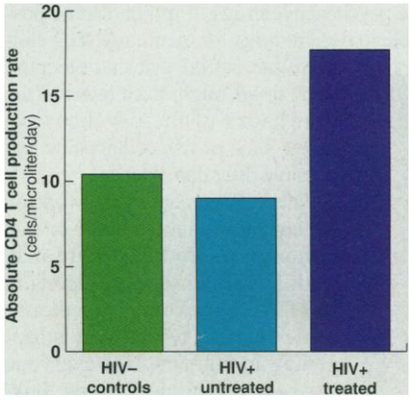
AIDS

# 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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could be given signaling molecules called cytokines to prompt immune system cells to divide. But whether these measures are warranted depends on discovering what HIV is actually doing to the immune system. The new methods, researchers say, are an important step in that direction. Says McLean: "We may now have a technique that can eventually bring the jury in." –MICHAEL BALTER

NEUROBIOLOGY

## How Stimulant Drugs May Calm Hyperactivity

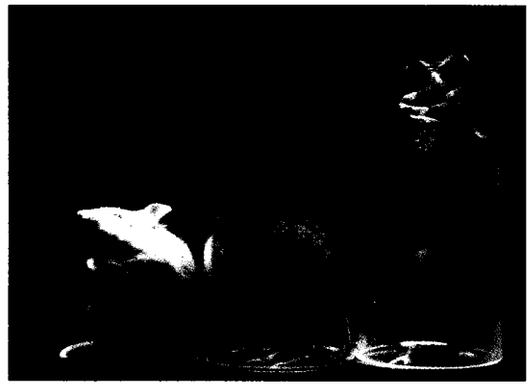
To calm down children diagnosed as hyperactive, pediatricians give them small doses of stimulants—drugs such as the widely prescribed Ritalin. It seems paradoxical. And the paradox is even more vivid to neuroscientists, who know that high doses of these drugs raise brain levels of dopamine, a neurotransmitter that promotes activity. New results from a research team at Duke University Medical Center in Durham, North Carolina, now point to a surprising explanation for the drugs' puzzling effectiveness: Rather than working through dopamine, low doses may instead raise the concentrations of another neurotransmitter, serotonin, known to have calming effects.

This conclusion comes out of a series of experiments that the Duke team, led by neurobiologists Raul Gainetdinov and Marc Caron, performed on a strain of genetically altered mice that have behavioral symptoms similar to those of children with attention-deficit hyperactivity disorder (ADHD). As the team reports on page 397, treatment with psychostimulant drugs, including methylphenidate (Ritalin), relieves the symptoms in the mice, apparently without affecting brain dopamine concentrations. Compounds that boost serotonin in the brain have similar effects, a result suggesting that this neurotransmitter is instead the one that tones down the animals' hyperactivity.

ADHD expert Russell Barkley of the University of Massachusetts Medical Center in Worcester describes the work as "an impressive series of studies, done very carefully." Many ADHD researchers are not convinced, however, that the mouse results apply to human patients. They think that in humans the stimulants probably work through dopamine in some way—perhaps by raising levels so high that neurons become inured to it. But if humans do respond in the same way as the mice, researchers might be able to design new ADHD therapies that work by mimicking serotonin's effects.

The new experiments use a mouse strain that Caron and his colleagues created 3 years ago by inactivating the gene for a protein called the dopamine transporter (*Science*, 16 February 1996, p. 909). The transporter, DAT for short, has the job of picking up dopamine released by nerve activity and transporting it back into the neurons that produced it. Because extracellular dopamine concentrations remain high in the brains of the knockout animals, they are much more active than normal mice. "They're hyperactive for a good reason," Caron says. "They have lots of dopamine."

Indeed, there is some reason to think that a DAT abnormality could contribute to ADHD. At least three genetic linkage studies have picked up an association between a particular variant of the gene that encodes DAT and the condition. And Gainetdinov, Caron, and their colleagues now have evidence that their knockout mice closely mimic the symptoms of hyperactive children. Novel environments, for example, can exacerbate the symptoms of ADHD in children. Similarly, the knockout mice were some 12 times more active than normal mice when first placed in new surroundings, and their high activity levels persisted for the entire 4-hour observation period.



**Climbing the walls.** The time-lapse photography shows the hyperactivity of the mouse at right, which has no DAT gene.

CREDIT: CHRIS HILDRETH/DUKE UNIVERSITY

Hyperactivity in children is also associated with an attention deficit. So the team tested the mice for a similar problem by putting them in a maze consisting of eight arms radiating from a central area, each of which is baited with food. The mice are supposed to learn to proceed from one arm to the next without backtracking—a task the normal animals learn within a half-dozen or so test sessions. "But the DAT knockouts don't ever learn," Caron says. Instead, they become distracted, returning to arms they've already visited, or rearing up and looking around the maze.

But methylphenidate and the other psychostimulant drugs tested had a dramatic effect on the knockout mice. The drugs calmed their hyperactivity in the novel environment. And they did this without measurable effects on brain dopamine concentrations. "This means that [the drugs] hit some other system" in the brain, Caron says.

Further tests pointed to the serotonin system. Although the researchers didn't measure brain serotonin levels, they found that giving the animals a serotonin mimic had effects similar to those of the psychostimulants. So did giving them an inhibitor of the serotonin transporter, the drug Prozac, or administering other treatments designed to raise brain serotonin levels, such as injecting the animals with compounds, such as 5-hydroxytryptophan or L-tryptophan, that are converted to the neurotransmitter in the brain. These results indicate, Caron says, that the psychostimulants calm the hyperactive mice by raising serotonin concentrations to balance the animals' high brain dopamine levels.

The next goal, he says, is to try to identify which of the 15 or so different receptors through which serotonin exerts its effects in the brain might be involved in the response to the psychoactive drugs. It might then be possible to design drugs for treating ADHD children that act on just that receptor. Such drugs might have fewer of the drawbacks of the psychoactive drugs, such as reduced appetite and possible drug dependence.

Other researchers who work on the condition caution, however, that although methylphenidate may work by raising serotonin levels in the DAT knockouts, the mouse model may not reflect what is happening in humans. Not everyone has been able to confirm the linkage between the variant DAT gene and ADHD, and even if the linkage does hold up, a defective DAT gene won't be the whole explanation for ADHD, which most researchers, including the authors of the paper, believe is caused by defects in several different genes.

What's more, any DAT defect in humans will likely be far less severe than that in a complete knockout. "A mouse that's never had a dopamine transporter is a very unusual creature," says Xavier Castellanos, who studies ADHD at the National Institute of Mental Health. "I'd be cautious about extrapolating to the idea that Prozac will help [ADHD children]." Indeed, some researchers have tried Prozac in ADHD children with what Barkley describes as "not very impressive" results.

Still, Barkley says, the Caron team's results raise the "very tantalizing hypothesis" that there might be a subtype of ADHD due to an altered DAT, which might respond to Prozac or other compounds that raise brain serotonin levels. The work is spawning fresh ideas about the disorder and how to treat it, agrees James Swanson of the University of California, Davis. "This is exactly what animal models are for." –JEAN MARX