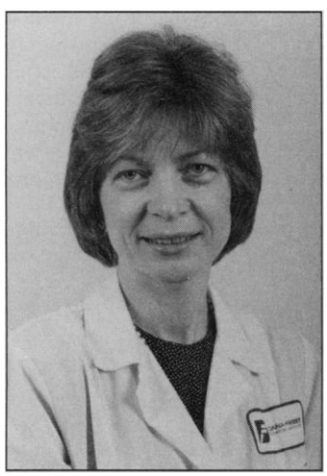
AIDS VACCINES

At Conference, Hope for Success Is Further Attenuated

AIDS vaccine research has been through tough times lately, with negative results overshadowing the positive ones. Yet in this gloom, there has been one shining light: the success, in monkey experiments, of "attenuated" vaccines, which rely on live but weakened forms of the AIDS virus. Most researchers argue that this strategy is too dangerous for a human AIDS vaccine because it might theoretically cause the very disease it is designed to prevent. But some have held out hope that it may offer a viable approach. And even the critics have agreed that attenuated vaccines could help steer the development of other preparations that would be safe and effective.

At an AIDS vaccine meeting held last week near Washington, D.C., two different sides of attenuated vaccines were on display. One side was a hint that these vaccines could prove as powerful in people as they have in monkeys. The other was a dismaying report showing for the first time that the dangers of this approach are more than theoretical.



Alarm bells. Ruth Ruprecht doesn't think attenuated AIDS vaccines are safe.

Because passions run so high both for and against an attenuated HIV vaccine, that downbeat report, by Ruth Ruprecht of Harvard University's Dana-Farber Cancer Institute, turned more heads than any other at the 5-day Conference on Advances in AIDS Vaccine Development, an annual gathering sponsored by the National Institute of Allergy and Infectious Diseases (NIAID).* Ruprecht revealed that a vaccine made from attenuated SIV (the simian cousin of HIV), which other researchers had found to be safe and effective in adult monkeys, can actually cause AIDS in newborns. "Based on our data, I truly believe that the live attenuated vaccines are dangerous," says Ruprecht.

The attenuated vaccine Ruprecht and her colleagues tested had been engineered with three key deletions in SIV's genetic material, including two entire genes. The working assumption behind this strategy is that deleting the right genes would allow SIV to replicate a little bit, thereby evoking an immune response, but prevent it from actually causing disease. As Michael Wyand of TSI Mason Laboratories in Massachusetts explained at the meeting, the approach worked well in adult monkeys, which were unharmed by the weakened virus and resisted a "challenge" from lethal doses of fully intact SIV.

Ruprecht took these promising results a step further, giving an oral dose of this attenuated SIV preparation to a newborn monkey immediately following a Caesarean section. Ultimately, she was asking what would happen if a mother passed on the vaccine virus to its infant. "We were in for surprises," she said during her presentation.

About 8 months after this "vaccination," the monkey infant had "profound and abnormal hematological values," said Ruprecht. In particular, the level of the key white blood cells called CD4s had plummeted, which is a hallmark of the immunodeficiency seen in AIDS. Unlike the vaccinated adults, the newborn also could not contain the virus's replication, and the researchers consistently found surprisingly high levels of SIV in its blood.

A subsequent analysis of the SIV in the monkey showed that the attenuated strain itself had apparently caused the illness: The virus had not mutated back into a known virulent strain. What is more, when blood from that monkey was given to another newborn and its mother, the newborn suffered severe drops in CD4s, while the mother remained healthy, again reinforcing the notion that the attenuated SIV had not become more pathogenic. Ruprecht has infected two other newborns with this attenuated virus. All four infants have had persistently high amounts of SIV in their blood, one has died, and at least two of the surviving monkeys have developed signs of AIDS-related diseases. In light of these findings, says Ruprecht, "I don't see [attenuated HIVs] as a viable approach for human vaccines."

These findings are "damaging to the concept," acknowledges Ronald Desrosiers of Harvard's New England Primate Research Center, the prime mover behind the attenuated approach, who first showed its remarkable power 2 years ago in a paper in *Science* (18 December 1992, p. 1880). But he urged his colleagues to keep Ruprecht's work in perspective. "It's a serious issue, but it would be premature to write off the entire attenuated approach," says Desrosiers, who stresses that if it were possible to make a relatively safe attenuated HIV vaccine, that preparation could play a major role in curbing the AIDS epidemic. "We're continuing to search for that right balance of attenuation and potency, and it's not going to be easy to establish where that line is."

Identifying that line will require answering some important scientific questions raised by Ruprecht's finding. As she asks, "Why is this virus pathogenic in the absence of these auxiliary genes?" The answer to that riddle—which Ruprecht and Desrosiers agree will depend heavily on further studies with attenuated SIV vaccines in monkeys—may also help explain how AIDS viruses cause disease, a fundamental question that has dogged both AIDS vaccine and drug developers for more than a decade.

And if that weren't enough to keep researchers interested in attenuated vaccines, Desrosiers offered intriguing evidence that attenuated strains of HIV may already have benefited some humans. Desrosiers presented data on a hemophiliac who has been infected with HIV since at least 1983. This man has had perfectly stable CD4s and is in fine health. An analysis of his HIV shows it lacks a large section of the *nef* gene—the very gene Desrosiers deleted from SIV to create the attenuated vaccine that first succeeded in monkeys. "What we like to think is that this is an individual who already got the vaccine," Desrosiers said. "[He] is our first safety study."

This "vaccine" not only appeared safe; it may have been effective as well, says Desrosiers, noting that after the man was initially infected with the attenuated virus, he likely was transfused with HIV-infected lots of clotting factor and resisted infection. Desrosiers currently is testing a variety of attenuated vaccines, which have up to four HIV genes deleted, in chimpanzees.

When the dust had settled at the meeting it was clear that attenuated HIV vaccines have to face a new negative that might seriously harm their chances of ever being tested in humans. But because attenuated vaccines remain the focus of considerable research interest, this backward step, by stimulating new experiments, may eventually wind up taking the field a step or two forward.

–Jon Cohen

* "Conference on Advances in AIDS Vaccine Development," Seventh Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS, National Institute of Allergy and Infectious Diseases, 6–10 November, Reston, Virginia.