WHAT TRIGGERS AIDS?

Could other infections or genes boost a symptomless AIDS infection into full-blown AIDS?

By JOANNE SILBERNER

One of the great mysteries of AIDS is why some people who have been infected by the AIDS virus go years – if not their lifetimes – without developing the syndrome. Many AIDS researchers believe one or more additional elements, or cofactors, are necessary to turn an AIDS-virus infection into actual disease.

According to the U.S. Public Health Service, about 1 million to 1.5 million people in the United States are infected by human immunodeficiency virus (HIV), and roughly 20 to 30 percent of them will develop AIDS within five years. Who among the infected individuals will get the syndrome and when that will happen are open questions. Finding a cofactor would enable physicians to identify these people and possibly show how to prevent the progression from infection to illness.

Among the many possible cofactors that have been proposed, two of the strongest candidates are the presence of specific, genetically determined proteins in the infected individuals, and exposure to other viruses. If the virus co-infection hypothesis, whose proponents include researchers from the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md., is true, avoidance of a second virus could be the key to health. But a genetic predisposition, as suggested by researchers at the University of California at San Francisco, would be more difficult to counter.

With most viruses, infection does not always mean a person becomes sick – for example, the majority of people infected with hepatitis B virus or with poliovirus don't develop symptoms. But while cofactors are evidently an element in these and other serious viral infections, there has not been a lot of research into the issue, says epidemiologist Harold Jaffe of the Centers for Disease Control in Atlanta. Questions about cofactors "could be asked for lots of other diseases," he says. The sudden, mysterious and deadly onset of the AIDS epidemic has lent the question "a sense of urgency," he says.

Because many members of the two highest-risk groups, male homosexuals and intravenous drug abusers, have histories of frequent sexually transmitted or blood-borne diseases, some researchers have been investigating whether a second infection can somehow "awaken" the AIDS virus. Recent results from Malcolm Martin and his co-workers at the NIAID provide biological support for the possibility.

Martin, Howard E. Gendelman and their co-workers studied the interaction of HIV and other viral infections in cells growing in culture. To avoid the hazards of working with the entire AIDS virus, they used only a segment of HIV's genetic material, linked to a bacterial gene that directs the construction of an easy-to-test-for enzyme.

Martin and his colleagues introduced the combination genes into a cell line and followed its activity by monitoring the marker enzyme. When they added any one of several viruses that commonly infect people, they found more of the marker enzyme, indicating that the AIDS virus material was much more active. Martin says subsequent experiments using the entire AIDS virus have confirmed the initial results, which were published in the December PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.83, No.24).

The viruses, Martin says, could push the AIDS virus in an infected person from a quiet to a lethal stage. "By simultaneous infection, there's a real possibility [of] inducing or activating latent virus."

The viruses used in the experiment are so different from one another that they couldn't possibly all be acting in the same way, he says. Rather than all the viruses producing an identical protein that travels to the AIDS virus and causes it to reproduce, Martin suggests the non-HIV viruses somehow induce the cell itself to stimulate HIV, perhaps by making the cell produce an HIV-stimulating protein.

Several laboratories, including Martin's, are searching for such a protein. Unfortunately, if the infected cell's own protein is responsible, interceding in the process may be difficult. "They [the proteins] are probably there for some important normal function," says Martin. Interrupting that function to keep the proteins from stimulating the AIDS virus could cause other problems. "The more we know," he says, "the less we know."

On the other hand, the cell may also be capable of producing other proteins that inhibit the system, Martin suggests. If so, stimulating those proteins could keep HIV quiet. And whatever the mechanism of action of other viral infections, if they are what's kicking off HIV, avoiding them would be a way to avoid getting AIDS.

While Martin's theory holds that a second infection kicks off AIDS, John Ziegler and Daniel P. Stites of the University of California at San Francisco suggest that the cofactor is a genetic one. They base their theory on the paucity of active AIDS virus found in

full-blown, or "frank," disease.

"It's very difficult to find infected lymphocytes [white blood cells] in infected blood," Ziegler says. In frank AIDS, only 1 in 10,000 to 1 in 100,000 lymphocytes show evidence of viral infection.

To explain how so few viruses could cause such a devastating disease, Ziegler and Stites have suggested that the virus sparks an immune reaction that attacks not only the virus but also the body's own healthy cells (SN: 12/20&27/86, p.388). According to the theory, what controls whether this autoimmune reaction occurs is the degree of similarity between certain immune-system components and HIV itself, and what determines the similarity is genetics.

The AIDS virus attacks and infects the CD4 cell, a type of white cell, at the location where the CD4 normally "docks" with other cells in the immune system. This docking process is a necessary step in a cascade of events that results in the recognition and neutralization of foreign substances.

In order to attach to the CD4 dock, Zeigler and Stites suggest, the virus must in some way "look" like the second set of cells. And this similarity results in the virus affecting the immune system not only by destroying the cell it infects but also by generating antibodies that attack the immune system in two separate ways.

