AIDS

Can Immune Systems Be Trained to Fight HIV?

Current antiviral therapies don't seem able to eliminate HIV from the body, so researchers are trying to coax the immune system to finish the job

MARNES-LA-COQUETTE, FRANCE—Every HIV-infected person struggling to keep up with a daily regimen of antiviral drugs must have the same recurrent dream: One day, he or she will toss away the plastic box crammed with pills that once made the difference between life and death and walk away, free from HIV and free from the specter of AIDS. Last month, at the Cent Gardes international AIDS meeting in this town outside Paris,* several researchers described bold new experiments that explore what it might take to make this dream a reality.

Among them are studies of patients who had been taken off drug therapy for short periods of time to see how effectively their immune systems could control HIV. Although for most of these subjects the answer was not very well, a minority—particularly those who began receiving treatment very early in their infections—did show signs that their immune systems could keep the virus at bay. But more important, these experiments are providing valuable new information about what kinds of immune responses are needed to control HIV. And other work is pointing to ways of boosting the immune system—for example, with a postinfection or "therapeutic" anti-HIV vaccine—to mount a stronger attack against the virus and perhaps one day eliminate the need for daily drugs.

For some AIDS researchers, these results represent the most encouraging news they have heard for a long time. "There are a lot of reasons to be excited" by the new work, says Ronald Desrosiers, an AIDS vaccine researcher at the New England Regional Primate Research Center in Southborough, Massachusetts. But others, recalling how many times hopes have been raised and then dashed during the nearly 2 decades of the AIDS epidemic, are urging caution. "No one has presented compelling evidence that the immune system will be successful by itself in the absence of therapy," says Norman Letvin, an immunologist at Harvard Medical School in Boston, although he adds that AIDS researchers are now doing "the right experiments" to determine if such approaches could actually work.

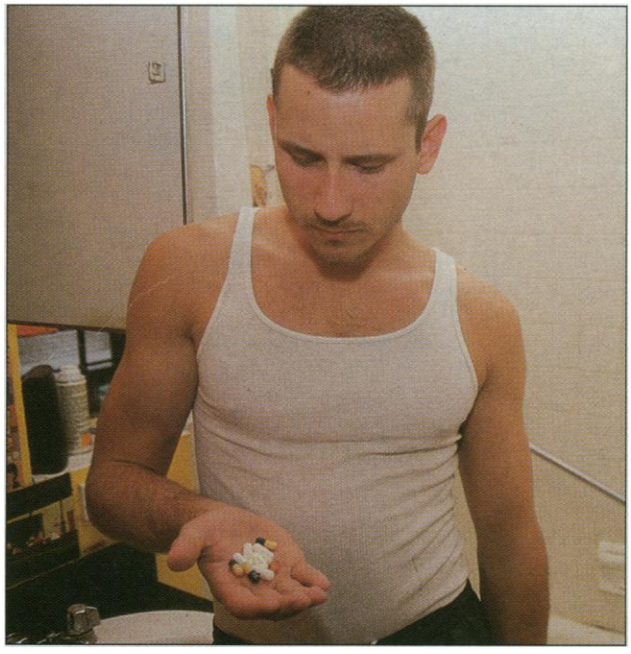
Until quite recently, many researchers had hoped that drugs alone might eliminate the virus. The powerful new anti-HIV therapies that came on the market in the mid-1990s seemed capable of suppressing the virus to undetectable levels in many patients who had been facing a likely death sentence from AIDS. Before long, the magic word "eradication" began appearing on the lips of patients and AIDS researchers alike. Alas, such hopes soon proved premature. Evidence quickly mounted that although the new drugs could drive HIV from the bloodstream, the virus continued to lurk in hidden "reservoirs" made up of so-called T helper lymphocytes, its primary target in the immune system (*Science*, 14 November 1997, pp. 1227, 1291, 1295). Moreover, calculations of how long it would take these latently infected cells to die out were disheartening: One 1999 paper in *Nature Medicine* concluded that it could take as long as 60 years for the reservoir cells to perish.

