To further test the cryptochrome hypothesis, Robert Lucas, a postdoc with Foster, suggests taking a cue from the fly experiments and crossing the rod- and coneless mice with cryptochrome mutants to see if knocking out both light-reception pathways blocks clock entrainment. Another test, says Houston's Cahill, would be to see whether the cryptochrome mutation alters the animals' action spectra for light entrainment of their clocks. If it did, he says, that would be good evidence that cryptochrome is a circadian photoreceptor.

Without such conclusive results in mice, many researchers won't accept cryptochrome as a mammalian circadian photoreceptor. Indeed, says clock researcher Carla Green of the University of Virginia in Charlottesville, Sancar's results suggest more convincingly that cryptochrome "could be part of the clock itself." That, she and others say, is the simplest explanation for overresponse to a flash of light. It could also explain the finding that the mice have altered behavioral rhythms in constant darkness, and the presence of cryptochrome in the suprachiasmatic nucleus, which governs rhythms but does not directly respond to light.

What's more, Sancar has localized cryptochrome to the cell's nucleus, where other key clock components such as PER and TIM go to regulate their own genes, a function that is at the heart of the clock's oscillating mechanism. "If I had got this data set," says Lucas, "I would be excited that maybe it has something to do with the machinery of the clock."

Indeed, what most researchers in the field find most intriguing about the new results is the suggestion that cryptochrome may have begun as a pure photoreceptor, a role it seems to maintain in plants, but during the evolution of animals may have insinuated itself into the mechanism of the clock. That would add cryptochrome to a growing list of clock proteins that evolved from photoreceptors, including a set of key clock components that are evolutionarily related to bacterial photoreceptor molecules.

One thing is for sure, says clock researcher Michael Menaker of the University of Virginia: "All of these data suggest that cryptochrome is very important. Whether it is important only as a photoreceptor, only as part of the circadian oscillator, or both, are secondary questions." For a protein discovered as a photoreceptor in plants to wind up involved in the mammalian circadian clock is quite an evolutionary leap, says Cahill: "We don't have that many evolutionary connections between plants and the mammalian nervous system."

–MARCIA BARINAGA

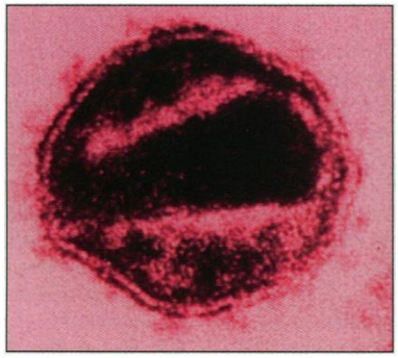
MEETING | AIDS RESEARCH

HIV's Early Home And Inner Life

LAUSANNE, SWITZERLAND—Until recently, Europe could boast only one major AIDS meeting: The Cent Gardes Colloquium, held biannually near Paris. This autumn, HIV researchers based in Switzerland inaugurated a second series to alternate with the Cent Gardes. The first meeting,* held here in the opulent Beau-Rivage hotel, attracted 230 researchers to discuss the latest in AIDS research from basic science to vaccine development.

The Core of The Matter

HIV's life cycle begins when it attacks target cells and ends when progeny viruses burst out to infect new cells. Current antiviral drugs target two enzymes involved in this cycle: reverse transcriptase, which copies HIV's RNA genome into DNA; and HIV protease, which snips viral proteins into the right sizes for assembly into mature virus particles. But some patients are resistant to these drugs or suffer side effects, and researchers are always looking for new targets to attack. A talk by biochemist Wesley Sundquist of the University of Utah, Salt Lake City, suggests that HIV's poorly understood inner core could present just such a target.



Ripe target? HIV's cone-shaped core might be vulnerable to new therapies.

