

Basic Research Comes to the Fore as Clinical Results Lag

YOKOHAMA, JAPAN—This year's 10th International Conference on AIDS, the first ever in Asia, set itself apart from its nine predecessors not so much by what happened, but by what did not. In contrast to past years, no clinical trials of anti-HIV drugs stirred the delegates. No AIDS vaccine tests in monkeys or chimps had the conference halls abuzz, as they have nearly every year in the past. Even the hordes of AIDS activists who have traditionally disrupted the conference sessions with provocative signs and blaring bullhorns failed to materialize.

What the 1994 conference did show, says the World Health Organization's (WHO) Peter Piot, outgoing president of the International AIDS Society—a co-sponsor of the meeting—is that two contradictory extremes that marked previous meetings should be put to rest: naive optimism and unfounded pessimism. "In the first conferences, people were using them to announce breakthroughs," says Piot. "It was going so fast and people got used to it." People also became far too pessimistic at last year's meeting in Berlin, when it became clear that both drug and vaccine strategies had serious problems. Now, urged Piot, the time had come for "realism" and to acknowledge that HIV will be with humans for years to come, although there are hints it can be controlled.

The new, more sober and realistic approach that Piot was urging fit in well with what was reported at the conference which was held from 7 to 12 August. Only a few new results of AIDS drugs and therapies were presented here. And since the attempts to find effective therapies against HIV have so far proved almost completely fruitless, the "new realism" seems to dictate that more money be spent on basic research—aimed at understanding the biology of the virus and the immune system—before even more money is thrown into clinical trials.

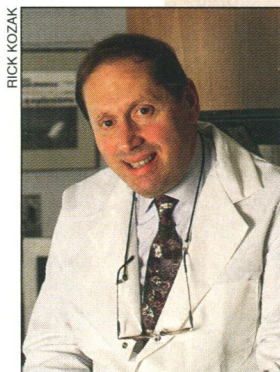
Indeed, at the conference, William Paul, head of the Office of AIDS Research at the U.S. National Institutes of Health (NIH), said that he intends to steer more money in the direction of basic research. What Paul did not say publicly is that to do so, he must cut the funding for AIDS clinical trials. But in today's world of flat NIH budgets, that is a pretty good assumption. And *Science* has learned that, behind the scenes, Paul is work-

ing to trim the NIH AIDS clinical program so that he can beef up basic research.

Just how scarce good news was at the conference is shown by the fact that the two clinical findings that got the most press were old news. Reports that a group of "outlier" HIVs known as subtype O have evaded some HIV blood tests, and that AZT can reduce the transmission of HIV from pregnant

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—William Paul



RICK KOZAK

women to their newborns were originally announced a few months ago and covered widely in the press. And while protease inhibitors, another major news topic, still look like the most promising antivirals being tested, virtually no significant new information about them was presented. The same was true for a factor that is produced by the CD8 type of immune cells and inhibits HIV replication. Still, a few basic research findings deserved the attention they got in the major dailies and on television from the news-starved media.

In particular, two related sets of studies are giving AIDS researchers a firmer grasp of why some infected people appear unfazed by HIV even after more than a decade, by which most of their counterparts have begun to develop full-blown AIDS. In one study of 14 of these so-called "long-term nonprogressors," Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, and his co-workers Giuseppe Pantaleo, Cecilia Graziosi, and Oren Cohen found that people who do not experience immune decline after more than 7 years of infection have lower HIV levels in their blood and more intact lymph nodes than people who become ill.

David Ho, head of New York's Aaron Diamond AIDS Research Center, presented the results of a similar study of 10 people who had been infected at least 12 years and had intact immune systems. These people had

even lower levels of detectable HIV than those studied by Fauci's group.

Though it is becoming increasingly clear that the amount of HIV in a person, or "viral load," is linked to disease progression, until now researchers have had little solid evidence that if a treatment lowered viral load, a person would fare better. At the meeting, UCSF's James Kahn presented data from one analysis of a study of the antivirals AZT and ddI that used the polymerase chain reaction to measure the HIV RNA in 100 people. The researchers found, Kahn says, that people who had a 50% reduction in viral load in their blood as a result of the treatment had a 32% reduction in progression to AIDS.

William O'Brien of the Veteran Affairs Medical Center in Los Angeles described how he and his co-workers had made a similar finding in 305 patients they studied in an AZT trial. Specifically, a drop in viral load predicted those who would benefit from AZT 90% of the time. Changes in the key white blood cells designated CD4—which often has been used to gauge a treatment's worth—predicted only 37% of the treatment effect. "For those who follow the literature, this is not a surprise," says Ho, but he adds that these studies should firmly convince skeptics that reducing viral load is a realistic target for therapy.

The realism theme even spilled over to the most futuristic therapies being tested. Philip Greenberg of the University of Washington in Seattle described a novel therapy he is testing in three HIV-infected people in which he first removes some of their CD8 cells. He then clones out the CD8s that specifically kill HIV-infected cells in the test tube. But before growing one billion of these cells and reinfusing them into patients, Greenberg stitches a "suicide" gene for a herpes virus enzyme called thymidine kinase into them so he can shut off the experiment with the anti-herpes drug ganciclovir if the test goes awry.

One reaction to the agonizingly slow pace of clinical research is to conclude that we simply do not understand HIV and its impact on the immune system well enough to design good therapies. For NIH's Paul, who oversees the institution's \$1.3 billion AIDS research budget, the answer to this dilemma is a renewed basic research effort. "If we do not provide innovative scientists with the resources and opportunities to attack basic unsolved problems related to AIDS and HIV, we may find that a decade from now, we are no further along in our struggle," said Paul.

