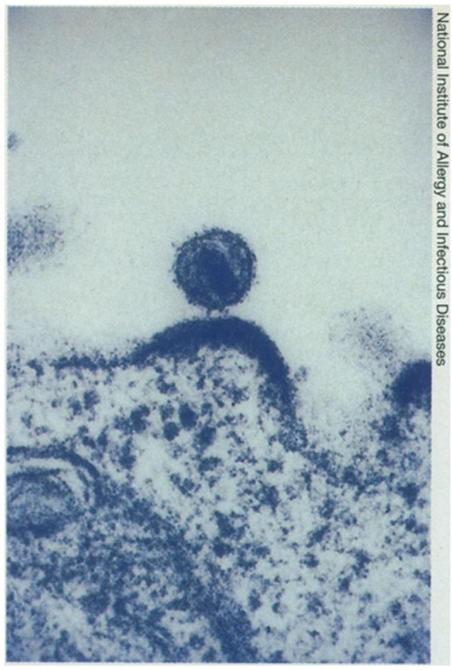
Staying Alive

Scientists study people who outwit the AIDS virus

By KATHLEEN FACKELMANN



The AIDS-causing virus, HIV, is shown budding out of a CD4 T lymphocyte. This virus can go on to infect other cells in the body.

It usually takes 8 to 10 years for a person infected with HIV to develop AIDS. Yet some people have carried the human immunodeficiency virus for more than a decade — and have remained healthy.

How do they keep this deadly destroyer of the immune system at bay?

Researchers are delving into this mystery with a fervor. If they solve it, their findings could lead to a treatment for HIV infection or even a vaccine against it.

Initially, HIV replicates rapidly, sometimes causing an illness resembling the flu. Weeks to months later, an infected person's immune system dampens the virus, ushering in several years of relatively good health. Yet during that period, the virus sustains its attack on the body's infection-fighting white cells. Finally, HIV gains the upper hand. The ravaged immune system can no longer do its job, and normally harmless microbes start to run amok. The HIV-infected person then develops countless opportunistic infections, notably *Pneumocystis carinii* pneumonia, that mark the development of AIDS. Death usually follows within a few years.

For an estimated 5 to 10 percent of HIV-infected individuals, however, the passing years haven't brought that final onslaught. New research suggests that such people stay "frozen" in a long period of robust health. Three articles in the Jan. 26 NEW ENGLAND JOURNAL OF MEDICINE (NEJM) present data on people who have beaten the odds.

"We've known for some time that there are individuals who remain healthy for long periods of time with HIV infection," says coauthor Susan Buchbinder of the San Francisco Department of Public Health. "Now we're starting to understand what the mechanisms are for delayed or arrested disease progression."

To get a more complete picture of long-term survivors of HIV infection, immunologist Giuseppe Pantaleo of the Bethesda-based National Institute of Allergy and Infectious Diseases, Buchbinder, and their colleagues recruited 14 men and 1 woman who had lived with HIV for more than 7 years. Of the 15, 13 had been infected with the virus for at least a decade. The recruits reported no HIV-related illness.

Even more important, all of these survivors had steady counts of CD4 T lymphocytes, the white cells destroyed by the AIDS virus. To enter the study, the volunteers had to show a T cell count of at least 600 cells per cubic millimeter of blood. Seven had CD4 counts well within the normal range of 800 to 1,200.

The researchers also studied a group of 18 HIV-infected people whose progression toward AIDS was indicated by the appearance of disease-related symptoms. All had steadily declining CD4 counts, a sign of viral dominance. Once the concentration of CD4 cells falls below a critical level, hordes of microbes close in on the weakened body.

