Researchers Look Ahead to AIDS Meeting

There is growing optimism about vaccine prospects, but no startling developments are expected in San Francisco

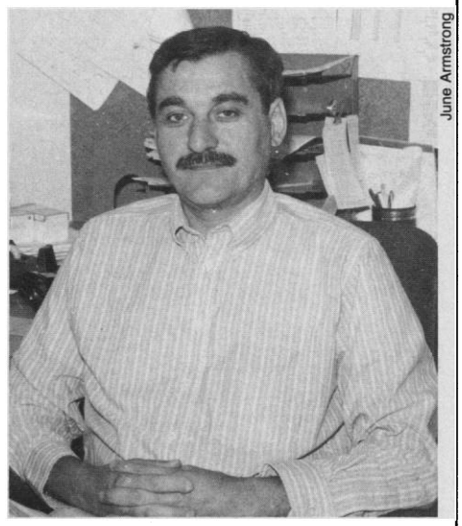
As the Sixth International AIDS Conference approaches, the possibility that the meeting will be disrupted by activists is capturing the lion's share of attention (see box, p. 1181). But what about the science, you may ask. The conference will, after all, feature some 2500 talks and posters detailing the results of research on all aspects of AIDS. Although AIDS experts don't expect any startling developments in San Francisco, they do expect to see a continuation of the steady incremental progress toward understanding HIV, the virus that causes AIDS, and toward developing effective AIDS vaccines and therapies.

The past year has, for example, seen a marked upturn in optimism about the feasibility of an AIDS vaccine, a switch from the previous pessimism that had been fueled by several experimental failures, as well as by knowledge of the insidious way that HIV invades and destroys key immune cells.

But last year researchers began getting positive results in monkeys for the first time. Experiments, conducted independently by the teams of Ronald Desrosiers at the New England Regional Primate Center in Southborough, Massachusetts, Michael Murphy-Corb of the Delta Regional Primate Center in New Orleans, and Murray Gardner at the University of California at Davis, showed that rhesus macaques could be protected against the AIDS-like disease caused by simian immunodeficiency virus (SIV), an HIV relative, if they were first immunized with whole killed SIV.

Although promising, these results led some researchers to suspect that effective protection could be achieved only with whole killed virus, a vaccination method considered by many to be too risky. The concern is that whole virus preparations might be incompletely inactivated or the genetic material that they contain might recombine with the genes of another virus to generate a disease-causing hybrid.

But recent findings suggest that something less than a whole virus might work, says Dani Bolognesi, an AIDS vaccine researcher at Duke University School of Medicine. Preliminary results from a number of groups indicate that animals might be successfully immunized with viral proteins or protein fragments. One such report has come from Marc Girard of the Pasteur Institute in Paris. At an AIDS meeting held in April in Keystone, Colorado, he presented the results of experiments in which chimpanzees were protected from HIV infection with a cocktail of HIV proteins. And Genentech, Inc., of South San Francisco announced last week that two chimpanzees had been protected from HIV infection by vaccination with a viral coat protein. More reports of successful immunization with proteins or peptides are expected at the San Francisco conference, Bolognesi says.



June Armstrong

Protecting monkeys against SIV. *Ronald Desrosiers leads one of the groups working with animal AIDS models.*

He points out that some big obstacles still lie ahead, however. "What is being done now are the most simple experiments you can do," he says. In the successful experiments so far, vaccinated animals have been challenged by injecting them intravenously with the same viral strains used for their immunization. But that laboratory situation does not reflect the real-life transmission of the AIDS virus.

For one, the virus is extremely variable and to be effective a vaccine must protect against any strain a person might encounter. There are hints that immunization with one strain might protect against another, most notably in experiments by Erling Norrby of the Karolinska Institute and Gunnel Biberfeld of the National Bacterial Laboratory in Stockholm. These researchers vaccinated three cynomolgus macaques with HIV-2, a close relative of SIV, and subsequently challenged the animals with SIV. They did not come down with disease. "This means we can obtain broad-spectrum protection within a type," Norrby told *Science*.

