AIDS Meeting: Unexpected Progress

At the International AIDS Conference in San Francisco the news wasn't the hoopla but—surprise!—a variety of interesting scientific results

HARRIED—AND, BY NOW, NO DOUBT EXHAUSTED—the organizers of last week's Sixth International Conference on AIDS can point to two very gratifying surprises arising from their meeting: not only did the meeting proceed without disruption of the scientific sessions, but there was also more new science than many participants had expected.

Fears of chaos had run high in advance of the meeting because of its site—San Francisco, a center of AIDS activism—and because it happened to coincide with the annual Gay Pride Week—an accident of scheduling, according to conference organizer Paul Volberding, an AIDS researcher from the University of California at San Francisco.

The last hurrah. *One of the few outbursts at the AIDS meeting: Drowning out Louis Sullivan on the conference's last day.*

But the potentially volatile mix of cultures never ignited, perhaps largely because the activists and researchers made common cause. They turned their anger on the Bush Administration and its restrictive immigration policy for people infected with HIV, the AIDS virus.

In the end, a closing panel of top scientists, several of whom wore red armbands to protest the Administration's immigration policies, criticized the federal policies even as U.S. Secretary of Health and Human Services Louis Sullivan sat awaiting his turn to make a closing address to attendees. When it was Sullivan's turn to speak, several hundred activists with whistles, sirens, and airhorns staged a noisy demonstration, drowning out his words. The conference organizers and security force made no effort to remove the protesters, and Sullivan resolutely delivered his speech into the din.

There were no such disruptions of the scientific sessions during the days leading up to Sullivan's controversial appearance, although some researchers complained privately that activists participating in the meeting as delegates monopolized the question and answer periods with political questions, thus stifling scientific exchange. Nevertheless, a good deal of fruitful scientific interaction did occur. "I was worried [about disruptions], but the meeting has been a pleasant surprise," said Robert Yarchoan of the National Cancer Institute.

The pleasantest surprise of all was the quantity of new and intriguing data on the AIDS virus and the means by which it causes disease. Some of the conference's most promising results were at the molecular level—concerning the virus's means of genetic regulation and also the mechanism by which HIV develops resistance to AZT. More mixed were the clinical results announced at the meeting, while some of the epidemiological results were fraught with gloom.

On the molecular front, there were new findings that clarify and perhaps redefine the role of the key HIV regulatory protein known as Nef. Some 4 years ago William Haseltine, of the Dana-Farber Cancer Institute in Boston, found that Nef seemed to be a down-regulator of HIV growth. Haseltine and his colleagues showed that a laboratory strain of HIV called HXB2, which had an inactive *nef* gene, grew better in cultured cell lines than the same virus with a functional *nef* gene. It was thought at the time that by down-regulating viral replication *nef* might play a role in the long latency period typical of HIV infection.

New evidence suggests that finding was a special case, Haseltine says. But that's not entirely disappointing, because the new work may help to clarify another central question in AIDS research: the variation in the cell specificities or tropisms of HIV strains. Several research groups have observed that isolates of HIV from patients generally contain a mixture of strains with different tropisms. For instance, only certain strains will grow in the phagocytic blood cells called monocytes.

By swapping *nef* genes between HXB2 and another HIV strain called Eli, Haseltine and colleagues Ernest Terwilliger and Erik Langhoff changed HXB2 from a strain that grows only in established cell lines into one that grows well in three different kinds of primary blood cells. That result suggests that mutations in *nef* could be responsible for creating different cell tropisms. And for that reason "*nef* may be a very important gene in the natural infection," Haseltine says.

Also at the molecular level, light was shed on the question of HIV resistance to AZT, the main drug so far approved for use in AIDS therapy. AZT acts by inhibiting reverse transcriptase, the enzyme that converts the viral RNA into the DNA that is then inserted into the host genome. Brendan Larder, of the Wellcome Research Laboratories in Beckenham, England, has begun to pick apart the mechanism of resistance to the drug.

Larder and his colleague Sharon Kemp recently identified four mutations that arise in the viral gene for reverse transcriptase, making it resistant to the action of AZT. In the reverse transcriptase of the most highly resistant viruses, amino acid changes corresponding to all four mutations are present; viruses with lower levels of resistance have some, but not all, of the four. Larder and Charles Boucher, of the Human Retrovirus Lab in Amsterdam, took this work one step further, as they reported at the conference. They followed the development of AZT resistance in virus isolated at intervals throughout the course of AZT treatment, from two types of patients: those who were HIV-positive but asymptomatic, although they had falling levels of T4 cells, or those who already had AIDS or AIDS-related complex (ARC) when they began taking AZT.

Larder and Boucher found that, once AZT is administered, HIV seems to develop resistance to the drug at a faster pace in patients with more advanced disease. Virus isolated from most people with AIDS or

ARC shows a high level of AZT resistance after 6 months of drug treatment. But HIV from asymptomatic patients who have been taking AZT for 2 years shows only partial resistance. That may be because patients with more advanced disease have more virus, and the virus is multiplying faster; hence, it has more chance to generate the full complement of four mutations conferring high resistance. This finding supports the idea that early AZT therapy may be more beneficial than AZT administered after patients already have the full-blown disease. "Our impression is that very sick patients are getting a much shorter period of benefit," Larder told *Science*.

