'Mystery' Virus Meets the Skeptics

At a hastily called meeting in Atlanta, 300 researchers heard about AIDS-like illnesses without HIV. The evidence for new viruses is, to put it mildly, sketchy.

ATLANTA—Try this as the plot for a thriller: a new, unidentified, "mystery virus," which causes AIDS but isn't the AIDS virus, is afoot, playing havoc with the blood supply and killing thousands while researchers scurry to develop diagnostic tools and yet another blood test. Great story, right? Well, that isn't precisely the story *Newsweek* broke right before the international AIDS conference in Amsterdam 3 weeks ago. In fact, all that was really known was that a dozen or so people seemed to have some AIDS-like symptoms but showed no traces of HIV in their blood. Yet after *Newsweek*'s article was picked up by other publications and put through the media megaphone, that's the message most people around the world heard.

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Pondering the evidence. David Ho *(left)* and Sudhir Gupta were two of the key presenters at the CDC's Atlanta meeting.

A huge international conference packed with hungry reporters in search of a story isn't the place to puzzle out a sketchy new scientific phenomenon. So, before the worldwide panic index climbed out of sight, the U.S. Centers for Disease Control (CDC) called a smaller meeting on 14 August where all scientists who know of HIV-negative people with severe immunodeficiency could come and put the evidence to a tough, dispassionate review. In a jam-packed auditorium here, that's just what 300 researchers did. The verdict? After 7 hours of presentations, most in the audience left Atlanta distinctly underwhelmed. The evidence for any new virus is somewhere between sketchy and nonexistent. What's more, it isn't even clear that the scattered cases represent anything other than the results of more sophisticated detection of immune disorders that have always been present in the populace, but have remained undetected until the age of AIDS, with its sophisticated diagnostic tools.

"At the risk of being destroyed because of giving you my opinion, I personally don't think this is really terribly new," Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, told the researchers and the 60 journalists present. Mirroring the day's mood, Fauci expressed considerable skepticism that a new immune-suppressing virus would be found. "There are footprints of virus," he conceded, "but in fact all of us who've been in the laboratory for any length of time have been down that road before where you're thinking you've found something and in fact it's either nothing or it's unrelated to what you're looking at."

As for the safety of the blood supply—the question that excites the most public alarm—James Curran, head of the CDC's HIV/AIDS program, said there is no cause for concern, as of yet. "I've seen no convincing evidence so far that the syndrome or syndromes are transmitted by an agent, let alone an agent that is blood borne or is spread through the blood supply," he said. Still, the meeting's take-home message, as offered up by Curran, was: "Keep an open mind." Curran, Fauci, and the other scientific notables gathered in Atlanta stressed that every effort—including setting up CDC and NIH hotlines—is being made to collect all cases to find out what, if anything, HIV-negative immune suppression really means.

Who, What, Where, When?

By sending the alert far and wide through the medical community, the CDC was able to turn up a fair sampling of people who have a low count of CD4 cells (the white blood cells that HIV infects and kills) but don't seem to be infected by the AIDS virus. These cases were presented in the morning session of the Atlanta meeting. More than 80 candidate U.S. cases were discussed. But of that total, only 30 met the CDC's recently formulated definition for what is now being called by the tongue-twisting name of "idiopathic CD4+ T-lymphocytopenia" (ICL).

The new criteria for ICL include: two separate CD4 tests below 300 cells per cubic millimeter of blood (the normal count ranges from 800 to 1200) or CD4s less than 20% of the total lymphocytes; no known causes of immunodeficiency or therapy that could deplete T cells (the family CD4 cells belong to); and, of course, no evidence of infection by the AIDS viruses, HIV-1 or HIV-2. Of the 30 cases that meet these criteria, 13 have had illnesses that are considered hallmarks of AIDS—such as *Pneumocystis carinii* pneumonia, extrapulmonary cryptococcosis, and cytomegalovirus infection.

The 30 cases constitute a remarkably varied grab-bag. They have been collected over more than 7 years, they live in 15 states, range from 18 to 70 years old, and the majority (54%) have no known risk factors for HIV. This heterogeneity led the epidemiologists present at Atlanta to conclude that, whatever is going on here, there probably isn't a single cause for all the cases. And the notion that a single transmissible agent doesn't account for all these cases was bolstered by the fact that although most of the patients' sexual and household contacts have yet to be studied, the few that have been examined appear to have normal CD4 counts.

