Research News

New Hope on the AIDS Vaccine Front

Vaccination protects chimpanzees against the AIDS virus. Other developments include new genes for the virus and a disturbing finding about the virus variability.

NEW DEVELOPMENTS reported at the International AIDS Congress in Montreal are lifting the fog of gloom that has enshrouded efforts to develop an AIDS vaccine for the past few years. Two separate groups of researchers, using different approaches, have for the first time shown that vaccination can protect chimpanzees against infection by the AIDS virus. "Some of the animal experiments are turning out now. A year or two ago things were much bleaker," says Dani Bolognesi of Duke University School of Medicine, who is a member of one of the groups.

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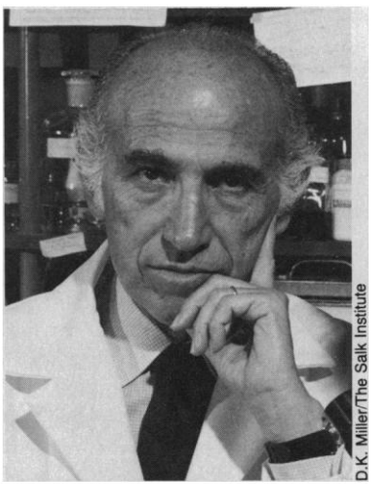


D.K. Miller/The Salk Institute

Alexandra Levine and Jonas Salk: *the results they reported on vaccine work in humans and chimps caused a stir.*

By far the most controversial vaccine approach is that of polio-vaccine developer Jonas Salk, director of the Salk Institute in La Jolla, California. He engendered a great deal of skepticism a year or two ago when he proposed that it might be possible to use an inactivated AIDS virus to boost the immunity of people who had already been infected and thereby keep them from developing full-blown AIDS.

Salk was proposing to use a preparation that includes the viral genetic material. The fear was that if the viral material were not completely inactivated, the AIDS virus might reproduce in the patients, possibly making them worse instead of better.

At the AIDS conference, however, Salk and his colleagues Clarence Gibbs of the National Institute of Neurological and Communicative Disorders and Stroke in Bethesda, Maryland, and Alexandra Levine of the University of Southern California in Los Angeles had only positive results to report.

In one series of experiments, Gibbs vaccinated three chimpanzees, two of which had already been infected with the AIDS virus, with the inactivated virus preparation. After the vaccination, the AIDS virus could no longer be isolated from the previously infected chimps. "That's the fascinating part—that they were able to clear the infection. That is very surprising," Bolognesi says.

There may be a handful of exceptions, but people who have been infected with the AIDS virus have not been able to rid their system of it. That was another of the reasons for the original skepticism about Salk's AIDS vaccine proposal.

Not only were the two chimpanzees able to rid themselves of their original infections, but their immune systems were apparently able to fight off the AIDS virus when they were subsequently challenged with high doses of the active agent some 13 to 15 months after the original vaccination. "The two previously infected chimpanzees did not get superinfected. We have not been able to isolate the virus from them," Gibbs told a crowded press conference.

The third animal, who had not been exposed to the active virus before, did become infected by the challenge dose, but only transiently. "We have somehow ameliorated the course of infection in this animal," Gibbs says.

Levine, meanwhile, has vaccinated 19 people who have AIDS-related complex, a mild form of AIDS that usually progresses to the full-blown disease, with the inactivated AIDS virus preparation. Although it is not possible to tell whether the vaccination has helped these patients, it does not appear to have hurt them. None has suffered any serious side effects during the year since they have been vaccinated, and only two have developed AIDS.

The vaccination also appears to have improved the cell-mediated immune responses of the patients. If so, this could be very important. Most researchers think that control of AIDS will depend as least as much on priming immune cells to kill cells infected by the AIDS virus as on stimulating the production of "neutralizing" antibodies that recognize and inactivate the virus itself.

In fact, a series of failed experiments had raised serious doubts about whether neutralizing antibodies would work at all. But that situation, too, is getting better.

