ginning AZT, and whose pretreatment testing placed them in the 'normal' IQ range, also had significant increments in their IQ scores after beginning continuous infusion of AZT," Pizzo reported recently in "AIDS updates."* The findings suggest, he says, that subclinical brain damage may be an early manifestation of AIDS. The catch is one cannot spot the damage until there are signs of its repair.

Why does HIV injure the brain? Many hypotheses have been put forward. Some postulate that HIV stimulates production of toxins, or cytokines, or chemotactic factors that impair neurons and glial cells. Others propose that HIV is able to infect neurons and glial cells directly. The fact that these symptoms can be reversed suggests that "factors other than direct cellular damage by the virus" play a key role, Pizzo has reported.† If true, this is good news clinically. If you can stop a virus from making a product that destroys the brain, you can protect the brain even though the virus may not be completely wiped out.

This is what appears to be going on indirectly with AZT. The drug inhibits the reverse transcriptase enzyme that HIV needs to replicate. Studies have shown that HIV can be found in the brains of children and adults with AIDS dementia, and data from adults support data from children that if you can suppress the virus you can control (or at least modify) the neurological damage. Richard W. Price and his colleagues at the Sloan-Kettering Memorial Hospital in New York published a review of the data from adults last year in *Science*.‡

Although the infecting virus is the same, the course of AIDS is different in children and adults—the onset of dementia being one of the more notable. In adults, dementia is usually a late-stage complication; in children it shows up very early on.

"The way we give AZT or other antiretroviral drugs may be crucial," says Pizzo, who advocates continuous infusion or sustained-release capsules for children and adults because the drug has a short half-life and has to be taken every 4 hours, round-the-clock. A steady state of drug keeps the virus at bay. Low levels of virus mean minimal levels of toxin production, which means maximum protection for the brain. Continuous infusion through an implanted device has long been used for cancer therapy. Sustained-release is common in cold capsules.

But the good news about AZT must be seen in context with the bad. Although AZT can reverse dementia, there is no evidence that it can cure AIDS. Ultimately, the children die. Furthermore, AZT's toxicity puts limits on its use; eventually the dose must be reduced or stopped altogether. The brain again becomes vulnerable to HIV and dementia returns. One of Pizzo's longest success stories is that of a hemophiliac who contracted AIDS from a blood transfusion. For 2 years, AZT kept him intact. At one point so mentally debilitated that he could not go to school, AZT therapy enabled him to resume the life of a normal 12 year old. But when AZT finally took its toll on the patient's bone marrow and the AZT dosage had to be reduced, the boy deteriorated. In the end, he died.

"It leaves you feeling terrible, like you failed," Pizzo says. "But we've learned from parents that even if we cannot save their children, it is crucial that we reverse the dementia at least for a while. Parents tell us that it has given them a chance to say 'goodbye' to their child and that they are grateful for that." ■ **BARBARA J. CULLITON**


ADDITIONAL READING

*"Therapeutic considerations for children with HIV infection," *AIDS Updates* (May/June 1989).

†"Human immunodeficiency virus infection in children," *J Pediatr.* **114**, 1 (January 1989).

‡"The brain in AIDS: Central nervous system HIV-1 infection and AIDS dementia complex," *Science* **239**, 586 (5 February 1988).


# Hope for AIDS Vaccines

*Yverdon les Bains, Switzerland*

Pessimism about the prospects for a vaccine against HIV infection is giving way to guarded optimism. That, at least, is the opinion of Gordon Ada, chairman of the World Health Organization's Programme for Vaccine Development, after listening to a group of leading AIDS researchers discuss their latest results at an international meeting here. The gathering was organized by the Institut de la Vie, a Paris-based foundation.

Although no one approach to vaccine development is yet ready to sweep the field, there are several lines of research that, taken together, are producing the recent optimism. In fact, some new approaches are moving along so well that Ada is worried that older, less fashionable approaches may be overlooked.

***A radical idea for a genetically engineered live HIV vaccine is being pursued, but testing might pose a problem.***

One of the most welcomed talks at the meeting came from Dino Dina, director of virology at Chiron Corporation in Emeryville, California. Dina presented promising data from a trial in human volunteers of a vaccine consisting of one of the outer proteins of human immunodeficiency virus (HIV) grown in yeast cells.

Tested on people, it produced no side effects other than what Dina described as "mild stinging pain" that generally vanished after a few hours. While he is withholding full details until publication, Dina told *Science* that "results . . . indicated that the vaccine was safe and induced T-cell immunity."

A promising result in animals that had the meeting participants buzzing comes from the New England Regional Primate Center (*Proc. Natl. Acad. Sci. U.S.A.*, 2 August, p. 6353). Trials there tested killed simian immunodeficiency virus. Normally, SIV isolated from African monkeys causes severe illness and death when injected into Asian macaques. But a group of macaques immunized with disrupted SIV and then injected with live virus has not yet come down with simian AIDS.

"So far it looks like delayed disease, not success yet," commented Robert C. Gallo of the U.S. National Cancer Institute. "Maybe next year all the animals will get AIDS." But Dani Bolognesi of Duke University Medical Center reminded Gallo that "some of those experiments with killed virus also protected against infection, and that is something. We don't know what, but we have to find out."

Researchers at the meeting generally agreed that the most exciting animal model for testing candidate human vaccines is the so-called scid-hu mouse. These mice suffer from a genetic disease called severe combined immune deficiency, scid, which leaves them open to opportunistic infection, much like AIDS patients. But by transplanting human immune cells into them, they gain some human immune responses. They become, in effect, a living in vitro system, where the mouse is the test tube with its cargo of human cells.

Gallo, however, remained skeptical: "It's not much different than having a test tube," he said. Other researchers were more supportive. If SyStemix, a California company working with scid-hu mice, can put the complete human immune system into the scid mouse, it will open the door to much more thorough testing of potential vaccines.