After the morning's review of the clinical data, the throng of scientists took a lunch break and got down to the day's main event—parsing the virology data. On the witness stand were the four researchers who have the best evidence so far for non-HIV-viruses that might cause an AIDS-like syndrome: Sudhir Gupta of the University of California, Irvine, David Ho of the Aaron Diamond AIDS Research Center in New York, Jeffrey Laurence of the Cornell Medical Center, also in New York, and Robert Garry of Tulane University School of Medicine. Data from Laurence, Gupta, and Ho touched off the fuss at Amsterdam, and because they have yet to publish most of their results, the presentations were eagerly awaited.

Ho, Laurence, and Gupta described their efforts to isolate a new retrovirus from immune-suppressed patients. Despite the similarities in the four lines of work, there is one fundamental difference: Ho and Laurence are looking for one type of retrovirus, while Gupta and Garry are working with an entirely different category of retrovirus, one that, until now, was thought by many researchers to be incapable of causing human disease. The Gupta-Garry type is known as an "intracis-

Doing Science in the Spotlight's Glare

There were plenty of tough scientific questions to ponder at the CDC's hastily called recent meeting on the mysterious syndrome of immune suppression without HIV. But there was also plenty to ponder in the way the lay press, scientific institutions—notably the CDC—and the researchers themselves handled the media frenzy of the "mystery virus" story.

In all probability, there wouldn't have been such an international journalistic feeding frenzy if *Newsweek* hadn't chosen to run the story in the 27 July issue, which came out just before the international AIDS conference in Amsterdam—timing that even *Newsweek* writer Geoffrey Cowley concedes was "not entirely coincidental." Cowley and Jeffrey Laurence of the Cornell Medical Center, whose data formed much of the basis for the story, both deny the rumor—which spread far and wide at the Amsterdam conference—that the Cornell researcher leaked the story to Cowley. "I came to the story the hard way," says Cowley. "It's not something that was just plopped into my lap a week before the conference as part of a cynical ploy to get publicity."

Cowley was, in fact, not the only reporter who knew about the HIV-free AIDS-like cases. Lawrence Altman of *The New York Times* says he knew of cases for several months but did not break the story because he didn't think it was his paper's place to announce something the CDC was not confident enough of to publish. Altman was surprised to find, after the *Newsweek* piece appeared, that the CDC had presented six cases of the condition is now being called "idiopathic CD4+ T-lymphocytopenia," or ICL, at a Colorado meeting this spring.

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Meet the press. CDC's James Curran *(left)* with *Newsweek's* Geoffrey Cowley, who broke the "mystery virus" story.

But if the CDC was willing to make the six cases public in a small meeting in Colorado, they were not willing to alert the medical community to the syndrome by publishing the cases in the CDC's widely distributed *Morbidity and Mortality Weekly Report* (*MMWR*), at least not before the *Newsweek* article came out—an omission for which Curran took much heat at Amsterdam. And the heat had an effect: During the international conference, Curran conceded to *Science* that if he had it to do over again, he might well do it differently. But now, as more negative data pile up on the "mystery virus," Curran is having third thoughts. "I think we made the right decision not to publish," he says, emphasizing that a CDC epidemiologist who was "beating the bushes of the country for cases" could find only four and that there was thus no need for a medical alert. "If the CDC put something out, particularly if we put something out before Amsterdam, we would be like *Newsweek*."

Laurence, on the other hand, maintains that the CDC "absolutely" should have described the cases in *MMWR* before the *Newsweek* article broke. "I had contacted them when I got my third case and realized this was a real problem in April," says Laurence. "They said I should write it up as an *MMWR* and it took me about 50 minutes to do that." Laurence contends that because the CDC didn't publish the cases in *MMWR*, "it made the CDC look bad." Laurence thinks the heroes of the story are *Newsweek*'s writers and editors. "Someone should pin a medal on them," he says, for bringing attention to a syndrome that he thinks is real and needs explanation.

But if *Newsweek* and the CDC find themselves at the center of a controversy for the way the story broke, the researchers hunting for the "mystery viruses" are in an even more uncomfortable position. "This is extremely unusual—for basic scientists to open their lab notebooks to Nobel laureates and National Academy of Science members in front of 80 press," James Curran, director of the CDC's AIDS program told the audience at the recent meeting in Atlanta. "I admire them and feel sorry for them."

