A New Goal: Preventing Disease, Not Infection

Since the AIDS virus was first isolated, scientists have been hunting for a vaccine that can completely prevent infection. With a foe as stealthy and cunning as the AIDS virus, vaccine researchers feared that if even a single virus particle infected a cell, it might ultimately lead to full-blown disease. So the only safe course was to create a vaccine that blocked infection completely, producing so-called "sterilizing immunity." The testbed for developing such a vaccine has been monkey experiments using SIV, the simian cousin of HIV. But new monkey studies, combined with disappointing results from old ones, are giving researchers pause—and causing them to rethink this all-or-nothing strategy.

KEEPING SIV INFECTIONS IN CHECK
Immunizations That Protect Against Disease in Monkeys

Immunization	Results
Whole, killed SIV vaccine	Longer survival, decreased viral load
SIV peptides and subunits	Longer survival, decreased viral load, reduced transmission
SIV on mucosal surface	Transient or aviremic infection, protection from challenge
Low-dose SIV, given intravenously	Transient infection and complete protection from challenge

The reason for the shift in thinking is that new experiments point to a phenomenon that, just a few years ago, seemed utterly implausible: The immune system has a capacity to contain infection with the AIDS virus. If it indeed has that containment ability, then even a vaccine that fails to deliver sterilizing immunity may still be able to delay or, better yet, prevent disease. As a result of this new work, prevention of symptoms, rather than sterilizing immunity, is being taken seriously as a hallmark of vaccine success.

To many of the AIDS researchers who have been testing vaccines in monkeys, it's high time to change the standard. "Every viral vaccine protects not against infection but against disease," says Gerald Eddy, lab director at the Henry M. Jackson Foundation in Rockville, Maryland. "With HIV, we're attempting to set such strict criteria for efficacy that it's unrealistic, and a lot of money is possibly being wasted by attempting to reach that standard."

Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID), says that just 2 weeks ago he held a lengthy internal meeting where one of the main agenda items was sterilizing immunity versus protection from disease. "Most people agreed we need to rethink this," says Fauci, adding that "there may be a lot of primate data we need to reanalyze." Dani Bolognesi of Duke University agrees, noting, "There's a lot of data that says you can have an impact [with an SIV vaccine] even if you can't blockade the infection. The question is: How good is the data?"

Some researchers still are toeing the sterilizing immunity line. "Anything that can attenuate the initial burst of virus that causes the rapid spread of virus is likely to delay clinical disease," says Harvard's Norman Letvin, who has worked extensively with SIV. "But I'm not ready to say we've done enough work to give up on sterilizing immunity."

Others, however, are ready and willing. NIAID's Alan Schultz, who heads the AIDS vaccine branch at the Division of AIDS, says that true sterilizing immunity is "patently absurd" because the immune system relies on some level of infection to mount a full-fledged response. "If sterilizing immunity is the way a vaccine is going to work," says Schultz," we should put all our money into condom distribution."

To hell in a handbasket. Just a few years ago, sentiments like that would have been considered heresy in the AIDS vaccine community. In the 1980s, sterilizing immunity was the watch word, largely because HIV integrates itself into a host cell's DNA, and therefore infects the cell for life. As AIDS researcher Robert Gallo of the National Cancer Institute has repeatedly stressed, "An integrated virus is very different." Not only can integration trigger cancer, it also allows the virus to remain undetected by the immune system. One undetected virus could, in theory, bloom into AIDS.

Gallo's thinking was influential, but there were also logistical reasons for sterilizing immunity's emergence as the gold standard in vaccine trials. HIV infection takes an average of 10 years to cause disease. So staging a trial with disease as a clinical endpoint would probably require several years—and tens of thousands of people—to arrive at a statistically meaningful answer. And that makes it tough, since retaining people in a vaccine trial for more than a few years is difficult, and the costs of running multi-year tests are astronomical. On the other hand, a trial with infection as an endpoint might take as little as 3 years, according to NIAID estimates, and require fewer than 3500 people.

Once sterilizing immunity emerged as a goal, early monkey experiments, based on the field's unwritten master plan, seemed to provide evidence that it was attainable. The plan was to fashion an extra-potent crude vaccine, which was too risky for human use but could completely protect monkeys from infection. In theory, these vaccines would then be used to uncover the immune mechanisms that led to protection. Safer, genetically engineered vaccines could then be designed to trigger these same responses in human beings. Beginning in 1989, researchers showed that vaccines made from whole, killed SIV—one of the crude and risky preparations—could completely prevent infection, albeit under idealized lab conditions. "We were starting to march down the road toward real-world protections," says Schultz. "But then it went to hell in a handbasket."

