ANTIVIRAL THERAPY

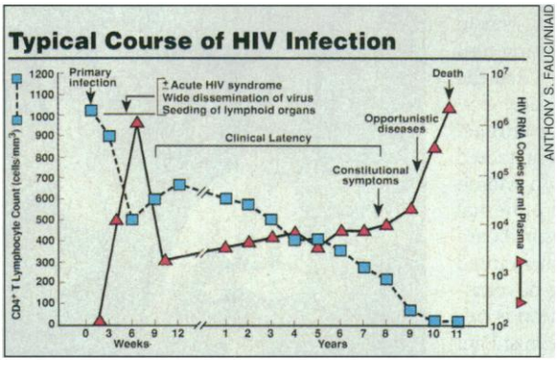
Eradicating HIV From a Patient: Not Just a Dream?

In 1993, *Science* polled 150 top AIDS researchers, asking them to list the outstanding questions hampering the search for a cure or a vaccine (*Science*, 28 May 1993, p. 1254). The key obstacle then facing vaccine developers—determining which immune responses can protect a person from HIV—remains. "We're no further than we were 3 years ago," says David Ho, head of New York's Aaron Diamond AIDS Research Center (see p. 1888). But work by Ho and others has brought scientists much closer to answering two questions that topped the 1993 list regarding the search for a cure: Why does the immune system collapse, and how can HIV replication be controlled?

Indeed, a new understanding of HIV pathogenesis that has emerged over the past 18 months has led AIDS researchers to pose what was recently an unthinkable question: Can HIV be eradicated from an infected person? "If you would have asked me in January 1996, can we eradicate HIV, I would have laughed in your face," says Julio Montaner, co-director of the Canadian HIV Trials Network and co-chair of the international AIDS conference to be held in Vancouver next week. But not now. Montaner and more than 80 colleagues, in fact, attended a conference in Washington, D.C., 2 weeks ago that focused on just that question.*

The excitement infusing the field stems from a mix of stunning results from both basic and clinical researchers. On the basic front, the labs of Ho and of George Shaw at the University of Alabama, Birmingham, showed last year how new, powerful anti-HIV drugs could uncover key mysteries—and their work has helped alter how researchers now discuss the disease process. In the clinic, Montaner and others have shown how new combinations of anti-HIV drugs can reduce viral levels in the blood so dramatically that it cannot be detected with the most sensitive tests (see p. 1886). "We're talking about complete suppression and the prospect of eradication," pathologist Douglas Richman, of the University of California, San Diego, said at the meeting.

Ho and Shaw's work, in the 12 January 1995 *Nature*, has received much attention because it blew out of the water the popular notion that the long lag time between HIV infection and disease meant that the virus lay quiescent in the body for years. As Ho and Shaw demonstrated, billions of HIVs were being made and removed from the blood every day during that supposed latent period. HIV's genetic material thus passes through about 180 generations per year, says John Coffin of Tufts University, a staggering replication rate that establishes a large pool of mutants shortly after infection occurs. This leads Coffin to challenge the popular idea that HIV mutates its way around drugs; instead, he says anti-HIV drugs exert Darwinian forces that simply select for preexisting viral mutants that can foil them.



A higher low. HIV levels *(triangles)* spike, then drop—but do not bottom out as previously thought. Instead, they rise steadily as CD4s (*squares*) decline.

That Darwinian point of view has recently led AIDS researchers to challenge another truism: the idea that HIV steadily confronts the immune system with ever more mutants until finally it wears down, and viruses can escape immune detection. In this view, viral diversity is bad. But molecular biologist Steven Wolinsky of Northwestern University and coworkers published a study in the 26 April issue of *Science* (p. 537) that reaches the opposite conclusion. They found that people who develop greater diversity shortly after infection fare better. In essence, extensive diversity reflects how the rapidly replicating virus behaves when confronted with a strong—not a weak—selective force such as the immune system. "This model predicts that if you treat early, when there's relatively limited diversity, you can abrogate infection," says Wolinsky.

"Treat early" was one of the mantras at the D.C. meeting. John Sullivan, a pediatric immunologist at the University of Massachusetts Medical Center in Worcester, reported that his group has treated two 10-week-old infants, who were both clearly infected at birth, with a potent three-drug cocktail. Now, after 1 year, HIV is no longer detectable in these infants, and they have even begun to lose antibodies to the virus—a sign that eradication might have occurred. At Aaron Diamond, staff investigator Martin Markowitz and co-workers last August began treating recently infected adults with potent triple combos. If after 9 months, no HIV is detectable, and antibodies are declining, some patients may opt to stop taking the drugs.

Part of Markowitz's study includes looking for HIV in lymph nodes, which can harbor virus even when none is detectable in the blood. The fact that stalwart HIVs can hide out makes some researchers question whether anti-HIV drugs by themselves are, in most situations, powerful enough to eradicate the virus. "We have all the hoopla about antiviral drugs, and you get any virologists aside and they'll say this is not how we're going to win," contends retrovirologist Jay Levy of the University of California, San Francisco. To clear all the virus from the body, Levy says, "it's high time we look at the immune system."

Several researchers are evaluating a combination of strategies that links antiviral approaches with efforts to boost the immune system—which, after all, has a black belt in virus killing. Immune-based approaches under way include: using interleukin-2; using HIV vaccines; and removing people's white blood cells known as CD8s, expanding them (or engineering hardier ones), and then returning them. Blocking molecules on the surface of CD4 white blood cells known as chemokine receptors, which HIV apparently uses to infect cells, is a new, exciting possibility (see pp. 1885 and 1955). Levy has evidence that CD8s secrete still another as yet unidentified factor that can stop HIV in an infected cell from copying itself.

Even if researchers can figure out a way to remove every last vestige of HIV from some people, that doesn't mean patients will be cured. "It doesn't necessarily follow that dropping viral burden to zero will result in immunoreconstitution," Louise Market, an immunologist from Duke University Medical Center in Durham, North Carolina, said at the meeting. Market and others suspect that one reason the immune system does not completely rebound in these powerful new drug studies is because HIV damages the thymus. Pediatrician Richard Hong of the University of Vermont has started treating patients with both triple-drug combos and thymus transplants. Market has a similar study in the wings.

In the past 3 years, AIDS researchers haven't solved all the questions of how to control HIV replication and prevent immune collapse. But they have discovered enough key pieces of the puzzle to see at least the outline of the answers.

–Elizabeth Pennisi and Jon Cohen

* "Can HIV be eradicated from an infected individual?" sponsored by Antiviral Therapy and the University of Amsterdam, 12–13 June, Washington, D.C.