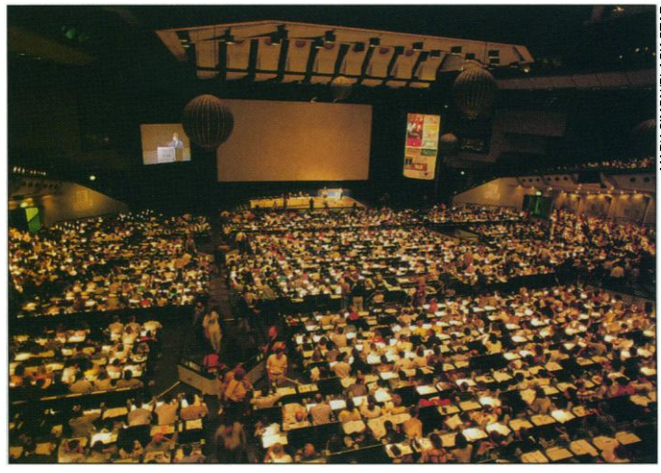
# Somber News From the AIDS Front

**Last week's mammoth AIDS gathering made it clear that, with effective drugs and vaccines still a long way off, only stepped-up preventive efforts can make a dent in the epidemic**

BERLIN—Some 14,000 of the world's leading AIDS researchers met in the futuristic International Conference Center here last week to exchange the latest information from the front lines of the battle against HIV. They came away with a simple message: back to basics. "Basics" in this case include some very straightforward—and definitely unglamorous—strategies, such as better treatment of sexually transmitted diseases other than AIDS. "Above all," said Michael Merson, head of the World Health Organization's (WHO) Global Programme on AIDS, "we must waste no time in scaling up the interventions that we know work."

Why, in this age of instant gene cloning and pyrotechnical retrovirology, should AIDS researchers be concerned about things as scientifically mundane as gonorrhea, syphilis, and chancroid? One reason is that, as several speakers noted, HIV appears to spread more easily among people carrying these diseases. But the more sobering answer is that the high-tech wizards don't have anything else up their sleeves that's even close to working against AIDS. Indeed, much of the most dramatic news at the conference was the drumbeat of downbeat reports on antiviral drugs. And the news from the preventive vaccine front was not much more upbeat, although a few promising leads were discussed.

Amid all this somber news, an observation repeated by several researchers did provide some hope for attacking HIV through the latest tools of molecular biology: Some people repeatedly exposed to the virus do not appear to get infected, and others who are infected do not appear to progress to AIDS. This observation focused attention back to another basic: the human immune system. As Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), put it while hustling between sessions, "The best antiretroviral in the world would be the immune system." Results from the most prominent effort to exploit natural immunity to HIV—tests of a therapeutic vaccine developed by Jonas Salk of polio vaccine fame—were greeted with both acclaim and savage criticism, however.



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**Gathering of the AIDS clans.** Berlin's futuristic conference center.

### Drugs: low-octane performance

If Salk's vaccine had a hard time, it was nothing compared to the beating taken by anti-HIV drugs. A few months before the conference, a large French-English trial, known as Concorde, had reported that AZT, currently the most widely used anti-AIDS drug, offers little benefit early in HIV infection. These findings sparked a heated transatlantic debate when they were recently published in a letter to the *Lancet*. Part of the outcry centered on the fact that the *Lancet* paper offered little data, yet the authors made some strong statements. What is more, a similar, although shorter, study in the United States came to a different conclusion—AZT appeared to delay the onset of symptoms. The stage was therefore set for a showdown in Berlin, where the Concorde data were discussed in two different sessions.

By the time these sessions were over, however, there was general agreement that the Concorde conclusions are valid. "I think the Concorde was an excellently performed study," said Fauci, who stressed that AZT does offer limited benefits to some people.

Another antiretroviral study that caused emotions to flare involved a combination of AZT and the drug ddC. The NIAID-sponsored trial had a total of 991 patients, 83% of whom had full-blown AIDS. Researchers had hoped that pairing AZT and ddC would help reduce the problem of drug resistance—and thus improve the efficacy of the treatment—that typically develops within a year of therapy with AZT alone. When Margaret Fischl of the University of Miami presented the results of this trial, one of the meeting's testiest public shouting matches ensued.

