.

However, Senator Orrin G. Hatch (R–Utah), one of the bill's chief Senate sponsors has vowed to see it become law after nearly 5 years of negotiation to come up with legislation that could win congressional approval. In the House, Representative Henry A. Waxman (D–Calif.) led the move to override the veto. Waxman has long sought greater congressional input in NIH's affairs. Speaking on the floor of the House just before the vote to override was taken, he said, "We feel that if the taxpayers' dollars, $5 billion a year, are being used for biomedical research, we ought to spell out some of the priorities. We ought to tell NIH what we think they ought to be looking at." Among those things are disease prevention (the bill mandates the appointment of assistant directors for prevention in several institutes), spinal cord injury and learning disabilities.

Although the President opposes this bill, the veto message revealed that the Administration had reconciled itself to the idea of a new institute for research on arthritis and related musculoskeletal diseases. "In recognition of the plight of the millions of arthritis victims and society's costs," the President said he would see to the creation of the institute by an administrative order. However, if the veto is overridden, the institute will be established by law.

In attacking H.R. 2409, the Administration signaled its opposition to congressional micromanagement of government agencies, and this bill seemed a safe vehicle for conveying that message because the veto had no effect on the NIH budget, which is handled through separate appropriations legislation.—BARBARA J. CULLITON