Thus more and more AIDS researchers are now convinced that so-called highly active antiretroviral therapy, or HAART, is not powerful enough to entirely eradicate the virus from infected patients. So just what would it take to do the job? Some scientists have advocated the development of more powerful antiviral drugs, while others have been looking for ways to "flush out" HIV from its reservoir hiding places (*Science*, 20 March 1998, p. 1854). At the Cent Gardes meeting, a number of researchers reported new data that might support another frequently discussed alternative: using the patient's own immune system to control the virus, either unaided or with the help of a therapeutic vaccine that would be administered to people already infected with HIV.

The most encouraging news was reported by immunologist Bruce Walker of Massachusetts General Hospital in Boston. Over the past few years Walker's team has been working with a cohort of patients who began treatment shortly after being infected with HIV, often before they developed antibodies to the virus. Patients who begin treatment later in their infections generally lose the ability to mount effective anti-HIV immune responses, which appear to be mediated by both T helpers and another type of white blood cell called a cytotoxic T lymphocyte (CTL) (*Science*, 21 November 1997, pp. 1399 and 1447).

But Walker saw a different picture in seven patients who had been receiving HAART for 1 year and whose therapy was then deliberately stopped and started again in what are called "structured interruptions." Most of these subjects had little or no anti-HIV CTL activity while on therapy, presumably because the virus had been controlled so quickly after infection that they had not mounted a strong immune response. As expected, HIV quickly reappeared in their bloodstreams, sometimes at very high levels, when they were taken off HAART. But for the first time, the patients also showed strong CTL responses, which persisted even after therapy was started up again.

Most dramatically, in some patients these CTLs seemed able to control the virus. For example, in one subject whose therapy was stopped twice, the HIV load rocketed to about 1 million copies of the virus per milliliter of blood after the



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Fistful of therapy. If the immune system could be provoked to control HIV, infected patients might one day be able to throw their pills away.

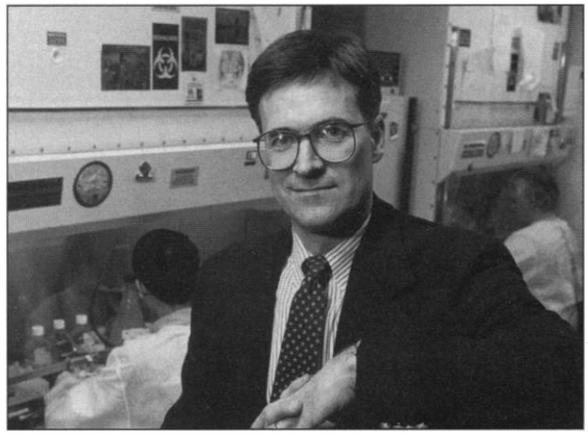
* 12th Colloquium of the Cent Gardes, Marnes-la-Coquette, France, 25 to 27 October.

first interruption, a level typical of many untreated patients. But after the second interruption, the viral load plateaued at only 6000 copies and was still at that level after 4 months without HAART. "The immune responses to HIV [in these patients] can clearly be manipulated by exposure to their own virus," Walker told the meeting. "Bruce is almost doing a vaccine study," says Jonathan Heeney, an AIDS vaccine researcher at the Biomedical Primate Research Center in Rijswijk, the Netherlands. "First he takes HIV away [with HAART] and then boosts the immune system with the virus, and then he does it again."

But Walker and others aren't sure how relevant his results are to HIV-positive patients who did not start treatment at a very early stage in their infections—so-called chronically infected patients. "These experiments involve quite a unique group of patients," says Giuseppe Pantaleo, an immunologist at the Vaudois Hospital Center in Lausanne, Switzerland. He points out that chronically infected patients also produce anti-HIV CTLs, but that these are usually not effective in controlling the virus. The reason, Walker thinks, is that whereas patients treated early retain T helpers that recognize HIV and work with CTLs to attack the virus, chronically infected people have lost these crucial cells.

