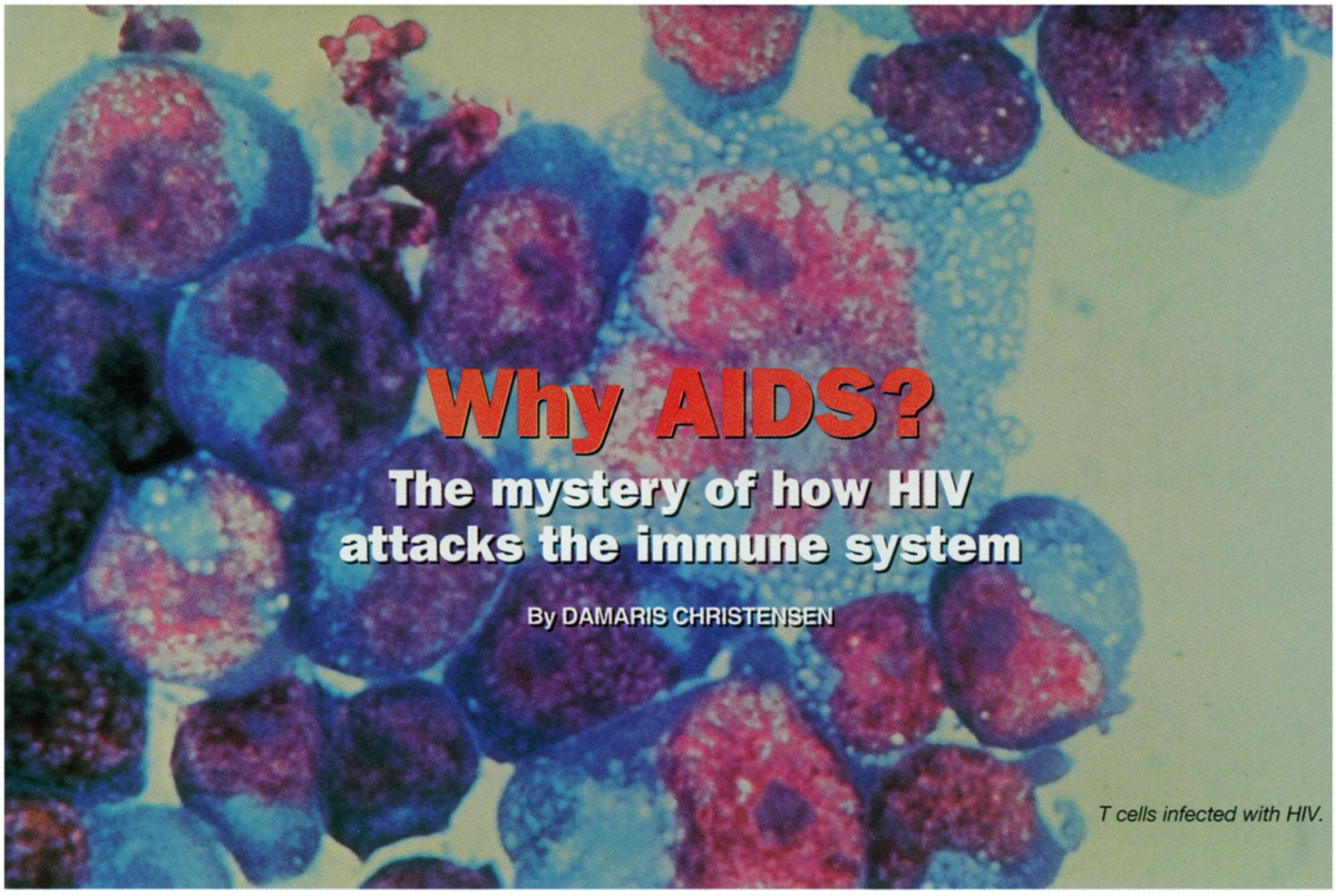

Why AIDS?

The mystery of how HIV attacks the immune system

By DAMARIS CHRISTENSEN

T cells infected with HIV.

NIAID/NIH

Over the past 15 years, governments and institutions have poured millions of dollars into AIDS research. Researchers and doctors have dramatically improved treatments for the disease and gained new understanding of how HIV, the virus that causes AIDS, infects cells. Nevertheless, scientists still understand relatively little about how HIV causes the immune system to collapse, the ultimate consequence of infection.

Most researchers have held that HIV directly kills the immune cells called helper T cells, or CD4 cells, eventually exhausting an immune system that is frantically making replacements. The latest studies, however, suggest that different pathways of CD4 cell disruption may be more important.