Now, researchers have shown that neutralizing antibodies do have a protective effect against the AIDS virus. The findings are the result of a collaboration between the groups of Robert Gallo at the National Cancer Institute, Scott Putney at Repligen Corporation in Cambridge, Massachusetts, Emilio Emini at Merck, Sharpe, & Dohme Research Laboratories in West Point, Pennsylvania, and Duke's Bolognesi.

These researchers have found that a specific segment of eight amino acids on the envelope protein is particularly important in eliciting antibodies that neutralize the AIDS virus. According to Emini, if neutralizing antibodies directed against this target are mixed with the AIDS virus before it is inoculated into chimpanzees, the infectivity of the virus is diminished. "We have established a correlation between the ability of the antibody to neutralize the virus and the ability to protect in vivo," Emini says.

Although the new findings raise hopes that vaccination can prevent AIDS infections, Jay Levy of the University of California, San Francisco, pointed to a potential hazard in efforts to raise antibodies to the AIDS virus. His group has found that some of the antibodies made by people infected with the virus may actually contribute to the worsening of their condition.

Hecklers and Protesters Liven up a Dull Meeting

Canadians sometimes have an inferiority complex about their bustling, often contentious, neighbors to the south. But when it comes to throwing an AIDS conference, they have nothing to worry about. Not only was the fifth International Conference on AIDS, which was held in Montreal last week, bigger and even more crowded than the 1987 meeting in Washington, it was also at least as marked by protests and dissent. "There's nothing like it," says Dani Bolognesi of Duke University School of Medicine of the annual AIDS conference. He's right.

Some 10,000 participants—up from about 6,000 in 1987—crammed into Montreal's Palais de Congrès for this year's event, stretching the convention center to its limits, if not beyond. They were pursued by perhaps 1,000 members of the press.

There are bigger meetings. And many have more scientific news to report. Short of some encouraging progress with vaccine work, the Montreal crowd heard little that promised to revolutionize the attack on AIDS. But for hecklers and organized demonstrations the AIDS megameetings are hard to beat.

On Sunday, the opening ceremonies were delayed nearly 2 hours when a group of Canadian and U.S. AIDS activists took over the stage to declare "Le Manifeste de Montréal." Their demands: among other things, better medical care and civil rights safeguards for AIDS patients. Although few of the conference participants are likely to quarrel with those goals, the protesters' tactics were another matter.

After dominating center stage for more than an hour, the activists appropriated the seats reserved for Canadian Prime Minister Brian Mulrooney, Zambian President Kenneth Kaunda, and other dignitaries. One conference participant noted that he did not think that this was a fitting welcome, especially for the African health officials whose seats were usurped.

And there was a reason beyond mere good manners to welcome the Africans. In the past, some African governments have been reluctant to concede that they have an AIDS problem. But as shown by the substantial African presence at the Montreal meeting, the continent's officials and researchers are beginning to come to grips with the high infection rates occurring in some areas.

As to the cadre of AIDS activists at the meeting, they didn't stop at taking Canadian Prime Minister Mulrooney's chair. Just as then Vice President George Bush was booed at the 1987 Washington meeting, so too was Mulrooney heckled in his homeland.

But the most raucous demonstrations were reserved for New York City Health Commissioner Stephen Joseph, who noted wryly that he had brought his "cheering section" along with him. Members of the New York activist group, the AIDS Coalition to Unleash Power (ACT UP), booed, chanted, and jeered "Doctor of Death" and "Resign! Resign!" throughout Joseph's talk, often drowning him out.

Joseph is generally unpopular with AIDS activists, who view his department's efforts on behalf of AIDS patients as inadequate. But he also floated what may be the single most controversial suggestion to come out of this year's conference—namely that AIDS be made a reportable disease, much as tuberculosis is.

