New Virus Reports Roil AIDS Meeting

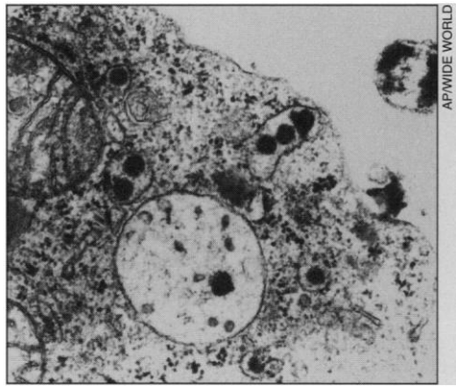
The possibility of a new human immunodeficiency virus dominated news reports from Amsterdam. *Science* brings you a behind-the-scenes account of what happened there

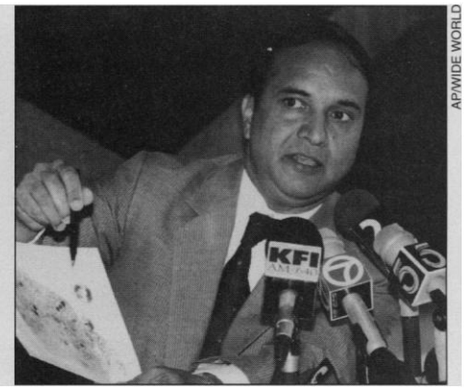
AMSTERDAM—An expensive jamboree...an activists' platform...an annual freebie for hundreds of government officials. These are the labels that have stuck to the International Conference on AIDS over the past few years. But 1992 may go down as the year when science reclaimed the AIDS conference. Leading the parade of highlights: reports that one or more new retroviruses might be causing a disease that's clinically indistinguishable from AIDS.

The more than 10,000 researchers attending the annual gathering—which was held in Amsterdam from 19 to 24 July and sponsored by Harvard University and a Dutch AIDS foundation—weren't scheduled to hear one word about the possibility of a new virus. But in the wake of a *Newsweek* article that recounted a dozen cases of people with AIDS symptoms—but with no signs of infection by HIV-1 or HIV-2—conference organizers added what proved to be the meeting's most memorable session to discuss these and similar cases. The result: a chain reaction that within 2 days had led to three separate reports of possible new human immunodeficiency viruses. It was as if the conference hall had been hit by "a real super-duper atomic bomb," said Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, although Fauci and many other researchers worried that the still sketchy data were being overinterpreted.

Indeed, as things now stand, the new reports have raised more questions than they've answered. It's not clear whether anyone has spotted a radically new virus, or simply an HIV variant that's being missed by existing tests. And if a new virus exists, is it causing immunosuppression, or is it just a harmless passenger? But the stakes are high: If there is a new agent that can cause AIDS-like disease, then there's a danger that it might contaminate the blood supply—although U.S. health officials emphasized that there was no evidence right now of any risk.

Immunologist Jeffrey Laurence of Cornell Medical University led off the impromptu session, describing five patients who had no detectable HIV in their bodies yet had all the hallmarks of AIDS, including low numbers of the critical CD4 white blood cells and *Pneumocystis carinii* pneumonia infections. Four of the five patients had known AIDS risk factors, but Laurence wouldn't discuss whether he'd found evidence of a new virus in any of these people—saying only that his group had a paper in press at *The Lancet*.





Puzzling particles. Sudhir Gupta displays a micrograph *(closeup on the left)* of retroviral particles detected in a woman with AIDS-like symptoms, but no sign of HIV infection.

Then James Curran, head of the HIV/AIDS program at the U.S. Centers for Disease Control (CDC) in Atlanta, said that over the past 3 years, CDC has identified six other similar immunodeficient people, at least three of whom had known AIDS risk factors. But Curran sounded one note of caution after another. No lab has yet conclusively demonstrated that any of these patients were infected with a new virus, he said. They might have surfaced just because the AIDS era has triggered a tremendous increase in surveillance for immune disorders. "Never before have so many CD4 tests been done in the history of the world," said Curran. Even if a new virus was found, he said, researchers would still have to prove that it is causing the disease. And so far, there doesn't seem to be the clustering of cases by lifestyle or locale that would be expected if the mystery immunodeficiency were caused by a transmissible agent.

