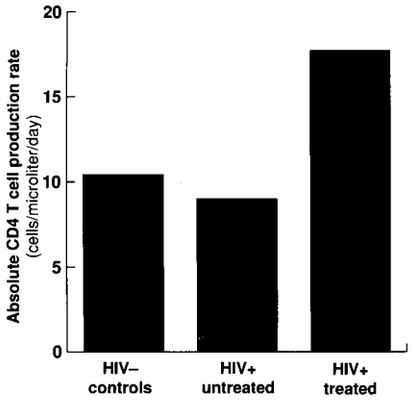
AIDS

T Cell Production Slowed, Not Exhausted?

Ever since the very early days of the AIDS epidemic, almost 2 decades ago, researchers have recognized the disease by its signature symptom: a progressive loss of CD4 T lymphocytes, the primary immune cell targeted by HIV. Yet just how HIV causes T cell depletion is still the subject of vigorous debate. Does it destroy T cells so quickly and efficiently that the immune system exhausts itself trying to replace them? Or does it disrupt the immune system's ability to produce T cells in the first place? Now, in the January issue of *Nature Medicine*, a team led by immunologist Joseph McCune of the University of California, San Francisco, and endocrinologist Marc Hellerstein of UC Berkeley reports results obtained by using a new technique that for the first time provides a direct measure of how many new cells are produced over a given time period. The findings, the team says, support the notion that HIV's most important and insidious talent is to interfere with T cell production.



Held back? HIV may inhibit the immune system's ability to replace lost T cells.

SOURCE: (LEFT) HELLERSTEIN, *ET AL., NATURE MEDICINE*, 5, 1, (JANUARY 1999); CREDIT: (RIGHT) JOHN DURICKA/AP PHOTO

For some researchers, the new paper essentially resolves the controversy. Immunologist Giuseppe Pantaleo of Vaudois Hospital Center in Lausanne, Switzerland, told *Science* the results show that although HIV may be destroying some T cells, "this is not sufficient to explain the loss. ... There is no exhaustion of the [production] machinery." In an accompanying article in *Nature Medicine*, Pantaleo summarily declares that the study "puts an end to four years of exciting (although often harsh) debate" over the issue. Not so fast, counters David Ho, director of the Aaron Diamond AIDS Research Center in New York City and a prominent exponent of the "immune exhaustion" model. He argues that the results do not necessarily contradict his model. "The jury is still out," Ho says.

To tackle the question, the UC researchers used an innovative method they first described last year (*Science*, 20 February 1998, p. 1133). They intravenously infused subjects with a solution of glucose—a precursor of deoxyribose, one of the chemical building blocks of DNA—in which the glucose molecules contain deuterium, a nonradioactive isotope of hydrogen. They then took blood samples at various times after the infusion had ended. As T cells divided, the deuterium-labeled DNA was progressively replaced by unlabeled DNA, allowing the team to calculate the production rate of new cells as well as their average life-span. The team conducted this test on three groups of subjects: uninfected controls, HIV-infected patients undergoing antiviral therapy, and infected patients not yet receiving therapy.

The team found that the average T cell life-span in untreated HIV-infected patients was one-third that in controls, consistent with a certain amount of cell killing by HIV. However, the T cell production rate was no higher than that of the controls, as would be expected if the immune system was working overtime to replace these destroyed cells. And patients taking antiviral drugs had higher T cell production levels than in the control and untreated groups, the opposite of what would be expected if increased production were simply a response to T cell destruction by HIV. Instead, the authors propose, antiviral therapy leads to a "disinhibition" of the production machinery.

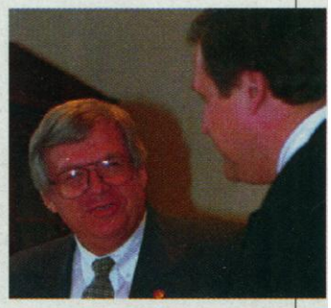
"The thesis of our paper is that HIV affects the system of production more than it induces destruction of mature T cells," McCune says. But some researchers believe this conclusion is premature. For example, immunologist Angela McLean of Britain's Institute for Animal Health in Compton says that the new technique may underestimate the actual rate of T cell production in the untreated patients, especially if new cells become infected by HIV and die before they can be counted.

Ho, while lauding the new methodology as "a powerful new technique," says that even if the untreated HIV-positive patients in the UC study did not produce greater numbers of T cells than uninfected controls, this does not necessarily contradict his model of immune exhaustion, because these patients had much lower CD4 counts than the HIV-negative group. This means, Ho says, that the same production rate would represent a much faster turnover of their total T cell pool. "The burden [to the immune system] is much greater."

McCune says that if HIV is indeed interfering with production of new T cells, the findings might point to new strategies for enhancing this production. For example, T cells could be cultured outside the body for reintroduction later in the disease, or patients

ScienceScope

Physicists Thank Monica A complex chain reaction has resulted in a politician popular with some physicists becoming the new speaker of the House of Representatives. Maury Goodman, a physicist at Argonne National Laboratory in Illinois, explained it this way in the *Long-Baseline Neutrino News*, an e-mail newsletter: "Monica did her thing, and Ken Starr went after Clinton, so Larry Flynt decided to go after Republicans. His first victim was Speaker-designate [Robert] Livingston (R–LA), who resigned, leaving open the position for Dennis Hastert (R–IL), the congressman who represents [the Department of Energy's Fermi National Accelerator Laboratory in Batavia, Illinois]. The same day Clinton was impeached, the headline said Hastert's speakership will be good for Fermilab."



Some statisticians, however, aren't so sanguine about the new Republican leader. In 1997, as chair of the House committee that oversees the 2000 census, Hastert doggedly opposed the use of statistical sampling to estimate the U.S. population (*Science*, 11 December 1998, p. 1969). So far, however, sampling proponents aren't blaming Lewinsky.

Southern Star Astrophysicist Catherine Cesarsky will be the next director-general of the European Southern Observatory (ESO), succeeding Riccardo Giacconi. The French researcher, currently head of a four-laboratory basic research group at the Commissariat à l'Énergie Atomique near Paris, will take over at ESO headquarters in Garching, Germany, on 1 September. Cesarsky's opening challenge in a 5-year term is to keep the world's largest telescope array on schedule. The $800 million Very Large Telescope, a quartet of magnifiers, is scheduled to begin operations in 2001 in the Atacama Desert in northern Chile (*Science*, 1 May 1998, p. 670). Cesarsky's administrative experience should help keep the project on track, says astronomer Michael Rowan-Robinson of London's Imperial College, who applauded the appointment.

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