The virologists featured in Atlanta—Laurence, David Ho of the Aaron Diamond AIDS Research Center, and Sudhir Gupta of the University of California, Irvine—aren't feeling sorry for themselves, but they are wary of doing science in the spotlight. Ho worries that by parceling out tidbits, the public will be misled. "People don't remember all the qualifiers," he says. "They'll just remember the conclusions and bottom lines." Laurence is uncomfortable "doing this in a bubble" and wants to make sure he spends enough time gathering and analyzing the data. "I don't want to be embarrassed," he says.

Like Laurence, Gupta sees good as well as bad coming out of the media barrage. Although he thinks it is "very important" that government agencies have mustered forces to evaluate the syndrome quickly, the fact that the story came out during the international conference was unfortunate. "It created a panic," says Gupta. "It went like fire." One researcher who feels the fire was out of proportion to the spark that lighted it is the National Academy member who submitted Gupta's paper describing his AIDS-like cases to the *Proceedings of the National Academy of Sciences*. Retrovirologist Ludwik Gross of New York, widely respected for contributions he made to virology during the 1940s and 1950s, says he puts little stock in the paper. "It will disappear," says Gross. "It has no significance."

Whether any of the papers published or in press on the mysterious viruses ultimately has any significance, the media flap is a phenomenon that needs further thought. Was any harm done by the way the story unfolded? To that question there are as many answers as there are people to answer it. Some argue that shining the media spotlight on the latest AIDS mystery story is dangerous. "It's irresponsible and harmful," says AIDS activist Martin Delaney, head of San Francisco-based Project Inform. "We had hundreds and hundreds of hysterical people calling our hotline and you can't talk them down."

Predictably, *Newsweek*'s Cowley, who started all the fuss, says he doesn't think it's "dangerous for people to worry a little bit." Less predictably, Nobel Prize–winning virologist Howard Temin also takes a mild view. Temin says he thinks that for many people this is "nothing more than the scare of the day," and that it will have no effect on behavior. "Without having done any social surveys, my sense is that most people take this as more a kind of excitement and a little degree of titillation," says Temin. The problem is that when the subject is AIDS, a little titillation goes a long way.

–J.C.

ternal retroviral particle" because it appears in cisternae, or internal compartments, in some cells. These viral particles are thought to be produced by viral sequences embedded in the human genome as the result of an ancient infection—and then transmitted in the germ line. Until now they have generally been thought to be "replication defective," that is, not only incapable of being transmitted but also incapable of reproducing themselves in viable new particles.

Garry, who first published evidence of a human intracisternal particle nearly 2 years ago in *Science* (23 November 1990, 1127), contradicted the received wisdom about its ability to cause disease. As Garry reported in his *Science* paper, he had detected a human intracisternal A-type retroviral particle in a patient with Sjögren's syndrome, an autoimmune disease that causes dryness of the eyes and mouth. In Atlanta, Garry offered evidence suggesting that these particles might cause disease: Antibodies from 35 patients with a form of lupus—another suspected autoimmune disease—reacted to his particle in a Western blot assay.

Gupta, meanwhile, in the 15 August *Proceedings of the National Academy of Sciences* (*PNAS*), reported detecting intracisternal retroviral particles in a 66-year-old woman who had *Pneumocystis carinii* pneumonia and met the ICL definition. He has also detected the particles in the woman's healthy 38-year-old daughter. One of Gupta's most iconoclastic conclusions is that his intracisternal particles are, in fact, infectious; his evidence includes passage of these particles into two cell lines and into normal blood cells. "I'm just amazed that a defective retrovirus can cause an infection," said the University of Wisconsin's Howard Temin, who won the Nobel Prize in 1975 as one of two discoverers of reverse transcriptase, the enzyme that enables retroviruses to copy their RNA genes into the cell's DNA.

If Gupta's intracisternal particles do indeed cause ICL, it should be possible to detect them in "blind" procedures on blood samples from patients with the syndrome. At Atlanta, Gupta reported making a start in that direction. Using 75 blood serum samples supplied by CDC and by Ho, he was able to identify nine of 13 ICL patients accurately, while turning in only 2 false positives. His testing relied on running the blood samples over cells infected with the intracisternal particles and identifying the matches with an antibody-based fluorescence method.