HIV's basic structure includes an outer coat, which attaches to the membrane of a target cell, and an inner cone-shaped core, which enters the cell. This core is made up of two proteins—a large molecule called capsid and a smaller one called nucleocapsid—along with reverse transcriptase and the virus's RNA genome. The protein core appears to be a vehicle that helps transport the enzyme and the genome into the host cell. In recent years, Sundquist and his colleagues, along with other workers including Hans-Georg Krausslich's group at the Heinrich-Pette Institute in Hamburg, Germany, have shown that, under lab conditions, purified capsid spontaneously self-assembles into long, hollow tubes whose diameters roughly correspond to the varying width of HIV's conelike core.

In new work presented in Lausanne, Sundquist reported that his team was able, for the first time, to replicate cone-shaped structures similar to HIV's core by adding nucleocapsid and RNA to the capsid proteins in just the right combinations under physiological conditions similar to those in living cells. Indeed, Sundquist showed electron micrographs demonstrating that these artificial cones bear a striking resemblance to those found in actual HIV particles. "These proteins just know how to assemble in vitro," remarks retrovirologist Mario Stevenson of the University of Massachusetts Medical School in Worcester. And Didier Trono, a molecular virologist at the University of Geneva, comments that the work sheds new light on the mechanism of viral assembly, which is "really the black box of retroviral replication."

Sundquist proposed a model for how the cones might be formed from protein subunits. He showed high-resolution electron micrographs of cross sections of the hollow tubes made of pure capsid, which indicated that the tube walls are a honeycomb of hexagonal rings consisting of capsid molecules. He suggested that the addition of nucleocapsid molecules and RNA could tilt the rows of hexagons into a spiral, forcing the entire structure to narrow toward one end. As support for this model, Sundquist cited recent work by physicists Maohui Ge and Klaus Sattler of the University of Hawaii, Honolulu, who showed that fullerenes, which have a similar honeycomb structure of carbon atoms, can also be coaxed into forming conelike structures.

Stevenson and Trono think that Sundquist's experiments could lead to an in vitro assay system to test drugs rapidly for their ability to disrupt cone formation, and Stevenson suggests that the experiments might even suggest new vaccine strategies. Although previous attempts to stimulate an anti-HIV immune response using capsid proteins have largely failed, Stevenson

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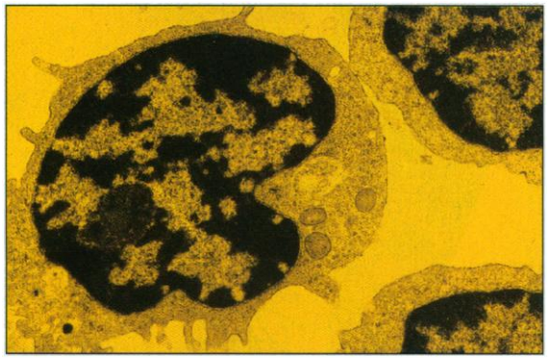
* Colloquium of the Lémanique Center for AIDS Research, Lausanne, Switzerland, 26–28 October.

says that a vaccine based on the artificial cones, which resemble actual viral structures, might be more successful. At the very least, the new work opens up these kinds of possibilities. Says Trono: "Any single event in HIV's life cycle is a valid target for therapy."

Finding HIV's First Home

Like most scientific fields, AIDS research has its share of dogmas. One of these concerns the kinds of immune cells in which HIV can replicate. Researchers have long assumed that T lymphocytes—the virus's primary target—must be in an active state to produce progeny HIV; that is, they must be immunologically stimulated to divide and proliferate. But because T cells are not activated against HIV in the earliest stages of the infection, many researchers have suggested that other immune cells, such as macrophages or dendritic cells—which can be infected and produce virus even when they are not dividing—are the main producers of HIV early on. T lymphocytes, according to this widely held view, become primary targets only after the immune system has begun trying to beat the virus down.



All is not calm. Quiescent T lymphocytes may be targets for HIV in early infection.

But in one of the most debated talks in Lausanne, retrovirologist Ashley Haase of the University of Minnesota Medical School in Minneapolis presented evidence that T lymphocytes may in fact be the most important target of early infection. Even more surprising, Haase reported that unactivated T lymphocytes can produce virus, a finding that flies in the face of much current wisdom. If correct, these new results might have important implications for how HIV gains a foothold in infected people, as well as for therapeutic strategies.