Fischl reported that, on the whole, the combination did not slow disease progression more than AZT used alone. But she said that AZT plus ddC did appear to be more effective for patients with more intact immune systems—those who had counts of CD4s, the key white blood cells that HIV destroys, between 150 and 300. Indeed, a NIAID press release distributed at the meeting highlighted this point. But NIAID, concerned that too positive a spin was being put on the data, later recalled it.

Fischl's focus on the subgroup analysis during her formal presentation of the data angered several infected people in the audience. David Barr of Gay Men's Health Crisis, for example, strongly objected when Fischl finished her talk and it was opened up for questions. Barr, who is infected and has been taking a combination of AZT and ddC for 2 years, criticized the post hoc decision to separate out one group. "The fact is the combination doesn't work," contended Barr.

### Boosting immunity

There is, however, one antiretroviral that does work powerfully, at least in some people at some times: the immune system. As the Berlin meeting showed, more and more researchers are trying to enlist its help in their attacks on HIV.

For several years now, enthusiasm has steadily been building behind the notion that infected people who remain healthy despite being infected with HIV for many years may provide answers to the puzzle of how to prevent the disease from progressing. Now a consensus is building that cell-mediated immunity, or CMI, is crucial in protecting these people against the ravages of AIDS. The CMI arm of the immune system attacks already-infected cells. In contrast, the humoral arm produces antibodies that latch onto free floating viruses and prevent them from infecting cells in the first place.

CD8+ T cells are the stars of the CMI system. Not only can they kill infected cells, but Jay Levy of the University of California, San Francisco, has found that they secrete an as-yet-unidentified soluble factor that sup-

presses replication of HIV in infected cells. Levy, who has long been searching for this soluble factor, has been studying HIV-infected people who remain healthy for up to 15 years. He boldly concluded at the end of his plenary talk that "efforts directed at these cellular immune processes and attention to the CD8-positive cell antiviral factor could lead to long-term survival for all HIV-infected individuals."

Fauci described a study that may be boosting CMI in people whose immune systems have been seriously damaged by HIV. NIAID's Clifford Lane and Joseph Kovacs have been infusing patients with interleukin-2 (IL-2), a chemical messenger that is known to stimulate CMI. Two patients repeatedly infused with IL-2 had enormous boosts in their number of CD4 cells—one skyrocketed beyond the number seen in normal patients. Fauci cautioned, however, that it is premature to draw conclusions from this study because it involved so few patients.

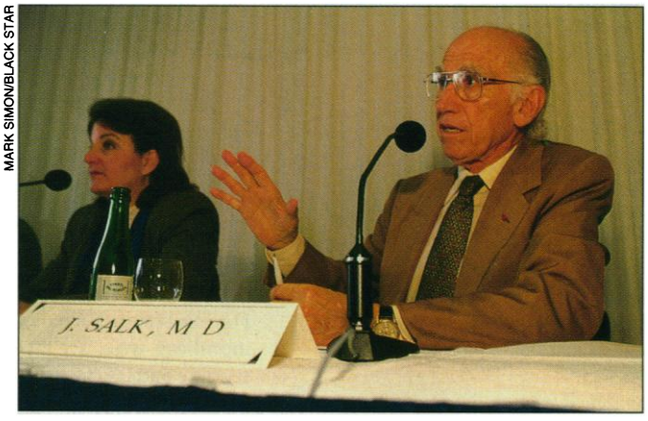
Jonas Salk also is a CMI acolyte. An early proponent of using HIV vaccines to treat already infected people, Salk believes he has evidence that the approach can boost the immune system, making it perform beyond its normal capacity. Since 1987, Salk, along with California's Immune Response Corp. (IRC), has been testing an HIV vaccine made from whole, killed virus (minus part of HIV's surface protein) in infected people. At Berlin, much-anticipated results were presented from a double-blind, placebo-controlled trial that ran for 1 year and involved 103 patients.

A great deal of hoopla surrounded the presentation of the data, which had never been revealed. With stock market analysts talking on cellular phones and throngs of TV cameras and journalists recording the event, Alexandra Levine from the University of Southern California presented the findings. Levine, who has been testing the vaccine since the start, said that tests of blood samples using the polymerase chain reaction, or PCR, showed that the amount of HIV in the untreated group rose faster than in the treated one. Levine also showed data suggesting that the vaccine had positively affected the immune systems of the treated group.