The Swedish workers used live HIV-2 for the vaccination, however, an option no one wants to attempt with the dangerous AIDS virus. In the next round of experiments, they will try vaccinating with killed HIV-2.

But even if cross-protection against multiple AIDS virus strains can be achieved, other hurdles will remain, such as the problem of producing immunity against cell-associated virus, something that has been traditionally possible only with live attenuated viruses. These, like whole, killed vaccines, carry the potential risk of regenerating a virulent virus strain.

One strategy Gardner, Murphy-Corb, and others are considering is developing local forms of vaccination that would raise antibodies in the mucosal membranes of the rectum or reproductive tract, through which the virus must pass during sexual transmission, to nab the virus before it can enter the bloodstream and gain refuge in blood cells. But that still doesn't address the problem of virus that enters the bloodstream already in cell-associated form.

So while AIDS experts are more hopeful than before about an AIDS vaccine, they do not expect one soon. Moreover, some 5 million people worldwide may have already been infected and will eventually develop AIDS. So the need for effective AIDS therapies will continue to increase for the foreseeable future.

Here the principal message from the past year is that less may be more. The anti-AIDS drugs furthest along in the clinical pipeline are AZT, already approved by the U.S. Food and Drug Administration, and two newer and still experimental drugs called ddI and ddC. They all work by inhibiting reverse transcriptase, an enzyme needed for the virus to reproduce itself, and the use of

Danforth Reapproached

Washington University chancellor William H. Danforth has been approached by Health and Human Services Secretary Louis Sullivan to be director of NIH, *Science* has learned. Danforth, who declined to be considered last year when a White House aide asked him his views on abortion, is the only candidate Sullivan is known to have called. ■ B.J.C.

AIDS Conference: Science or Circus?

The Sixth International AIDS Conference in San Francisco promises to be too large—and too tumultuous—for the tastes of some scientists. Despite the call for a boycott by some AIDS activists who disagree with the U.S. policy that restricts the entry into the country of AIDS-infected people, conference organizers say that registration is keeping pace with that for last year's meeting, which was held in Montreal. They expect 10,000 to 12,000 participants, the maximum the facilities can hold. But that number will be dwarfed by the 100,000 to 200,000 gay activists expected in San Francisco for that city's annual Gay Pride parade, scheduled for the last day of the conference. AIDS activists are hoping Gay Pride marchers will come early and join the conference picketing, a prospect that has given conference organizers and participants the jitters.

"I'm very concerned, like everyone else, that the meeting is going to be a zoo," says AIDS researcher Jerome Groopman of the New England Deaconess Hospital in Boston.

"Security is an important issue, there is no question about it," agrees conference program director Robert Wachter of the University of California, San Francisco, who adds that the organizers are working out a security plan with the San Francisco police and mayor's office. "We are highly concerned about disruptions."

And such concerns may not be an overreaction. Larry Kramer, AIDS activist and founder of ACT UP (the AIDS Coalition to Unleash Power), called for "massive disruption" and rioting at the AIDS conference in a column in the 14 March issue of the New York gay weekly, *OutWeek*. His column, entitled "A Call to Riot," has since been widely circulated in the gay community. And it's not as if things have been balmy between AIDS activists and the research community. On 21 May, for example, 82 activists were arrested during demonstrations at the National Institutes of Health in Bethesda and Rockville, Maryland.

Still, ACT UP, along with other AIDS activist groups, are distancing themselves from Kramer's remarks. "There has been no call for violence by any ACT UP [chapter] in the country," says Bill Struzenberg of ACT UP San Francisco. "We are not a violent organization."

But disruption is distinct from violence, and activist groups are promising demonstrations that could range from picketing with placards in the street to an occupation of the conference hall. One of the activists' main goals is to speed up what they view as the slow pace of development of AIDS therapies.

Meanwhile, the conference organizers are attempting to head off trouble in San Francisco. If there are demonstrations, Wachter says, they will arise not from anger at the conference format, but from anger over drug development and other AIDS issues.