Despite these results, the reception Gupta received at the conference was, in general, one of disbelief. Even Temin, one of the more open-minded panelists of the many who commented on Gupta's results, suggested that his apparent ability to infect other cells with the particles might simply reflect inadvertent stimulation of retroviral particles already present in the target cells. Gupta was well aware of the mood, claiming to *Science* that his data were "ignored" at the meeting. "It's just too much [positive data]," he said, "not to look at seriously."

The reception that greeted Laurence and Ho at Atlanta was less skeptical, if only because they are looking for retroviruses like HIV, which, in contrast to the intracisternal particles, are known to infect human beings and cause disease. Both are attempting to find a new virus by first looking for traces of reverse transcriptase (RT) activity in cells from ICL patients. Ho has now looked for evidence of RT in 17 patients with low CD4 counts who had negative tests for all the human retroviruses known so far. He co-cultured cells from these patients with cells from normal donors to see whether an agent could be induced to infect the normal cells. In 15 of the 17 cases, the results from all tests were "completely negative." Yet two patients did show "RT-like" activity. Ho focused on these two cases in his Atlanta presentation.

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Just between you and me. Anthony Fauci *(right)* of the National Institute of Allergy and Infectious Diseases and James Curran.

Enthusiasm tempered

Initially Ho, who was reticent about his findings in public, was enthusiastic in private. But in the past few weeks, his enthusiasm has been tempered by electron micrographs revealing no virus in his samples. He also spelled out other experiments he plans to do to make sure that he is really seeing RT. In addition, one of the two suspicious samples has tested positive for mycoplasmas, a bacteria-like microorganism known to wreak havoc with RT readings. In Atlanta, Ho was far from making a strong claim for a new virus. In fact, he said, "I'm not giving you a conclusion. I'm just showing you the data."

Cornell's Jeffrey Laurence has data that he told the assembled researchers are "quite similar" to Ho's. Laurence, who published clinical descriptions in the 1 August *Lancet* on five of the nine cases he is evaluating, reported at the CDC meeting that two patients had shown RT activity. But Laurence's electron microscopy, like Ho's, showed "no convincing evidence for retroviral particles." "That's disappointing," he said. "We expected to see something, given the RT activity."

Gerald Myers, who maintains a database of HIV sequences at the Los Alamos National Laboratory, offered a possible explanation for the puzzling results Laurence is getting. Myers analyzed DNA sequences from three of Laurence's patients and found that they may have fragments of HIV genes among their own, normal genes. Myers suggested these might be remnants of "hit and run" HIV infections—a conclusion that might fit in with a rash of recent evidence that there are people who have likely been infected with HIV but show no antibodies or other evidence of HIV in their systems (*Science*, 10 July 1992, p. 152).

Whatever the explanation for Laurence, Ho, and Gupta's results, the consensus at the CDC's symposium was that it's unlikely there is a new retrovirus lurking in the wings, causing an AIDS-like illness. Yet something must explain the cases of ICL. In Atlanta, three main possibilities were considered. First is another type of infectious agent. As Temin reminded the crowd, retroviruses are only one of 85 families of viruses. Second, as Myers' sequence analysis suggested, these might actually be HIV infections that aren't easily diagnosed. Finally, it may simply be that, as Fauci proposed, the syndrome isn't new at all and only surfaced now because of increased surveillance.

A presentation by James Mosley of the University of Southern California (USC) School of Medicine underscored the possibility that there isn't a new illness here. Mosley is director of the USC-coordinated Transfusion Safety Study, which since August 1985 has evaluated people who have received blood components, clotting factor, or both. The study found that the prevalence of ICL was the same in those who had received clotting factors and in those who had not, which suggests that in this case the problem may be related to hemophilia itself, and not to an infectious agent. "It has to be confirmed, but that suggests it's something related to hemophilia," said Curran.

That's one explanation, but clearly more work is needed to unearth all the facts about ICL. Whatever the actual cause of the condition, for now, the story of the "mystery virus" serves to underscore the difference between AIDS and every other medical condition—in journalistic terms. "Had this been a condition that was reported in *Newsweek* that was occurring at the same time as the American Heart Association meeting," asks the CDC's Curran, "would this have happened?" The answer to that question is obvious; the right way to handle the next AIDS scare that comes along isn't.

–Jon Cohen