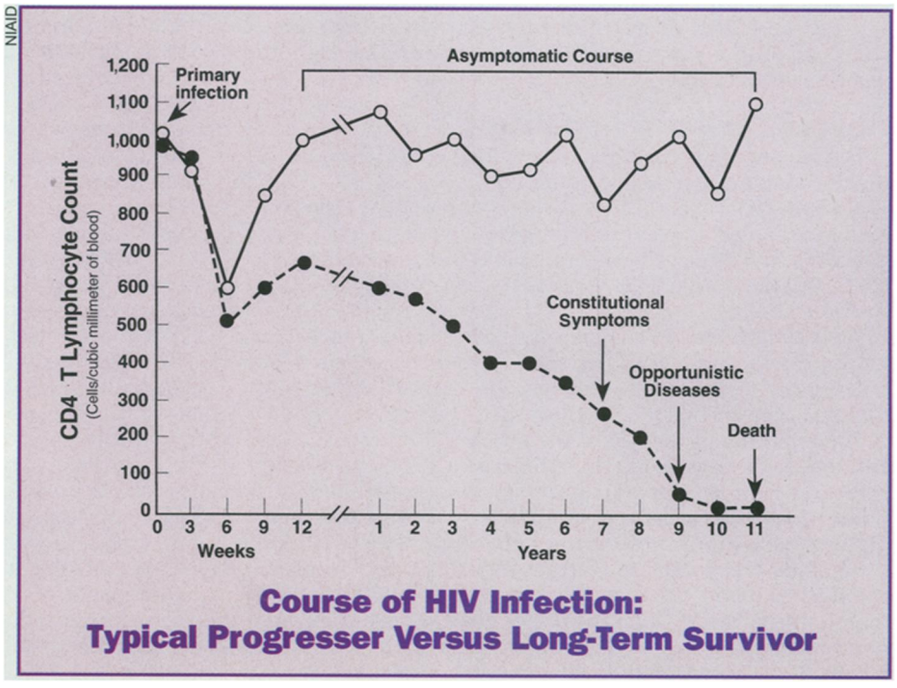
To get an idea of how HIV had affected the long-term survivors, the team first focused on the lymph nodes, bean-shaped nodules of the immune system. They studied tissue from the lymph nodes of 14 of the 15 survivors and found no evidence of HIV-associated deterioration. The samples appeared normal.

In one case, the researchers were able to compare lymph node specimens obtained 9 years apart. The specimens looked nearly identical.

However, when the team turned its attention to the 18 people with progressive HIV infection, it found that the virus had left behind a telltale swath of destruction: Lymph tissue from these people exhibited degeneration and scarring.

The researchers also discovered that nonprogressers trapped less HIV in their lymph node germinal centers, regions of cell proliferation, than the 18 progressers.

For progressers, the lymph nodes seem to act as reservoirs of infection, points out coauthor Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases. He specu-



lates that germinal centers loaded with HIV may infect the millions of white cells that move through the lymph nodes on their way to other parts of the body.

In this case, HIV may turn a healthy defense system against its host. "The body, in trying to contain and hold on to the virus, makes a phenomenal milieu, or environment, for more cells to get infected," Fauci says.

Other parts of the survivors' immune system appeared active despite long-term HIV infection. For example, survivors had very high concentrations of antibodies in their bloodstream, compared to their 18 counterparts. Antibodies are proteins manufactured by the immune system to combat infection. In the test tube, those antibodies destroyed two common strains of HIV, the researchers report.

More evidence of an especially vigorous immune attack on HIV came with the finding that viral replication in the survivors proceeded at a slower pace than in progressers. The researchers speculate that the immune system can't eliminate HIV, but does keep the virus under control. For example, HIV replication in blood and lymph node samples from the progressers appeared 4 to 20 times higher than that found in samples collected from the 15 survivors.

"If the virus does not replicate [effectively], then the disease is not very active," Pantaleo says. "If you have high levels of replication, that means the disease may be progressing."

Taken together, the data suggest that for the uncommon few, infection with HIV doesn't translate into an inevitable death sentence. "These people not only survive for 10 or more years, but they actually go on without any damage to their immune system," Fauci says.

David D. Ho and his colleagues at the Aaron Diamond AIDS Research Center in New York City conducted a similar study of long-term survivors.

The research team, based at the New York University School of Medicine, studied 10 HIV-infected people who had experienced no AIDS-defining illnesses despite 12 to 15 years of infection with HIV. The study included one woman.

All the volunteers had T lymphocyte counts in the normal or near-normal range, a sign that the virus had yet to gain an edge on the immune system. Furthermore, none had taken antiviral drugs for any extended period.

These data also point to a well-controlled HIV infection — one that doesn't produce disease.

