AIDS: Immune System Infighting?

New experiments lend credence to an unorthodox theory

By CAROL EZZELL

A lethal game of deception, rivaling a plot from the most cunning James Bond movie, plays out within the body of every person infected with the AIDS virus, contends Canadian physicist-turned-microbiologist Geoffrey W. Hoffmann.

Once the virus enters and hijacks the body's white blood cells, it orders them to mass-produce a guerrilla army of new viruses. But as these new viral terrorists spread, Hoffmann asserts, they wave a protein "flag" that confuses the body's virus-attacking antibodies.

The flag looks so much like that belonging to the body's own contingent of infection-fighting white blood cells, says Hoffmann, that the body is duped into civil war. While most antibodies continue to fight the intruders, he proposes that the AIDS-causing human immunodeficiency virus (HIV) deceives other antibodies into attacking friendly white blood cells bearing a banner resembling that of the enemy. This internecine warfare eventually lays waste to the immune system, leaving a person vulnerable to the eventually fatal opportunistic infections characteristic of AIDS, says Hoffmann, who works at the University of British Columbia in Vancouver.

His scenario appears to offer an intriguing explanation for some aspects of AIDS that have stumped researchers since the disease emerged in the early 1980s. Yet the unorthodox theory has gone virtually ignored since Hoffmann first proposed it last spring in a paper coauthored by colleagues Tracy A. Kion and Michael D. Grant.

Now, two new studies — one by virologist E.J. Stott, the other by Hoffmann and Kion — have thrust the concept into the limelight.

Stott, who works at the National Institute for Biological Standards and Control in Hertfordshire, England, wrote a brief letter to the editor of NATURE that astonished AIDS researchers worldwide. Published in the Oct. 3 issue, it describes the "surprising result" of attempts to vaccinate macaques against simian immunodeficiency virus (SIV), which causes an AIDS-like disease in monkeys.

Stott and colleagues in his laboratory stumbled upon this preliminary finding while conducting a relatively routine vaccination experiment using 12 macaques. In an ongoing study to determine whether injections of cells infected with inactivated SIV would make a good vaccine against SIV, they injected four of the monkeys with SIV-infected human cells and four others with a "sham" vaccine consisting only of uninfected human cells. The human cells were from a white-blood-cell line grown in the laboratory that the researchers could easily infect with SIV. Another four macaques went without any vaccination, real or sham.

Afterward, when the researchers challenged all 12 animals with injections of live SIV, they were stunned to discover that two of the four sham-vaccinated monkeys carried protection against infection. Three of the four macaques given the real vaccine were also protected, whereas none of the uninjected monkeys resisted the infection.

Five months later, to double-check the unusual result, the researchers gave all five of the previously protected monkeys booster shots of their respective vaccines, whether real or sham. One of the two sham-boosted monkeys again fended off SIV infection, as did two of the three monkeys receiving the real booster.

But the most startling finding of all emerged from the monkeys' blood tests. None of the sham-vaccinated macaques had antibodies to SIV before they were challenged with the live virus, indicating that the ones that resisted the infection did so by some other, unknown means. Moreover, the two that resisted infection after sham vaccinations had 10 times the level of antibodies against the human cells compared with the five vaccinated monkeys that succumbed to infection.

Normally, researchers expect a vaccine to protect against viral infection by spurring the body to generate antiviral antibodies. "But that's not what we're finding," says Stott. The macaques' protection correlated "not with antibodies against the virus, but with antibodies against the human cells."

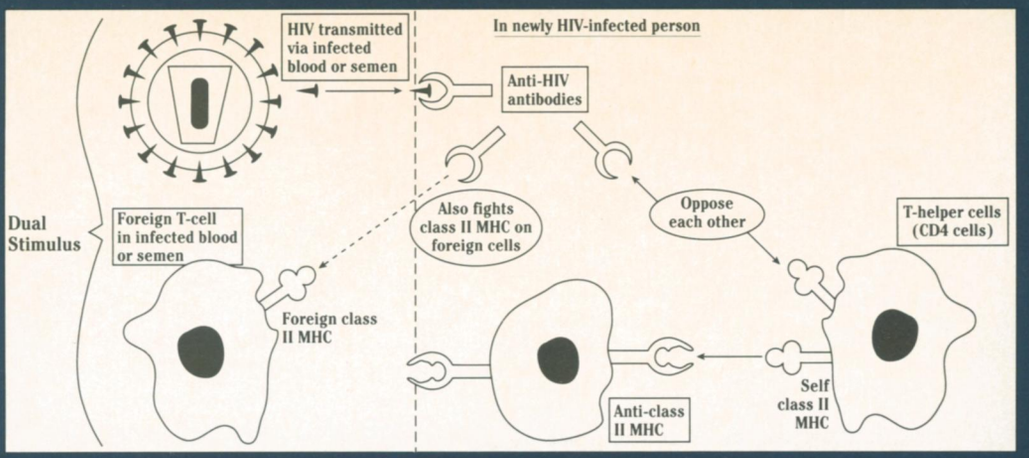
"I am as surprised as anybody," Stott told SCIENCE NEWS. "I have never come across an example of this type of protection in virology before."

Did antibodies against the human cells somehow protect the monkeys against SIV infection? And if so, how? Immune rejection of the "foreign" human cells couldn't account for the results, Stott says, since the virus itself would not have been affected by such a defense.

Already, AIDS researchers around the world are scrambling to answer these questions. To explore one possible explanation, some are reading or rereading the paper in which Hoffmann and his colleagues originally outlined their theory.