Alternatives to a virus. Several explanations were floated to explain what—if it isn't a new retrovirus—might be damaging these people's immune systems. "Are we dealing with an immunosuppressive drug?" asked Curran. "Are there any other sources, like an underlying tumor or lymphoma?" It could be just a hard-to-detect HIV-1 variant, suggested the Pasteur Institute's Luc Montagnier, whose lab first isolated that virus.

Because of all the uncertainties, CDC had made no mention of these cases in its *Morbidity and Mortality Weekly Report*, particularly since seven similar reports had already appeared in the literature without causing a fuss. But when Curran asked the researchers jamming the special session, "Should we have done this a year ago?" the impassioned reply came: "Yes! Yes! Yes!" Suitably chastened, Curran called for clinicians who have HIV-negative patients with AIDS-like symptoms to send details to CDC immediately.

He shouldn't have to wait long for those reports. When researchers in the special session audience took to the microphones, several described more patients who'd tested negative for HIV yet had developed immunodeficiencies. The most dramatic revelation came from retrovirologist David Ho, head of New York's Aaron Diamond AIDS Research Center. Over the past 4 years, Ho and his colleague Eric Daar from the University of California, Los Angeles, Medical School have identified 11 patients with low CD4 counts who seem to be negative for HIV-1 and HIV-2, both with antibody assays and the ultra-sensitive PCR (polymerase chain reaction) test.

The next day, 22 July, speculation about a new agent soared even higher when the *Proceedings of the National Academy of Sciences* (*PNAS*) lifted the embargo on an upcoming article that describes the detection of retroviral particles in an immunodeficient 66-year-old woman and her apparently healthy 38-year-old daughter, neither of whom had any known risk factors for AIDS. In the *PNAS* paper, Sudhir Gupta from the University of California, Irvine—who did not attend the Amsterdam meeting—and colleagues report that PCR and antibody tests on the mother and daughter revealed no evidence of infection with any of the known human retroviruses. Yet their cells contained traces of reverse transcriptase, a key enzyme that retroviruses need to propagate them-

selves. And when Gupta's team examined cells from an immortalized CD4 cell line that had been exposed to the women's cells, they saw viral particles in the cisternae—the flattened membrane sacs that form a key part of the cell's protein synthesizing machinery.

With the story mushrooming—journalists began joking that the mystery agent was an "MTV," or media transforming virus—meeting organizers called a press conference, where many researchers said they doubted that Gupta's "human intracisternal retroviral particles" could be causing AIDS-like symptoms. Max Essex from the Harvard School of Public Health said that many cells contain similar intracisternal particles that have never been linked to disease. His verdict: The odds that Gupta has found a new retrovirus are "maybe 5% or below."

Contacted at his Irvine lab, Gupta stressed that he has not yet established a causal link between intracisternal particles and disease. "I've reiterated that 10 times over," said Gupta, who is attempting to purify the virus in sufficient quantities to produce a test that can prove causality.

Still more evidence. The pessimism about Gupta's virus didn't stem the flow of disclosures at the press conference. Near its close, Aaron Diamond's Ho dropped his second bombshell, saying that he'd detected reverse transcriptase in at least two of his 11 immunodeficient patients. This enzyme, he claimed, is different from those made by HIV-1 and HIV-2. "I think there's a virus there," Ho told *Science* later, adding that the microscopy that will provide a definitive answer is almost completed. But Ho still isn't sure if his probable virus is linked to the mystery disease, and he hasn't yet ruled out the chance that it's a contaminant.

In the wake of Ho's announcement, CDC's Curran revealed yet more tantalizing details. Although Cornell's Laurence wasn't at the press conference, Curran confirmed that there is "potential evidence of viral activity" in some of Laurence's five patients. Evidence described by Gerald Myers of the Los Alamos National Laboratory implies, however, that Laurence has found an HIV-1 variant that's not detected by standard tests.

The dust from last week's meeting will likely take months to settle. But for those who've written off the international AIDS conferences as worthless festivals, consider this: During a few days in Amsterdam, CDC has learned about more cases of HIV-negative people who have AIDS-like symptoms than it had detected in the past 3 years. And the explosion of scientific interest has also led Michael Merson, head of the World Health Organization's Global Program on AIDS, to launch "a worldwide study of this situation" as quickly as possible. Would that the response to the first five cases of AIDS reported 11 years ago had been so swift.