For example, with standard culture techniques, the researchers could find no HIV in plasma, the clear portion of the blood. "It's very difficult to isolate virus from these patients," says coauthor Jeffrey Safrit. With a more sensitive test, they found HIV in the plasma of four of their volunteers.

Next, the researchers turned to the peripheral blood mononuclear cells, a hodgepodge of white cells, including CD4 T lymphocytes, in the bloodstream. Using standard techniques, they found HIV in the white cells of four recruits. However, the remaining six had no detectable virus in those cells. By using polymerase chain reaction, a powerful molecular technique for copying DNA, the researchers finally detected small amounts of virus in the white cells of the six holdouts.

"Overall, the viral burden [amount of HIV] in the plasma and [white cells] of long-term survivors was orders of magnitude lower than that typically found in subjects with progressive disease," the authors say.

That low viral burden hints that survivors mount a more vigorous immune response to HIV. Ho's group found that these survivors exhibited revved-up activity of white cells called CD8 T lymphocytes. These immune cells seek out and kill HIV-infected cells in the body.

Finally, the New York team's findings suggest that the strains of HIV infecting survivors are less virulent than the strains that sicken most people. The HIV isolated from long-term survivors grew very poorly in the laboratory, a hint that it may be a particularly flimsy version of the virus.

Ronald C. Desrosiers of Harvard University's New England Regional Primate Research Center in Southborough, Mass., and his colleagues also believed that some people escape AIDS because they carry a weakened form of HIV.

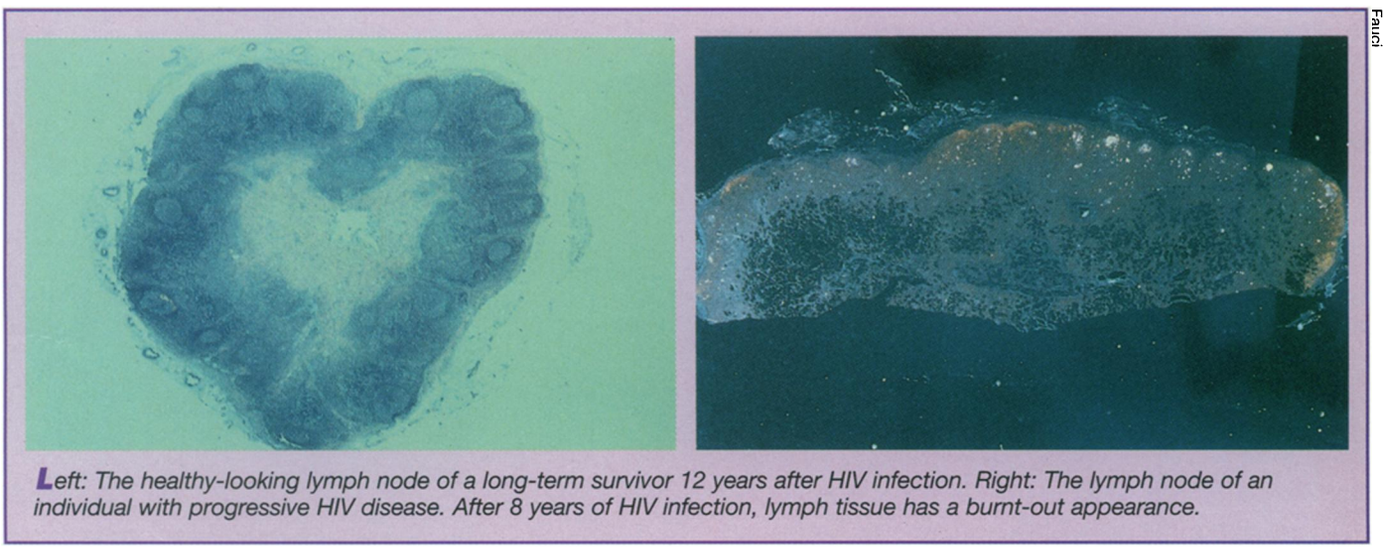
Previous work had shown that rhesus monkeys infected with the simian immunodeficiency virus (SIV) develop an AIDS-like illness. However, monkeys given a mutant strain of SIV seem to develop a low-level infection without ever getting sick. And like their human counterparts, these SIV-infected primates do not show dramatic declines in CD4 T lymphocytes.