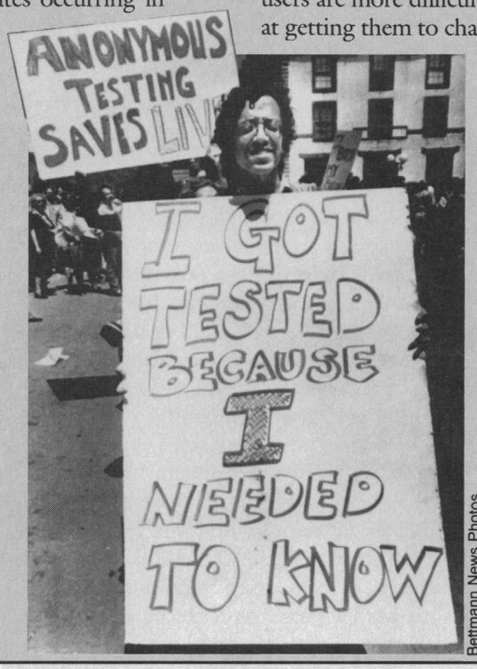
This would mean that testing for the AIDS virus would no longer be done anonymously. Instead, the names of those individuals who test positive would be reported to health authorities who could follow up to see that the virus-infected people received treatment. Any contacts to whom a virus-infected individual might transmit AIDS would also be traced.

These ideas are anathema both to AIDS activists and to some public health officials because of worries that people will be less likely to be tested and receive treatment if they think that their names will be become known and they will consequently become victims of discrimination.

But Joseph thinks that the time has come for a change in AIDS testing policies. As presentations at the conference showed, encouraging results in AIDS therapy and vaccine development are raising hopes of controlling or preventing the disease. If that comes to pass, Joseph maintains, it would warrant reporting persons infected with the AIDS virus, and tracing their contacts, because then these persons could be helped. In the past little could be done.

Whether or not mandatory reporting comes to pass, everyone does hope that the new vaccine and drug research will pan out. The need is still great. According to Jonathan Mann, director of the Global Programme on AIDS of the World Health Organization, the AIDS situation will be even worse in the 1990s than it was in the 1980s. From 5 to 10 million people worldwide have already been infected by the AIDS virus and may develop the full-blown disease over the next few years.

Also disturbing are findings that as the AIDS epidemic progresses, the burden of the disease is falling increasingly on the poorer, less educated members of society, and in particular on drug users. "This is a nearly universal trend," says Peter Piot of the Institute of Tropical Medicine in Antwerp, Belgium. Drug users are more difficult to reach with education campaigns aimed at getting them to change their behavior to prevent the spread of the AIDS virus.



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On balance, the news about potential new AIDS therapies and vaccines made the Montreal meeting less gloomy than the one in Stockholm. The meeting survivors nevertheless had an exhausting week. They were buffeted by crowds as they tried to sample the 5500 talks, posters, round tables, and other presentations offered up there. All too often, they found their way into popular sessions barred by the dreaded "Complet/Full" signs. And even when they did get into the lecture halls, they often could not read the slides because of an apparently unsolvable focusing problem.

The annual AIDS jamborees have drawn greater numbers year by year. Will the trend hold for next year's meeting in San Francisco? Everyone is waiting with bated breath. ■ **J.L.M.**

These "enhancing" antibodies, as they are called, do not neutralize the virus when they bind to it. Instead, Levy says, they may serve to promote the entry of the virus into cells, including macrophages, that the virus might not otherwise penetrate. There have been no problems with enhancing antibodies in the limited vaccine experiments so far.

No one is currently willing to predict how long it will be before an AIDS vaccine will be ready for human use. However, Bolognesi in his talk pointed out that when researchers were developing a hepatitis B virus vaccine, it took 10 years just to identify the viral antigen to use to stimulate a protective immune response. That is the stage that AIDS vaccine work is at now.

With the exception of the vaccine developments, scientific news from the AIDS conference was sparse. Still, there were a few surprises. Even the well-studied AIDS virus, known as HIV-1, has not yielded up all its secrets. William Haseltine's group at Harvard's Dana-Farber Cancer Center in Boston has found that the genome of HIV-1 has at least one, and perhaps two, previously unrecognized genes.

One of the new genes codes for a protein that stimulates the synthesis of HIV-1 proteins. "We believe it promotes the growth of the virus," Haseltine says. The Dana-Farber workers consequently call the new gene "*rap*" for "rapid growth gene."