Some researchers now suspect that the virus chokes off the supply of new immune cells. Still others are beginning to suggest that HIV changes the signals that send immune cells migrating through the body, directing CD4 cells away from the blood where they normally circulate and toward sites where they may be destroyed.

The disagreement is more than an academic issue. Understanding how HIV triggers immune-cell depletion may eventually enable researchers to block its devastating effects. Also, new knowledge could reveal strategies for AIDS therapies that go beyond the drugs that patients now take to slow replication of HIV.

Without knowing more about how HIV ultimately destroys the immune system, however, it is unclear whether drug treatments alone will be enough to restore a person's immune system and perhaps eventually cure the disease.

Early infection with HIV is marked by symptoms similar to mononucleosis: fever, enlarged lymph nodes, rash, muscle aches, and headaches. Within 1 to 3 weeks, the immune system gets some control over the virus by producing antibodies and cells that recognize and kill some of the infected cells.

HIV reproduces itself quickly, however, and continues to replicate throughout the course of infection. Because HIV contains RNA and uses it as a template for DNA during reproduction, the agent is classified as a retrovirus. Six months or so after infection, HIV reproduction reaches a set point, which varies from patient to patient. In this stage of disease, a person is unlikely to notice any symptoms. However, the higher the set point, the greater the amount of virus carried, and the faster a person is likely to develop AIDS.

Over the next 8 to 10 years, the virus slowly overwhelms the immune system, eventually causing a catastrophic decline in the number of CD4 cells. When the concentration of CD4 cells drops below one-quarter the normal concentration, a person is said to have AIDS. The ensuing immune deficiency renders the person vulnerable to the opportunistic infections that mark the disease, such as tuberculosis and the rare cancer known as Kaposi's sarcoma.

Exactly how HIV eludes the immune system so long and effectively is unclear. Researchers suspect that part of the virus's elusiveness lies in its tendency to infect the very cells that are activated to fight off the infection. CD4 cells, the white blood cells that HIV primarily targets, marshal responses from two other kinds of immune cells: those that produce antibodies and those that destroy infected cells directly.

Only a small proportion of a person's CD4 cells are typically dividing—posing a problem for HIV. The virus can't replicate efficiently without hitching a free ride on the protein-making machinery of a T cell that is already reproducing. However, when researchers began to measure how much virus infected people typically carry, concentrations of HIV were higher than would be expected given CD4 cells' reproduction rate.

In 1995, David D. Ho of the Aaron Dia-

mond AIDS Research Center in New York and Alan S. Perelson of Los Alamos (N.M.) National Laboratory calculated that HIV infects and destroys several billion CD4 cells each day throughout the course of disease.

That rate of cell destruction would lead to AIDS more quickly than has been observed unless the immune system increases CD4 cell production above normal, they said. While replenishing the population, rapidly dividing CD4 cells present additional targets for the virus.

The stresses of initiating massive production of new cells in response to depletion of CD4 cells must be what eventually triggers the especially marked decline in CD4 levels, asserted Ho and Perelson. Just as an ovary can only produce so many eggs over a woman's lifetime, so can the immune system manufacture only a certain number of new cells, they reasoned.

This model accounts for several characteristics of HIV treatment, says Ho. These include the rapid drop in HIV concentration and the quick rebound in CD4 cell counts detected in blood samples after a person begins antiretroviral therapy and the rapidity with which drug-resistant viruses develop.

On the other hand, Ho's theory fails to account for the observation that CD4 cells move from tissues and lymph nodes to the blood soon after antiretroviral therapy begins. The model also assumes that the dynamics of CD4 cell turnover are similar in both early and late HIV infection, which may not be the case, according to Mike McCune of the Gladstone Institute of Virology and Immunology at the University of California, San Francisco.

If Ho's model is correct, antiretroviral drugs, which slow the destruction of helper T cells, reduce the need for production of CD4 cell replacements. A study by McCune and his colleagues, however, indicates that antiretroviral therapy actually allows the immune system to boost its production of new T cells above normal levels. This suggests that HIV acts, in part, by inhibiting the production of new CD4 cells, the scientists propose in the January NATURE MEDICINE.

If HIV blocks the production of new helper T cells, then "to treat the disease, not only do we need potent antiretroviral drugs to stop the virus from spreading and destroying T cells, we may also need additional therapies to ensure that T cell production starts anew," says McCune.

Using a new technique that biochemically labels dividing T cells, including CD4 cells, the researchers compared the blood of HIV-positive patients who were not yet receiving antiretroviral drugs, HIV-positive patients who had just completed a 12-week course of antiretroviral therapy, and volunteers not infected with HIV.