Hoffmann, Kion and Grant (who is now at McMaster University in Hamilton, Ontario) described the scenario of HIV-induced immune system infighting in the April 15 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. They set out to address two puzzling aspects of AIDS: that HIV infects only a small percentage of its targeted white blood cells, and that AIDS patients sicken and may die even with large amounts of antibodies against HIV. These points suggested two possibilities to Hoffmann's group: Either HIV needs to team up with another infectious agent in order to do its deadly damage — a hypothesis now being explored by a number of research groups (SN: 3/2/91, p.133) — or HIV magnifies its lethal effects by initiating a chain reaction that causes the immune system to turn against itself.

Scientists know that early in development, the body teaches certain white blood cells, called T-cells, to distinguish between "self" and "nonself." In this way, the T-cells — which constitute a major part of the immune system — learn to tolerate



One phase of the hypothetical autoimmune response triggered by HIV infection. A newly infected person forms antibodies against HIV's envelope protein, gp120 (thumbtack-like structures). These antibodies may attack a subset (lower right) of the person's own T-helper cells.

cells belonging to the body, but to fight intruders.

One of the insignias that immune system cells use to tell friend from foe is a set of large proteins called the major histocompatibility complex (MHC). These proteins exist in various combinations on the cells' outer membranes. When white cells called macrophages gobble bacteria, they chew the invaders up and then sandwich the pieces within class II MHC proteins on their surfaces. The macrophages present their digested prey to a second type of immune system cells named T-helper cells (also called CD4 cells, after a surface receptor through which HIV can enter and infect them). The T-helper cells have other surface receptors that recognize class II MHC and respond when they detect nonself protein. They then churn out a chemical alarm to alert other infection-fighting cells called killer T-cells, and to stimulate the production of antibodies by a separate class of immune system cells named B cells.

The class II MHC proteins play a key role in the theory that HIV devastates the immune system by triggering an autoimmune response. Hoffmann believes that some of the T-helper cells develop receptors that identify the anti-class II MHC receptors of the other T-helper cells, controlling the cells' growth. These receptors would be mirror images of mirror images, and as such would resemble the original class II MHC molecules—just as a mold taken from the inside of a lock would resemble the key to that lock.

Other researchers have found that class II MHC resembles gp120, a glycoprotein found on the outer membrane envelope of HIV. Because of this similarity, Hoffmann and his colleagues suspect that some antibodies against the virus might paradoxically stalk the body's own T-helper cells as well.

This ironic scenario becomes further complicated by the fact that people contract HIV through exposure to infected blood or semen, both of which contain white blood cells. In 1988, Hoffmann's colleague Anwyl Cooper-Willis found that T-cells among the foreign white blood cells can attack their new host by sprouting receptors that bind to the host's class II MHC, much as bone marrow transplants sometimes strike out against a patient in a reaction called graft-versus-host disease.

When a person infected with HIV makes antibodies against the foreign white cells' receptors, another mirror-image trick takes place, Hoffmann's group proposes. This time, the antibodies end up almost identical to the person's own class II MHC.

These two immune responses—one yielding T-cells carrying receptors that mimic class II MHC, the other producing antibodies against class II MHC—build up to a clash, according to Hoffmann. And when they do, the real feud erupts, pitting the body's immune system against itself.

"You've got these two immune responses that don't really know the difference between the other response and the thing that initially triggered them," says Hoffmann. "These two responses eventually wreck the entire immune structure."

Hoffmann and Kion demonstrated their autoimmune AIDS model in a mouse study reported in the Sept. 6 SCIENCE. Each of two groups of mice received injections of T-cells taken from the other group. As predicted, the mice developed antibodies against the class II MHC receptors on the foreign cells. They also produced antibodies against the gp120 protein of HIV, even though they were never exposed to the virus.

Strikingly, Hoffmann and Kion detected those same anti-HIV antibodies in a special strain of mice with a disorder resembling a human autoimmune disease called systemic lupus erythematosus. "It is thus plausible that the mechanisms of pathogenesis are related, even though [lupus] occurs spontaneously and AIDS is provoked by HIV," they write in their SCIENCE paper.

Hoffmann thinks a similar mechanism may have operated in Stott's macaque experiments. The monkeys injected only with human cells fended off SIV infection because the cells caused them to make large amounts of antibodies that could also attack SIV, he speculates.

"I'm very glad to have somebody saying something at least vaguely similar to what we're saying," he says of Stott's report. "It's very comforting, but at the same time, the systems need to be worked out in more detail."

"The idea that AIDS is partly an autoimmune disease is certainly tenable," says Stott. "I think the original naive assumption we had, that AIDS was caused by infection and reduction of CD4 helper cells, is too simple. There's got to be more to it."

He cautions, however, that his monkey experiment is not an exact representation of Hoffmann's model, since he immunized the monkeys with human cells. "We're not talking about antibodies against macaque cells; we're talking about antibodies against human cells," says Stott.

Others warn against accepting Hoffmann's theory too readily.

Michael Murphey-Corb, who studies SIV at the Delta Regional Primate Research Center in Covington, La., is among those who await stronger evidence. Two years ago, she led one of the first teams to show that whole, killed SIV could protect rhesus monkeys from SIV infection (SN: 12/9/89, p.372). She is now trying to replicate Stott's experiment using monkey cells in place of the human cells.

A finding that these cells can protect the monkeys from SIV infection would support Stott's findings and Hoffmann's model. However, Murphey-Corb says, "I have no unambiguous evidence . . . in any experiments that I have underway that will either prove or disprove Hoffmann's hypothesis."

For now, she contends, "waiting is the best advice. . . . We're doing everything we can to figure out [the Stott and Hoffmann results], but I haven't bought their explanations yet." □