Indeed, Brigitte Autran, an immunologist at the Pitié-Salpêtrière Hospital in Paris, and her colleagues had shown that fewer than 20% of chronically infected patients treated with HAART demonstrate anti-HIV T helper responses. That may explain the lackluster results she saw in chronically infected patients briefly taken off therapy. At the Cent Gardes meeting, Autran reported preliminary results from new experiments with 10 patients whose therapy was stopped and then restarted when viral load rose, a process that was repeated up to four times in some subjects. Most of these patients showed an increase in CTL activity with the rise in viral levels, but they did not mount a vigorous immune response or control the infection, as Walker's patients had. Still, HIV-targeted T helpers did appear during treatment interruption, although they disappeared again before the virus was brought back under control with HAART.

Autran's conclusion was hopeful, however. To her, the brief appearance of T helpers implies that restoration of these critical anti-HIV cells might be "feasible" if the immune system could be properly stimulated to produce them. The stimulus might be a therapeutic vaccine given before trying to take patients off therapy. But researchers say developing an effective therapeutic vaccine will not be easy. Didier Trono, a molecular virologist at the University of Geneva, questions whether a therapeutic vaccine would be able to stimulate immune responses that were more effective than what the body was already producing. "The virus is providing the body with all the antigens you can think of; why doesn't that work?"



Stop-start. Some of immunologist Bruce Walker's patients seem able to control HIV when therapy is interrupted.

"Just because [immune system control] is intuitively comfortable does not necessarily mean it will be borne out in fact."

—Norman Letvin

But some encouraging signs are coming in from trials of the only therapeutic vaccine currently undergoing extensive testing: Remune, which is marketed by the U.S.-based companies Immune Response Corp. and Agouron Pharmaceuticals. Remune is based on a vaccine developed by the late Jonas Salk and consists of a whole HIV particle, inactivated so that it is no longer infectious. So far, large-scale Remune trials taking place in the United States and Europe have not produced conclusive results about its effectiveness. But at the Cent Gardes meeting, immunologist Fred Valentine of the New York University Medical Center in New York City presented data from an ongoing Remune trial with several dozen subjects who had just begun HAART. Half of these patients were inoculated with Remune 4, 12, and 24 weeks after starting HAART, while the other group received placebo injections. T lymphocytes were then taken from these patients and tested for their ability to mount an immune response to whole HIV as well as a variety of HIV proteins.

Although the placebo group's T cells failed this test, the Remune-vaccinated group's T cells reacted strongly against HIV. "Fred is showing some pretty impressive responses," says Desrosiers. But Pantaleo, who has been participating in a large European trial of Remune, says that although the vaccine can clearly induce anti-HIV responses, "there is no evidence that Remune can slow down the progress of the disease. Perhaps it can play a role, but it is not the solution."

Other investigators working with Remune are more optimistic. Frances Gotch —an immunologist at the Chelsea and Westminster Hospital in London who is co-leader of a 60-patient Remune trial at the hospital— told *Science* that preliminary results from her study show that subjects receiving the vaccine have developed anti-HIV T helper responses as strong as or stronger than those in so-called long-term nonprogressors, a small minority of patients who are able to control their virus without drugs. Moreover, Gotch says, the number of latently infected reservoir cells in Remune-treated patients appears to be dropping at a faster rate than in nontreated patients.

Gotch is now talking with some of the participants in this trial to see if they would be willing to interrupt their drug therapy to find out if Remune vaccination can help control HIV without HAART—a study that is the logical next step in the view of many AIDS researchers. But this kind of trial, like all treatment interruption experiments, is fraught with medical and ethical risks. Autran, for instance, notes that a rise in viral load when treatment is stopped could allow HIV to infect and destroy the very T helpers the immune system had sent to fight it. And Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, warns, "If at each interruption of therapy more [latently infected] reservoirs are replenished, this could be counterproductive."

Letvin agrees that the jury is still out on whether the immune system could ultimately be induced to control the virus: "It is a seductive idea, but just because it is intuitively comfortable does not necessarily mean it will be borne out in fact." On the other hand, Letvin adds, "I hope to God it works." **–MICHAEL BALTER**

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