They found much higher concentrations of new CD4 cells in the blood of patients who had received antiretroviral therapy than in HIV-positive patients yet to receive drugs and in uninfected volunteers. The studies also indicated that CD4 cells actually survive longer in HIV-positive patients who had not been given antiretroviral drugs than in patients who had been given the drugs. These findings suggest that the net gain in CD4 cell count during aggressive antiretroviral therapy results from an increase in CD4 production rather than a decrease in CD4 destruction, McCune said.

McCune's study "puts an end to 4 years of exciting debate" and confirms that HIV's effect on CD4 cell production is at least as important as its effect on CD4 cell destruction, says Giuseppe Pantaleo of the University Hospital of Lausanne in Switzerland. Pantaleo, who has used a different technique for estimating CD4 cell production, has likewise found that HIV inhibits CD4 cell production.

Further confirmation of the observation that HIV limits the production of new CD4 cells came last month from research in the Netherlands. Scientists there isolated precursors of CD4 immune cells from blood samples of HIV-infected patients and then cultured these cells in the laboratory to see how they developed.

The initial blood samples were taken soon after the patients learned they were infected with HIV. Six months later, blood samples taken from patients who went on to develop AIDS had lost about 90 percent of their ability to develop new CD4 cells compared with the initial sample, according to Frank Miedema of the Sanquin Blood Supply Foundation in Amsterdam and his colleagues. In contrast, blood from HIV-positive people who had not progressed to AIDS had retained about half of its original ability to grow new CD4 cells, he found.

This suggests that HIV blocks the ability of the immune system to produce new CD4 cells, he said last February in Chicago at the Sixth Conference on Retroviruses and Opportunistic Infections.

Not everyone agrees that Ho's model of immune system exhaustion is on the way out. A team of German researchers reported at the same conference that among 13 HIV-positive patients, the concentration of actively dividing CD4 cells in their lymph nodes dropped during 9 to 12 months of therapy. This suggests that in the absence of treatment, HIV replication in the lymph nodes causes CD4 cells to divide more rapidly than normal, says H. J. Stellbrink of the University Hospital Eppendorf in Hamburg.

There's yet a third way that HIV might reduce the number of CD4 cells in the blood. The virus might redirect many of these cells to tissues and lymph nodes, where they may be destroyed. A paper published in the January JOURNAL OF IMMUNOLOGY supports the idea that HIV—at least in immunodeficient mice—commandeers a natural immune process known as homing, which causes CD4 cells to flood out of the bloodstream and into the lymph nodes.

Immune cells, including CD4 cells, constantly patrol the body for invaders and move along a daily route from the lymph nodes, through tissues, into the blood, and then back to the lymph nodes. In February 1997, virologist Miles W. Cloyd of the University of Texas Medical Branch at Galveston and his colleagues showed that when HIV binds to any of several types of immune cells, including CD4, those cells produce higher than normal amounts of a protein known as CD62L and then move directly into the lymph nodes.

"It appears that once HIV-exposed helper cells are triggered to leave the blood, they are programmed to self-destruct," says Cloyd, who noted that about half of the HIV-infected CD4 cells entering the lymph nodes were destroyed in his experiments on mice.

Cloyd's newly published research confirms that HIV infection triggers the molecular homing signal. It also indicates that after being infected with HIV and moving into the lymph nodes, CD4 cells are more likely to die than are another type of infected T cell called CD8 cells. Cloyd says that this finding could explain why the number of CD8 cells does not dramatically decline during HIV infection.

Although Cloyd's theory remains to be tested in humans, he suggests that enhanced homing might explain several apparent quirks of HIV infection. For instance, homing could underlie the disappearance of immune cells from the blood and their accumulation in lymph nodes in HIV-infected people, he says.

The theory could also explain how so many CD4 cells could die during HIV infection although they are not actively dividing and producing the virus. According to his model, such HIV-infected cells may self-destruct, says Cloyd.

As research progresses, the picture of HIV infection seems to become even more complicated. McCune suggests that none of these models is exclusive. HIV may destroy many CD4 cells, block the production of new cells, and also redirect the movement of immune cells throughout the body. "Data gathered during the next few years will give us a much better picture about what is happening," he says.

So, are there any clear answers about how HIV causes the drastic drop in CD4 counts seen in AIDS patients? "It's still an open question," says Anthony Fauci, director of the National Institutes of Allergy and Infectious Diseases in Bethesda, Md.

The need for more data is pressing. "We need to understand more and more how the [immune] system is working so that we can develop different treatment approaches," Pantaleo says. □