The organizers have worked closely with the AIDS activists for over a year, to be sure the activists' perspective was represented in the program. Representatives of community groups have been included throughout, and well-known activists Martin Delaney, of Project Inform, and Larry Kramer himself are scheduled to speak. Moreover, for the first time, scholarships have been provided to allow 375 people infected with the AIDS virus to attend for free. "From the standpoint of conference organization, I think we've done everything we can do," Wachter says.

But even if demonstrations are held to a minimum, some researchers will still have reservations about the AIDS conference in its current format. They argue that it has become too big and tries to cover too many topics, everything from the basic molecular biology of the AIDS virus to social and policy issues, for meaningful scientific exchange.

Rich Lipski, **Washington Post**

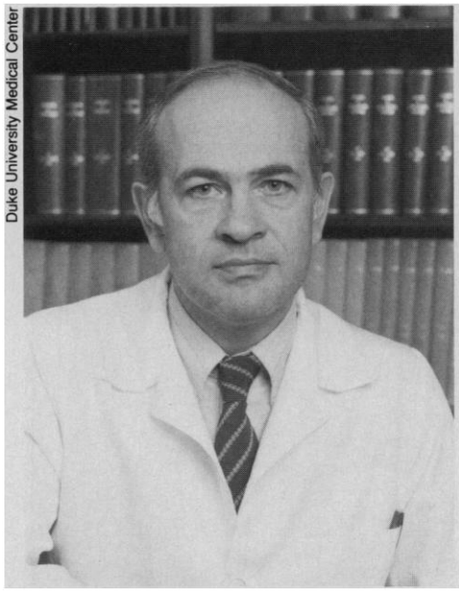
San Francisco preview? *AIDS activists hold demonstration at the Bethesda campus of the National Institutes of Health.*

Smaller meetings, such as the UCLA Symposium on AIDS, which was held last April in Keystone, Colorado, with only 600 participants, are more useful, Groopman says, because "you can talk, exchange information, and have critical discussions. You can't do that with 4000 people in the audience, newspaper reporters, and ACT UP demonstrators. It just doesn't work."

Donald Abrams, of UC San Francisco, says that some of the discontent may arise from the pendulum swings the conference has taken in the past 2 years. He recalls that the AIDS conference held 2 years ago in Stockholm was weighted heavily toward basic and clinical science. Last year, he says, the Montreal organizers may have overcompensated, sacrificing too much science to make room for policy. In trying to strike a balance, this year's organizers have made social science and policy one of four equally weighted tracks, along with basic science, clinical science and trials, and epidemiology and prevention.

There has been talk for several years of splitting the conference into two—one meeting for laboratory and clinical science, and the other for social science and public policy. But San Francisco's Abrams says that would be a mistake. "One has to come to terms with the fact that this won't be an intense scientific session—the meeting has evolved to something other than that . . . it's more of a convention for people who have been tackling all the various aspects of the disease to come together and learn."

Conference organizers acknowledge that discontent with the meeting format has been running high. That puts the pressure on them and the attendees alike to maintain a reasonable balance between science and policy, keep disruptions to a minimum, and provide a more satisfying conference. Groopman thinks the days of a large, all-encompassing AIDS conference could be numbered. "If San Francisco fails," he says, "if the meeting is impossible to attend because there are people throwing bricks at cell biologists—then that will give a major impetus to reorganize the meeting." ■ **M.B.**



Seeing cause for optimism. *Dani Bolognesi points to several promising developments in AIDS vaccine work.*

all of them has been limited by their side effects. But newer work is showing that lower doses may not only minimize the drugs' harmful side effects, but may actually increase their benefits.

"We tended to [approach the] drugs with an oncology point of view, that it's probably better to give a little more," says Thomas Merigan of Stanford University. "Now we're in a more chronic disease treatment mode. With less [drug], we may be able to get more enduring effects on T4 cells; that's really going to be exciting, and we may hear more about that at the meeting."

If low doses can reduce the side effects of ddI and ddC, making them clinically useful drugs, says Merigan, they will likely be useful in alternation with AZT to prevent HIV from developing drug resistance.