Haase and his co-workers, including research associate Zhi-Qiang Zhang, inoculated rhesus macaques with a strain of SIV, the simian version of HIV, that is capable of infecting both T lymphocytes and macrophages, and then analyzed a wide variety of tissues to see which cells were producing virus. Using molecular probes for SIV RNA, the team found that T lymphocytes made up almost all of the virus-producing cells, even in the earliest days after infection. Moreover, most of these infected cells did not show signs of activation or cell division, usually signaled by the appearance of cell surface proteins such as HLA-DR, Ki67, and CyclinA. Haase and his co-workers then went back and looked at lymphoid tissue from HIV-positive patients, where most T lymphocytes in the body are found, and discovered that they, too, harbored large numbers of unactivated but virus-producing T lymphocytes.

The macaque results, in particular, show that "T lymphocytes and not macrophages or dendritic cells are the main targets at the very beginning of infection," says pathologist Paul Racz of the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany. Haase told the meeting that these quiescent cells, which produce progeny HIV at a low rate and may be more resistant to anti-HIV therapies than activated cells, could be key vectors for spreading the virus to other unactivated lymphocytes during transmission of HIV and early infection. Moreover, these cells seem to differ from previously identified "reservoirs" of HIV infection: T lymphocytes that harbor latent viral DNA in their chromosomes but produce no virus until activated (*Science*, 14 November 1997, p. 1227).

If so, some researchers say, current experimental attempts to "burn out" the latently infected reservoir cells by activating them so they will be destroyed when virus progeny burst out could backfire, because the virus might infect new populations of drug-resistant quiescent cells. "This may be telling us that instead of activating, we should be trying to shut down residual replication in these cells," says immunologist Giuseppe Pantaleo of the Vaudois Hospital Center in Lausanne.

As intriguing as these findings are, many researchers are treating them with caution. Brigitte Autran, an immunologist at the Pitié-Salpêtrière Hospital in Paris, told *Science* she was not yet convinced that Haase's HIV-producing cells are fully quiescent. Autran says that some of the markers Haase used to determine their activation state, such as the appearance of HLA-DR, can lag many hours behind activation. Similar concerns are expressed by molecular virologist Didier Trono at the University of Geneva, who says that T lymphocytes may not fall into simple categories of "quiescent" and "activated" but that there might be a gradient between these two states.

Although Haase's results need further confirmation, AIDS researchers will be following this story very closely. "This is really a major concern," says Pantaleo, especially if "these [quiescent] cells are the ones that are not responding very well to antiviral therapy." –MICHAEL BALTER

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MATHEMATICS

From Solitaire, a Clue to the World of Prime Numbers

The strange sort of randomness seen in a simple version of solitaire may hold a key to proving a hypothesis about how primes are distributed

"I am convinced that God does not play dice," wrote Albert Einstein in a 1926 letter to physicist Max Born. With this now-famous quote, Einstein expressed his reservations about the emerging theory of quantum mechanics, which has randomness at its very core. But recent mathematical results might suggest that Einstein simply forgot to finish his sentence: "God does not play dice—He plays solitaire."

Solitaire is a subtler game than dice. Although the probability of winning at various dice games can be computed easily, no one knows the theoretical odds of winning at solitaire. "One of the embarrassments of our field," says Persi Diaconis, a probabilist at Stanford University, "is the fact that we cannot analyze the common game of solitaire." But a simpler version of solitaire has now been cracked, Diaconis announced at an October workshop on mathematics and the media at the Mathematical Sciences Research Institute in Berkeley, California. In work that is still being refereed, Percy Deift, a mathematician at New York University, along with Jinho Baik of New York University and Kurt Johansson of the Royal Institute of Technology in Stockholm, has proved that a deep similarity exists between a simple form of solitaire and a mathematical tool called random matrices, originally developed to understand the quantum be-