Though Paul did not speak of cutting back the NIH's clinical research program—indeed he repeatedly emphasized its importance—*Science* has learned from government officials who have reviewed Paul's proposals that, in fact, he is attempting to cut the 1996 budget for the network of researchers in the

Japanese AIDS Activists Adopt a Milder Form of Protest

In a speech at last year's international AIDS conference in Berlin, AIDS activist Aldyn McKean from ACT UP/New York urged the world to "tear down the walls" of discrimination and ignorance surrounding people infected with HIV. Nowhere have those walls been higher, say Japanese AIDS activists, than in Japan, site of this year's international AIDS conference. "The government is trying to cover [the AIDS problem] up and make it so people do not understand," asserts Hiroshi Niimi, head of Tokyo's OCCUR, the Association for the Lesbian & Gay Movement. But unlike McKean and other U.S. activists, AIDS activists in Japan have been slow to criticize their government or their society.

As Niimi's words indicate, that appears to be changing, if slowly. Sadly, the change was perhaps most evident at a funeral procession for McKean that began at the AIDS conference center in Yokohama. McKean died in February, and his friends brought his ashes to Japan to give him "a hero's funeral" at the meeting. Marching side by side with them in a procession to Yokohama Bay were a few dozen Japanese AIDS activists, who were rarely seen in such force at the conference.

If Japanese AIDS activists are silent, it is not because there's nothing to shout about. Niimi charges that government figures of 3075 HIV-infected people and 764 with AIDS grossly underestimate the magnitude of the disease in Japan. He says the low numbers are low because the Japanese people are afraid to be tested for HIV because of a prevention law that allows a physician to report patients who pose "a risk to society" to the health ministry—which can then interrogate, fine, or even imprison them.

Yoshiaki Ishida, an infected hemophiliac who spoke at the meeting from a wheelchair, says many infected hemophiliacs in Japan hide their HIV status. "They're still in denial and cannot accept the position they're really in." He says hemophiliacs, some of whom blame the government for their infections and have filed suit, are particularly worried about being quarantined in



Acting up, Japanese style. Hiroshi Niimi (far right) and other Japanese AIDS activists are beginning to protest—but much more quietly than their U.S. counterparts.

AIDS hospices that the government plans to open next year.

Hiroki Nakatani, a medical officer at the Ministry of Health, concedes that because of poor reporting, HIV infections and AIDS cases in Japan are probably 3 to 10 times higher than the official figures. But he insists jailing is "never, never thought about" and that no one will be forced into a hospice, which he says are being built because "AIDS people have special needs."

In spite of their concerns, Japanese activists have not chosen to emulate McKean and his ACT UP comrades—as the funeral ceremonies made clear. While a friend of McKean's read a passage from his Berlin speech

that began, "We activists have been screaming for years," Niimi and his friends quietly lit incense and passed out flowers and bells to the crowd that gathered under the broiling sun. They then marched in the procession for a man few of them had met and quietly tinkled bells as McKean's ashes were poured from a small plastic container labeled "Silence = Death" into the bay.

The difference between ACT UP's in-your-face activism and the Japanese way of acting up did not escape Niimi. "In the West, you have individual wills conflicting with each other," Niimi explained. "But in Japan, just like there are four seasons and the wind blows, things are going along despite what individual wills prefer. OCCUR is trying to adapt itself to this natural flow."

The singular nature of Japanese activism was revealed again at the conference's closing ceremony. There Niimi joined other Japanese, European, and North American AIDS activists, filing onto the stage blowing whistles and waving banners, urging that the rights of people living with HIV and AIDS be upheld. While this protest resembled the Western-style activism that was absent from the rest of the meeting, there was one sharp difference: The protesters did not take the stage until they were invited by the conference organizers. And so, despite signs of increased Japanese AIDS activism, there is little chance it will ever be as raucous.

—J.C.

adult AIDS Clinical Trials Group (ACTG) from a proposed \$68 million to \$60 million.

Paul would not confirm these numbers, but he told *Science* that the ACTG will be "one of the places where we're going to find some money, but not the only place." He also agreed that if such a 12% cut in the proposed ACTG budget does take place, researchers will feel it. "It gets your attention and makes you decide what's really important to do," said Paul, who added that he does not plan to cut vaccine research and testing.

In the conference hallways, some clinicians were as concerned about Paul's emphasis on basic research as they were about what was happening in the sessions. "We run the risk of destroying the best clinical trials group," said AIDS researcher Fred Valentine

of New York University. UCSF's Donald Abrams also is concerned. "If you continue to suffer cuts in government-funded research programs, then major advances are going to be even [rarer]," said Abrams.

While researchers in the West wrestle with the agonizing choices needed to get AIDS research moving again, in the East the epidemic is exploding, as Michael Merson of WHO hammered home in the conference's opening plenary session. During the past year, Merson said, the number of cumulative infections estimated in Asia has jumped from 1 million to more than 2.5 million—taking the region from 12% to 16% of the global total of 17 million. "Enormous population movements, the inferior status of women, and the reluctance to acknowledge the huge

threat posed by AIDS make many Asian countries very vulnerable," warned Merson, noting that in Thailand new infections have increased 10-fold since 1990. "I appeal to all Asian leaders to face reality and make AIDS prevention a national priority....Do not believe as many others have believed that it will not happen to you."

It was fitting for Merson to emphasize prevention, because the best evidence from the Yokohama conference suggests that, at the moment, prevention is the only reliable way to attack HIV. And while William Paul's basic research prescription for the field may be the right one, no one claims that basic research is a rapid route to an effective treatment for AIDS.

—Jon Cohen