There are several potential AIDS drugs that act at sites other than reverse transcriptase, although it is too soon to tell how effective most of them will be since they have had little or no clinical testing yet. For example, the protease inhibitors, which block an enzyme needed for the formation and maturation of AIDS virus particles, are just beginning to move from test tube to clinical studies, says Robert Yarchoan of the National Cancer Institute, but clinicians will be eager to hear the reports on them at San Francisco because the drugs may provide a second point of attack on the AIDS virus.

Meanwhile, α-interferon is one drug that already has shown promise in clinical trials. In a recent development, Clifford Lane of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, and his co-workers published a study in the 1 June issue of the *Annals of Internal Medicine* that indicated that the interferon slows the development of disease in people who are infected by the AIDS virus but not yet symptomatic. Even if drugs such as interferon don't turn out to be as effective as AZT, Lane says they offer promise in combination therapy. The early results of such combination regimes should be presented at the conference.

The molecular biology of the AIDS virus will also be a major topic at the conference and a recent finding in that area may shed some light on one of the enduring mysteries of the AIDS epidemic: Where did the virus come from? The epidemic only became apparent about 10 years ago. Had the causative agent been present in isolated groups and not noticed until it made its way into the more general population? Or was it new to the human population, perhaps transmitted from another primate?

In the 24 May issue of *Nature*, Simon Wain-Hobson and his colleagues at the Pasteur Institute report that they have isolated a virus from the chimpanzee that may be the missing link in HIV-1 evolution. The new virus is more closely related to the AIDS virus than any of the other animal and human immunodeficiency viruses found so far.

If the virus is a bona fide chimpanzee virus, Desrosiers wrote in an editorial accompanying the article, that might suggest that chimpanzees were the source of human HIV-1. But even if they were, Wain-Hobson points out, that doesn't mean that transmission to humans was coincident with the beginning of the AIDS epidemic. It could have occurred 100 or more years ago, and only blossomed into an epidemic with recent population movements.

But wherever the AIDS virus came from it has now spread around the world. And while the activists will be sounding a loud message that governments should be doing more to combat the disease, the quieter message coming from the scientists is that the AIDS virus is yielding its secrets, but slowly. ■ **MARCIA BARINAGA**

One Step Closer for Gene Therapy

Later this year, a young child whose life is threatened by severe immune deficiency disease is likely to be the first patient to receive true human gene therapy.

Last week the National Institutes of Health's human gene therapy subcommittee unanimously endorsed a proposal by R. Michael Blaese of the National Cancer Institute to try to correct ADA, or adenosine deaminase, deficiency by inserting the ADA gene into patients who are not doing well with alternative methods of treating this disease. The disease leaves its victims vulnerable to infections that usually take their lives during adolescence, if not before.

For some of the world's handful of ADA patients (there are probably no more than 50 worldwide) bone marrow transplantation has proved to be a useful therapy. Others are resisting infection with the help of a drug called PEG-ADA, which is injected once or twice a week. But some patients are not good candidates for marrow transplantation and are not doing well enough on PEG-ADA to be considered effectively treated. (The drug is not a cure.) It is these patients—perhaps four or five in number—who will be considered for the NIH experiment.

The subcommittee's enthusiastic endorsement of the experiment, a collaborative study that also includes W. French Anderson and Kenneth Culver of the heart institute, and NCI surgeon Steven A. Rosenberg, came as something of a surprise in light of the panel's fractious review of a draft of the protocol 2 months ago (*Science*, 13 April, p. 159). By contrast, last week's meeting was a paradigm of reasoned discourse.

In the interim, two things happened to change the subcommittee's collective mind. First, Blaese and Anderson redrafted their protocol, making substantive changes that included a new definition of which patients will be eligible for the first trials. In addition, colleagues in Italy completed studies in SCID mice (animals with severe combined immunodeficiency) that provide good experimental data to support the likelihood that the Blaese-Anderson experiment will work.

Technically, the subcommittee's approval at its 1 June meeting was provisional, pending further modifications in the gene therapy protocol that were worked out during the meeting. If all goes well, final approval will come on 30 July when the subcommittee meets jointly with its parent body, the NIH's recombinant DNA committee whose "Yes" vote is also required before final approval is sought from the director of NIH and the Food and Drug Administration which also has jurisdiction.

■ **BARBARA J. CULLITON**