It turns out that the milder version of SIV has a defect in a single gene known as nef. Without a properly working nef gene, SIV may not be able to replicate efficiently — thus giving the immune system an edge in its battle to quash the virus.

Would the same reasoning hold true for HIV, a close cousin of SIV? The Massachusetts team decided to look at the nef gene in five people whose HIV infection wasn't progressing. One of them, a 44-year-old with the blood-clotting disorder hemophilia, had a defective form of nef.

"The virus that we've tracked consistently shows a 118-base-pair deletion in the nef gene," says coauthor John L. Sullivan, a geneticist at the University of Massachusetts Medical School in Worcester.

The 44-year-old man tested positive for HIV in 1983 after receiving a contaminated infusion of a blood-clotting factor.



Fauci

Left: The healthy-looking lymph node of a long-term survivor 12 years after HIV infection. Right: The lymph node of an individual with progressive HIV disease. After 8 years of HIV infection, lymph tissue has a burnt-out appearance.

Yet he remains healthy, with very low concentrations of poorly replicating virus in his blood, Sullivan notes.

"We think the defect slows down the ability of the virus to replicate," he says. "That allows the host immune system to stay on top of [HIV]."

The researchers speculate that the man was exposed to additional strains of HIV from the time of his infection until mid-1985, when centers began routinely screening blood products for the virus. Yet this man never got a second infection with a more lethal form of HIV.

Did that first exposure lead to a natural "vaccination?" Does a simmering infection with a mutant virus stave off an attack by a more virulent strain of HIV?

That's certainly the hope. Yet even if nef plays a role in protecting some HIV-infected people, it's probably not the whole story.

Ho and his colleagues found no flaws in the nef gene in HIV isolated from their 10 long-term survivors. In the January JOURNAL OF VIROLOGY, they describe their examination of the nef gene in those patients.

"We therefore conclude that deletion or gross sequence abnormality within nef is not likely to be a common explanation for the well-being of long-term survivors of HIV-1 infection," the authors write.

David Baltimore of the Massachusetts Institute of Technology in Cambridge concurs. "The finding [of a nef deletion] in this patient appears to be very rare," Baltimore wrote in an editorial that appears in the Jan. 26 NEJM.

That doesn't rule out the possibility that additional, as yet unidentified mutations in HIV underlie other cases of long-term survival. Indeed, Ho's team continues to hunt for genetic flaws in HIV. Desrosiers, Sullivan, and their colleagues are doing the same.

"We're going to take these viruses apart piece by piece and try to figure out where the defect is," Sullivan says.

Are the long-term survivors really as lucky as they appear to be?

Scientists can't rule out the idea that some nonprogressers have yet to hit a threshold in their battle with the AIDS virus. They may simply represent outliers destined to undergo immune destruction and develop AIDS at some point in the future.

Yet most researchers believe that some of these people will never succumb to the disease.

The new data give researchers some tantalizing clues but offer no blueprint for long-term survival.

"There's no simple answer as to what makes a person a long-term nonprogresser," comments Kathleen E. Squires, assistant director of the AIDS clinic at the University of Alabama at Birmingham.

"Obviously, there's something right about these patients," Safrit says, noting that the studies reported in the NEJM suggest that a variety of factors may be involved in keeping the HIV-infected person healthy. "It's probably going to be a combination of some form of a weakened virus and a strong immune response that allows a person to survive for a long period of time," he says.

If researchers can clarify the mechanisms of staying alive, they may be able to devise a therapy aimed at freezing the infection in its asymptomatic phase. Thus infected people could never rid their bodies of HIV, but they would live a long, healthy life.

"These observations will hopefully help us in terms of different management strategies," Squires says.

In addition, such studies may suggest new ways to devise a vaccine against HIV. Researchers wonder whether an infusion of crippled HIV would protect people from infection with the virulent strains of HIV that cause AIDS. Desrosiers' group and others are searching for mutations in HIV that would produce immunity but no overt disease. Eventually, such vaccines might be offered to people at high risk of infection.

Still, researchers warn that they have lots of basic laboratory work to do before they can turn such dreams to reality.

"We have not identified precisely what it is that makes these people long-term nonprogressers. But we're very hard at work on it." Fauci says. "Sooner or later, we're going to get the answer." □