While observers like David Ho of the Aaron Diamond AIDS Research Center had serious questions about the PCR assay's margin of error, others were skeptical about the meaning of the small changes observed. "It's difficult to tell whether those changes are going to mean anything at all," said Dani Bolognesi of Duke University. "There's not much precedent for this type of approach and my sense is it's going to take a lot of change to convince people. I didn't see a lot." IRC and its joint partner, Rhone-Poulenc Rorer, said they are planning to carry out longer and larger trials.

As for preventive vaccines, researchers don't know what works, but a few hot leads have recently surfaced. Like several other researchers, the University of Manitoba's Francis Plummer has been evaluating people who presumably have been exposed to HIV but have not become infected. Plummer, who works in Kenya, has been studying prostitutes in Nairobi since 1985. Out of 263 of these prostitutes, 24 have remained free of HIV infection for more than 2 years even though they have had an average of four partners a day. "We started out thinking about why people get infected and then started asking why people don't," says Plummer. He has preliminary evidence that the answer may lie in the fact that the uninfected women have rare alleles to genes coding for the class I major histocompatibility complex (MHC I), an integral part of the immune system that allows the body to distinguish self from nonself.

Mario Clerici and Gene Shearer of the National Cancer Institute are also pioneering studies with people who presumably were exposed but remain uninfected. They have found evidence of a strong CMI response, but no antibodies to HIV, in many such people. In Berlin, for the first time, Clerici described experiments to see whether a similar pattern shows up in macaque monkeys. Clerici found that four monkeys exposed rectally to low doses of SIV, the simian cousin of HIV, did not become infected with the virus. The monkeys did not develop antibodies to SIV, but they did show evidence of a CMI response. He now is "challenging" these monkeys with infectious doses of live SIV to see whether their CMI responses had protected them.



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**Immune reaction.** Alexandra Levine and Jonas Salk describe their long-awaited results to a skeptical audience.

### Basic prevention

While Clerici and a host of other researchers test out their theories, something needs to be done about the epidemic now—and that's where control of sexually transmitted diseases (STDs) fits in.

Though it has not been definitively proven that controlling STDs can prevent HIV infections, Marie Laga of Belgium's Institute of Tropical Medicine made a convincing case in her plenary talk that, for much of the world, this strategy is currently the most powerful tool available. "In most countries, STD control has been a failure or has not been attempted at all," said Laga, who has conducted STD studies in Africa.

The link between STDs and HIV infection is clear. Laga cited epidemiological evidence in both the United States and Africa, focusing on one Nairobi study showing that female to male transmission of HIV was five times more likely when the women had a genital ulcer. She also cited what she called "staggering" numbers about the prevalence of STDs in commercial sex workers: More than 35% of commercial sex workers in the Ivory Coast and Kenya had gonorrhea, more than 20% had syphilis, more than 15% had a genital ulcer, and more than 90% were infected with HIV.

Laga presented evidence from several investigators that might explain why STDs appear to increase the risk of HIV infection. One is that the inflammation associated with STDs means more white blood cells are present, and white blood cells can harbor HIV. Indeed, tests with PCR have shown that HIV is more frequently found in cervico-vaginal secretions of infected women who have cervical inflammation.

A presentation by WHO's Merson strongly echoed Laga's plea for more attention to STDs. Merson also implored scientists to develop a vaginal microbicide that could defeat HIV and other pathogens, and he called for better promotion of condom use and needle exchange for intravenous drug users. A new WHO study estimates that such a comprehensive prevention effort in developing countries would cost between $1.5 billion and $2.9 billion a year. WHO projections, said Merson, show that this type of effort could slash in half the number of new infections expected by the year 2000 from 20 million to 10 million. "The world can find this kind of money when it wants to," declared Merson.

Merson later stressed that he is not attempting to create a dichotomy between AIDS research and AIDS prevention. "Our priority is to give people the best they can get, but in developing countries, antiretroviral drugs are not realistic options." As the meeting made clear, realistic options, basic as they may be, are the only things right now that have a shot at denting the epidemic.

**–Jon Cohen**