First, antibodies to the virus also attack the cells that normally link up with the CD4 cells, since the virus and the second set of cells have something in common. According to the hypothesis, these antibodies block the interaction of the CD4s and the other cells — even though neither may be infected by the virus. Second, the virus-prompted antibody also triggers the production of other antibodies against both itself and the CD4s, again including those that have not been infected by the AIDS virus. As a result, an entire and vital arm of the immune system is wiped out.

"In this way," says Ziegler, "just a handful of HIV could kick off immune system self-destruction."

Genetics comes into play because the proteins on the immune system cells to which the CD4s attach differ from person to person, and these proteins are inherited. People whose proteins "look" like proteins on the surface of HIV would develop the two sets of antibodies that attack the immune system, and go from infection to full-blown AIDS. People whose proteins differ markedly from the HIV strain would be spared.

If the hypothesis is proven true, it has both positive and negative implications for therapy. The immune self-attack aspect suggests that toning down the immune response could help. Therapeutically, "you'd want to think of ways to remove antibodies to see what happens to patients," says Ziegler. French researchers already have tried damping the immune response with cyclosporine, and a small U.S. trial with cyclosporine began recently.

But it would also throw a wrench into vaccine development. If the part of HIV that is similar to the antigen-presenting cells were used as a vaccine, the antibodies generated against the vaccine material would also be capable of attacking the antigen-presenting cells themselves. Such a vaccine would have the unfortunate result of destroying a normal, necessary arm of the immune system.

Two discoveries would help prove the genetic hypothesis: identifying a single antibody that attacks both HIV and the cells to which the CD4s attach, and the preponderance in AIDS patients of particular classes of proteins on white cells that differ from those in people who are infected but have not developed the syndrome. Collaborators of Ziegler's at UCSF are now in the process of looking for similar classes of proteins among people with AIDS, and there have already been several reports from other laboratories indicating that such clustering exists. Ziegler's collaborators and other U.S. laboratories are also checking an antibody against white cells found in people with AIDS to see if it attacks HIV as well.

"My guess is that everybody who is exposed is capable of being infected, but the progression to illness may well reside in immunogenetic mechanisms," says Ziegler. "Obviously everything isn't going to be explained by genetics. But if it lies there we should be able to find it."

Ziegler's and Martin's theories aren't mutually exclusive — they could each be at work in different people. Nor are genetics and viral infections the only candidates that have been suggested. Ziegler, in fact, has worked with UCSF's Jay Levy on a study showing that some people have a white blood cell capable of suppressing HIV activity. This cell could be producing a protein that counteracts the co-infection effect of Martin's hypothesis.

Other research has pointed to the frequency of AIDS among infected individuals after they were exposed to herpesviruses or hepatitis B. With millions of people infected but not yet showing signs of illness, the problem is more than academic.

But for the moment, what causes infection to develop into AIDS, says Ziegler, "is a biological black box." □

The epidemiologic viewpoint

The first clues about the nature of AIDS came from epidemiology. When epidemiologists chronicled the emergence of the syndrome among male homosexuals, intravenous drug abusers and hemophiliacs, their findings suggested that an infectious agent carried by blood or other body fluids was at work. The biologists eventually found a virus.

Epidemiology has offered no solid leads on whether the virus needs a boost from a cofactor in order to cause disease, nor does it provide clues as to what that cofactor might be. But the suspicion of a cofactor is strong enough to have prompted a search for a common behavioral or lifestyle thread among people with AIDS that is absent in healthy infected individuals.

Studies done to date have not identified any causative cofactors. Epidemiologist Harold Jaffe and his colleagues at the Centers for Disease Control in Atlanta, along with researchers from several San Francisco institutions, are conducting an ongoing study of thousands of homosexual men in San Francisco. Information has been collected about the men's behavior, drug use and health. "So far none of these has really been predictive of illness," says Jaffe.

Of 104 men in the study who have gone from being antibody-negative, indicating they had not been exposed to the AIDS virus, to being antibody-positive, 15 percent were stricken with AIDS five years after infection. After seven years, 35 percent of the original group had AIDS, but no common behavior or health factor could be identified in the group that became ill. "The best predictor of illness seems to be the duration of infection," Jaffe says.

While the study argues against a single obvious cofactor, it doesn't rule out cofactors entirely. "It might be that there are a variety of things that slightly increase your chances of being sick," says Jaffe. "Instead of one thing increasing your chances by 50 percent, there might be 50 things that increase your chances by 1 percent, and it's not very likely we'll be able to sort out what those things are."

Proposed cofactors such as genetic proteins or co-infections identified in laboratory research are not necessarily at work in the real world, says Jaffe. "I have no doubt people have already found and will continue to find factors or agents that will activate the infection in the laboratory," he says. "But you don't know if these things are clinically relevant.

"In a sense I think we want to believe there's something else," says Jaffe, "because if there were something else, it would give us a potential intervention.... We'd like to believe there is such a thing, but so far nobody's found one." — *J. Silberner*