The benefits of early AZT therapy were also suggested by results presented at the conference by Margaret Fischl of the University of Miami Medical School. Fischl's data came out of a trial of high-dose AZT therapy for asymptomatic HIV infection conducted by the AIDS Clinical Trials Group (ACTG) of the National Institutes of Health. In that trial, known as 016, which was carried out for a year, about 350 patients received placebos and an equal number received AZT. Thirty-four in the placebo group progressed to AIDS or ARC, compared to 12 in the AZT group.

Last August, however, before the trial had run its full course, ACTG trial 019 showed that low doses of AZT could delay disease onset in asymptomatic patients. Trial 016 was then interrupted, and the remaining patients were offered low doses of AZT. Once they were on AZT, the rate of disease progression among those who had been receiving placebos fell to half its previous level, Fischl said, but overall they still have not done as well as those who were on AZT for the entire period.

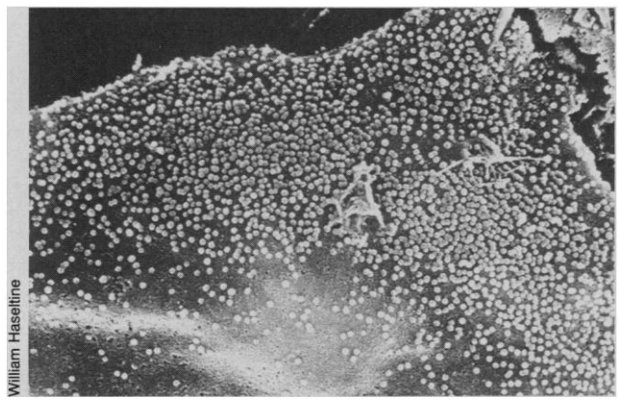
The likely reason, according to Fischl, is that although all the patients remaining in the trial last August were still asymptomatic, those who had been in the placebo group had more advanced disease before they began taking AZT. "There was some loss of the benefit of the drug by delaying therapy," she says. "Intervention should occur as early as possible."

But even if the results of early AZT therapy are encouraging, AZT is hardly a panacea. Some AIDS patients do poorly on AZT, either because of resistance or because of side effects that include severe anemia. While the search continues for more and better drugs, those drugs already available are being tried in combination with AZT, and conference participants heard some of the latest results of those combination trials, which have recently generated a good deal of interest.

One of the farthest advanced and most encouraging of them combines AZT with dideoxycytidine, or ddC, another reverse transcriptase inhibitor. Early results from trials of ddC alone were discouraging because a high number of subjects developed painful neuropathy and had to discontinue use of the drug. But a combination of ddC with AZT could reduce the side effects of both drugs and might also reduce drug resistance, since a mutant virus that eludes one drug could fall prey to the other.

In one trial, patients who took AZT in alternation with ddC on either a weekly or monthly basis had fewer side effects from either drug. In addition, the alternating scheme seemed to increase the beneficial effects of the drugs to a level that was greater than that of a therapy regimen of either drug taken alone, according to Thomas Merigan, of Stanford University, who presented some of the findings in San Francisco.

NCI's Yarchoan says combination trials show great promise. "All the drugs available now have low therapeutic indexes"—meaning that the effective dose is close to the toxic dose. Therefore, Yarchoan adds, "changing the way they're given can actually make a big difference."



William Haseltine

Within a budding grove. *William Haseltine and his colleague Heinrich Goettlinger have made a mutant AIDS virus that forms buds but does not detach from the host cell; here an infected cell is covered with stalled buds. This feat, accomplished by a mutation in the gene for the HIV capsid protein P6, might define a new target for AIDS drugs.*

Another bright spot at the meeting was a promising new class of drugs called the TIBO (tetrahydro-imidazo-benzodiazopinone) derivatives. All of these agents are relatives of the benzodiazopenes (the group that includes valium), and in a massive screening of more than 80,000 potential new drugs in Belgium they were found to have anti-HIV activity. The most potent member of the class has anti-HIV effects that are highly specific, and are based on an inhibition of reverse transcriptase that is five times as powerful as that of AZT. The drug is being tested in a small clinical trial in Europe, said Eric De Clercq of the Rega Institute for Medical Research in Belgium. Early results show TIBO is not toxic, but De Clercq cautioned that it is too early to draw any conclusions about its benefits.

While some of the results presented to conference attendees on molecular biology and clinical work were quite novel, the results on the epidemiological side were "not surprising, but concerning," according to James Curran, director of AIDS programs at the Centers for Disease Control in Atlanta.

In the United States, the pattern of the epidemic continues to change, as AIDS spreads from the original risk group—gay men—into minority populations. That shift was illustrated at the conference by a 1988–89 CDC study that used random sampling of blood from newborns to determine the infection rate among childbearing women. The overall infection rate was found to be 0.15% for childbearing women nationwide—not such a startling figure. Yet among black women the rates were 5 to 15 times higher than they were among white women.

The infection rate is also high in some groups of adolescents and young adults. A study of 15- to 20-year-old runaways in Florida, Louisiana, Texas, and New York found rates ranging from 2.1% in Texas to 5.7% in New York. And a recent CDC study showed, that among 20- to 24-year-old gay and bisexual men who were coming to sexually transmitted disease clinics in 44 cities, the rate was 25%. "It's clear that prevention messages aren't reaching all teens," said Deborah Wendell, who presented the findings.

Because teenagers are notoriously impervious to perceptions of risk, those who work in AIDS prevention are wringing their hands as they look for effective education methods. And although the science of AIDS is yielding results, the outlook for the epidemic has its dark side. "I don't know what it's going to take to produce a behavior change in adolescents," said one AIDS prevention worker. "If it takes what it took in the gay community—watching large numbers of friends die—we're really up a creek."

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