–Jon Cohen

Progress on Other Fronts

With reports of a possible new human immunodeficiency virus stealing the show at the Eighth International Conference on AIDS (see story on page 604), it was easy to forget the established villains: HIV-1 and HIV-2. But the meeting still had plenty to offer the thousands of researchers who are trying to understand HIV infections so that they can be prevented or cured—the central issue in AIDS. Here are some of the high points:

■ **Some HIV strains may be more readily transmitted sexually than others.** Chin-Yih Ou of the Centers for Disease Control reported that HIV-1s isolated from 41 people in Thailand segregated into two genetic subtypes. One, designated subtype A, appears to be transmitted mainly by the sexual route; it was found in 86% of the people who had probably been infected through sexual contact whereas 76% of those infected with subtype B were intravenous drug users. "This distribution is not explainable by chance," said Ou. So far, the reasons for the segregation aren't clear, but it may be that subtype A finds it easier to pass through the sexual mucosa than subtype B does. Consistent with this idea, subtype A is similar to strains from Africa, where heterosexual sex is the main mode of transmission. Subtype B resembles strains prevalent in North America and Europe, where contaminated needles are an important route of transmission.

■ **AZT may only work for people who have less pathogenic HIV strains.** It's been known for years that some strains of HIV cause syncytia—clumps of fused white blood cells that quickly die. But data released in Amsterdam revealed that only people infected with strains that don't form syncytia—and are presumably less pathogenic—respond to AZT. Frank Miedema of the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service recently completed a 2-year, double-blind, placebo-controlled clinical trial of AZT in 52 HIV-positive asymptomatic people. None of the 20 people who were infected with nonsyncytia-inducing HIV and took AZT developed full-blown AIDS—compared with six of 18 in the no-drug control group. Only 12 of Miedema's subjects had syncytia-inducing HIV, too few for him to do reliable statistics. But a separate study from Burroughs Wellcome, AZT's manufacturer, found that the drug didn't help people infected by syncytia-inducing HIV. The Burroughs study matched 17 HIV-positive patients who had taken AZT for 3 years without progressing to AIDS with another 17 who had, despite also taking the drug. In all but one of the pairs, the progressor was infected with a strain that induces syncytia and the nonprogressor with one that doesn't.

San Francisco General Hospital's Paul Volberding, who's head of the International AIDS Society, was particularly impressed with these studies. The story looks "very convincing," he said. But until larger studies confirm these initial findings, Miedema said that he's reluctant to advise people with syncytia-inducing HIV not to take AZT—although he suggested that they should combine it with another antiretroviral drug.

■ **Some people who have no HIV antibodies may still have encountered the virus.** Immunologist Gene Shearer of the National Cancer Institute has identified 49 high-risk people without detectable antibodies to HIV, but whose T-cells behave as if they've seen the virus before. Shearer offered an explanation for the paradox: The TH1-TH2 theory, which holds that TH1 cells, which stimulate the production of cytotoxic T-cells, and TH2 cells, which trigger antibody production, suppress each other. If Shearer is right, his HIV seronegative people may be more resistant to infection because they're locked into the TH1 state and are fighting the virus through cellular immunity.

This is sobering news for just about every HIV vaccine developer—as it follows that boosting production of antibodies to HIV, the standard vaccine approach, may actually undermine protection. One exception, however, is Jonas Salk, from California's Immune Response Corp., who made a big splash at the meeting when he announced that he's working on a preventive approach building from Shearer's ideas.

■ **Vaccine therapy may be able to reduce the amount of HIV in infected people.** Robert Redfield of the Walter Reed Army Institute of Research claimed that he's reduced the amount of HIV in the blood cells of infected people who have been treated for 2 years with a vaccine made from the HIV surface protein gp160. In more than 85% of the treated patients, Redfield found that the amount of virus in their blood cells had stabilized or decreased. Redfield had no placebo controls, but 47% of a nontreated group of 19 patients showed an increase in HIV. "If it is a drop in viral load," said National Institute of Allergy and Infectious Diseases director Anthony Fauci, "that's very significant." But he cautioned that HIV decreases in the peripheral blood may not be matched by decreases in the lymphatic system—especially during the first few years following infection. The jury is now out, pending the results of a large clinical trial that's already under way.

–J.C.