The *rap* gene may have been missed in previous studies, Haseltine suggests, because the viral isolates used carried subtle mutations that inactivated it. The AIDS virus is notorious for its high mutability. A single infected individual can carry many different genetic variants of the virus.

The Dana-Farber workers have also discovered a second possible new gene in the HIV-1 genome, but have not yet found a function for it.

Simon Wain-Hobson of the Pasteur Institute in Paris also raised a warning flag about the extreme variability of the AIDS virus and what it might mean for attempts to correlate the molecular properties of the virus with its pathogenic effects in patients. Researchers have to grow the virus in cultured cells to get enough to study its molecular and genetic properties.

But Wain-Hobson and his colleagues have now compared gene sequences from cultured isolates with those of viral genes obtained from AIDS patients. "What we see in vivo is not the same as what we see in culture. To culture is to disturb," Wain-Hobson says. This means that studies of cultured virus isolates may not be relevant to what is happening in the patient. That, in contrast to the vaccine developments, is not good news. ■ JEAN L. MARX

Illuminating Jet Lag

Experiments show that bright light can reset the human internal clock by any desired amount, offering treatment for sleep disorders

WANT TO BEAT JET LAG? Spend a day at the beach once you get where you're going. That's the advice of sleep researchers Charles Czeisler and Richard Kronauer.

Czeisler and Kronauer headed a team of researchers from Brigham and Women's Hospital, Harvard Medical School, and Harvard University who studied how the human circadian clock responds to bright light. Their results, reported on page 1328 of this issue, indicate that our internal clocks respond to light in a fundamentally different way than previously thought. In particular, these clocks can be set forward or back as much as desired, with only two or three doses of light exposure. The discovery may open the door to treatment of sleep problems in not only international travelers but also shift workers and other people whose inner clocks malfunction for various reasons.

The claim of strong light resetting will be "very controversial among some people in our field," Czeisler predicts. Since the mid-seventies, many sleep researchers have held that humans are not sensitive to light resetting, and that people's internal clocks are synchronized by social contact. The new results contradict that view.

The first evidence that humans' internal clocks are indeed sensitive to light came in 1978, when Czeisler showed that ordinary room light of about 200-lux intensity is enough to synchronize the human circadian system to a 24-hour day. (Without some clues as to what time it is, a human's sleep/wake pattern, body temperature, hormone secretion, and various other physiological functions all follow a rhythm of approximately 25 hours.)

Then, in 1986, Czeisler began to wonder if he could take people whose circadian clocks were set to the wrong time of day and reset them. He exposed a 66-year-old woman with a chronic circadian disorder to 4 hours of bright light (7,000 to 12,000 lux, comparable to outdoor brightness at twilight) every day for a week, and even he was surprised at the result. Previous studies had shown that exposure to light would reset primate clocks by no more than 1 or 2 hours a day, Czeisler recalls, and "we thought her system would respond no more briskly than other mammals." Instead, within 2 days, the woman's clock was reset by 6 hours, enough to get her back in sync with the world.

Working from data obtained in resetting the older woman's clock, Kronauer, a mathematician, produced a theoretical model of how light affects the human circadian clock. Using the model as a guide, Czeisler began a new series of trials. He put subjects through 3 days of treatments, with 5 hours of bright light (about 10,000 lux) each day, timing the light at various points during the subjects' internal cycles.

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Airline terminal: *Circadian clocks awry.*

The results were dramatic. In subjects who were exposed to light during subjective nighttime, the treatment reset internal clocks by as much as 12 hours, unprecedented in human research.

The treatments involve more than simply exposing someone to bright light, Czeisler and Kronauer note. Getting the desired response demands timing the exposures properly. To this end, they have generated a phase response curve—a drawing that indicates how much a person's clock will be reset, depending on when the light exposures are given. ("Phase" refers to the time on a person's internal clock.)

Arthur Winfree, a specialist in circadian rhythms at the University of Arizona, says that as far as he knows this is the first published phase response curve for humans. He adds, however, that for years he himself has been using a "best guess" phase response curve gleaned from the little data available. To overcome jet lag when traveling, he spends a couple of hours in bright sunlight at the time indicated by the response curve—in the late afternoon after flying