Despite the apparent good news from inactivated viruses, Ada pleaded for scientists to focus on live vaccines, pointing out

that almost all the successful vaccines of the past have been able to multiply in the subject. A growing organism is particularly potent at stimulating all facets of the immune system. It provokes the immediate production of antibodies to neutralize the infection, stimulates the cells needed to kill infected cells, and also generates the immune memory that ensures a swift and lasting response in case of a future infection.

A live vaccine based on a weakened strain of HIV would probably be unacceptable, Ada thinks. The reason: a disabled strain of HIV might regain its virulence through mutation or genetic recombination. Several groups are trying to get around this problem by fusing antigen-producing genes from HIV into a live vector such as vaccinia, the virus that immunizes against smallpox. Similar engineered vaccines have been successfully developed against rinderpest and rabies.

But a far more radical approach was described by Reinhard Kurth of the Paul Ehrlich Institute in Frankfurt. Kurth is planning to create a strain of HIV that is more virulent than natural strains yet is incapable of establishing a long-term infection.

HIV is unusual in that it contains many genes that seem to suppress its activity. Flossie Wong-Staal, who is about to move from Gallo's lab to the University of California at San Diego, suggests that these genes may be important in allowing the virus to establish itself in the body. By damping down the virus's activity, they enable it to evade detection by the immune system. Kurth proposes getting rid of the down-regulating genes to make the virus in some sense more virulent. Deleting the *ref* gene, Kurth has shown, enables the virus to replicate ten times better. More replication, he thinks, might offer the immune system greater stimulation in the early stages of the infection, allowing it to clear the engineered HIV from the body and withstand a future invasion from real HIV.

Other genetic changes would also be needed to make the engineered strain nonpathogenic. And in addition, Kurth proposes deleting the genes that HIV uses to integrate its own DNA into the human DNA.

Would anybody volunteer to test such a vaccine? Many researchers here think a lack of volunteers might be a significant problem. Frederick Valentine, director of the AIDS clinical trials group at New York University Medical Center, sees no opposition to tests with live vaccines based on vaccinia virus or other vectors. But a live HIV vaccine, no matter how debilitated, "would be very threatening to people."

■ JEREMY CHERFAS

# DOE Calls in the Labs for Defense Waste Cleanup

*Plans for expanding applied and basic research programs are exciting researchers. But will the funding really be there?*

ENERGY SECRETARY JAMES WATKINS wants to put researchers to work cleaning up the nation's waste-laden nuclear weapons production complex. Not that scientists haven't been working on the problem—in the Department of Energy, a number of research efforts have been struggling along for years, often with marginal funding and little priority. But Watkins is an impatient—and stingy—man. He's not willing to allow the United States to spend an estimated half century and $130 billion to do a job he thinks can be done in 30 years for possibly half of that.

In fact, he's ordered up a master plan to find ways to deal with radioactive and chemical wastes where they exist, rather than digging them up and trucking them away. Said Watkins before the National Press Club on 1 August, "I am challenging our national labs to solve [the problem of] how to treat such contamination without moving it."

This initiative, which involves the preparation of a 5-year plan for applied research and a 15-year plan for basic research, is getting many chemists, engineers, geologists, and microbiologists in the research community fired up. "I think that there are going to be enormous opportunities for researchers in the academic and industrial world," says William C. Luth, a geochemist who heads the geoscience department at Sandia National Laboratories. "For the first time in the history of the agency, this area of research is being recognized at top levels as significant and important."

But despite the enthusiasm of researchers like Luth, the effort is likely to encounter formidable technical problems—and political hurdles. The research undertaking is complex because it involves low- and high-level radioactive wastes and toxic chemicals that are contaminating land and water sources to varying degrees. Solutions that may work at Savannah River, South Carolina, may not be useful in Hanford, Washington, because climate, soil conditions, and waste chemistries are different.

Also in question is whether Congress and the department itself are prepared to make a long-term commitment to expand R&D programs involving not only DOE laboratories, but also university researchers and private industry. Such support is essential, DOE officials say, if sufficient numbers of researchers and engineers are going to be attracted to work on problems related to the cleanup of defense wastes. "When you try to justify basic research with a payoff that is 10 or 15 years out, it is hard to convince people that it is a good investment," says Frank Wobber, director of DOE's subsurface science program.

The fears may be justified. In spite of publicity given to the defense waste problem last year, DOE proposed no increase in spending on basic research on cleanup technologies for fiscal year 1990. Right now, DOE is spending only $14 million a year for basic research and $150 million for applied research directly related to defense wastes.

Environmentalists also wonder whether Watkins' expectations for lowering cleanup costs are real—or just a ploy to defer budget outlays until later years. Says Jim Werner of the Natural Resources Defense Council, "Let's see them put some action behind their words."

Leo Duffy, Watkins' special assistant for defense waste management, insists that the department is committed to expanding its R&D. With the cleanup bill climbing to more than $2.4 billion in 1990 and perhaps $4.1 billion by 1995, "it is mandatory that we invest in research that might lower our costs and eliminate the hazards. Today's technology does not solve the problem," contends Duffy.

The applied research plan, which will not be unveiled until early next year, is expected to focus on developing technologies that can be deployed within 5 years to stabilize contaminated sites, restore affected lands, and reduce waste volumes produced in ongoing weapons production operations. The technologies that will top the department's list of priority projects are not yet clear, but they are likely to include a mix of approaches—some that have been toyed with for years and others that are just emerging:

■ Glassification of soils contaminated with radionuclides, heavy metals, soluble organic compounds, and inorganic ions, such as nitrites. Referred to as in situ vitrification, this technology has been under development since 1980 at Pacific Northwest