The handbasket ride began in 1991, with an experiment reported by James Stott and his colleagues at England's National Institute for Biological Standards and Control. Essentially, the Stott experiment showed that the effect of the whole, killed vaccine was due to a lab artifact that offered little to designers of "safer" vaccines (*Science*, 17 January 1992, p. 292). When the artifact was corrected for, the vaccines failed. The hoped-for protection suddenly seemed far away.

Several other dispiriting results over the next 2 years from monkey experiments with vaccines aimed at triggering sterilizing immunity left vaccine researchers at their wit's end. And in their frustration, some scientists began turning toward prevention of disease as a new source of light in the darkness.

Redefining protection. One of those researchers is NIAID's Vanessa Hirsch. Two years ago, Hirsch and Philip Johnson (now at Ohio State University) ran a typical whole, killed SIV test in which they vaccinated monkeys and then "challenged" the animals with infectious SIV. The experiment was a resounding "failure" under the sterilizing immunity paradigm: The five vaccinated animals and six unvaccinated controls all became infected.

But times change, and with them the definition of success. Eighteen months later, three vaccinated animals remained healthy, while all the controls had developed serious opportunistic infections. To date, two of the vaccinated animals remain healthy.

"We should redefine what we call protection," says Hirsch. "Even from a fairly ineffective vaccine—that I don't think is anywhere near optimal—there's some evidence that it's protective."

What happened here? Apparently, the immune systems of three of the five vaccinated animals were better able to handle the virus. Nor is Hirsch the only one whose results are leading to this conceptual shift. The Jackson Foundation's Eddy and Avigdor Shafferman of the Israel Institute of Biological Research have made a similar observation. Four years ago, they injected three monkeys with a vaccine made from small fragments of SIV and then challenged them. Though one of the monkeys died of AIDS, two show signs of SIV in lymph nodes only, not the blood—indicating that the infection is not widespread. In contrast, two control animals died and a third has SIV in the blood.

JEFF ROBERTS

A new meaning for safety. Vaccine trials with monkeys like these, at the California Regional Primate Center, suggest it may be possible to allow infection with SIV but prevent disease.

This milder infection also meant that the vaccinated monkeys were less likely to spread SIV, which the researchers showed by taking blood from the vaccinated animals and injecting it into uninfected animals.

Like Hirsch, Eddy acknowledges that his vaccine is far from ideal because it didn't protect all the animals from disease. "But if AIDS gets you after 30 years rather than after 10, as a vaccinee, you're ahead of the game," he says. "And if you are much less likely to transmit the virus, everybody's ahead of the game."

The way these vaccines are getting ahead may be their capacity to reduce the monkeys' "viral load"—the total amount of virus in their blood. In studies with 23 vaccinated monkeys that became infected, Edward Hoover, a pathologist at Colorado State University, found that they had 10% to 20% of the amount of SIV found in control animals. "Our studies reduced virus burden," says Hoover, though they "didn't protect against infection." He adds that "if one can heighten the immune response enough, it may be a realistic goal to try to achieve lifetime suppression of virus." Vaccine developer Dennis Panicali, who heads Therion Biologics in Cambridge, Massachusetts, also has preliminary data showing that if vaccinated monkeys do subsequently become infected, they have lower viral loads than do infected, unvaccinated animals.

More evidence of a connection between viral load and vaccine effectiveness comes from Stott and his colleague Martin Cranage of England's Centre for Applied Microbiology and Research (CAMR). In separate experiments with a similar combination of genetically engineered SIV vaccines, Stott and Cranage have found that when vaccinated monkeys became infected, it was harder to isolate virus from them than it was from controls.

Unfortunately, neither the British researchers, Hoover, nor Panicali had the lab space or the funds needed to keep their infected monkeys alive and see whether they developed AIDS. This is a reality faced by most everyone testing AIDS vaccines in monkeys—and because of these intriguing results, it is prodding researchers to find ways around it. "A lot of monkeys have been killed because it seemed like the experiment was over," says Patricia Fast of NIAID's Division of AIDS. "In retrospect, we wish we would have kept them alive."

New thinking. But longer trials are going to require more cages for the monkeys, who must be isolated after they are infected, as well as more personnel to care for them—all of which adds up to more money. Researchers and agencies are just beginning to talk about these fixes, and when and if they'll happen remains unclear.

Another effect of the new interest in containing infection is that it's broadening SIV protection studies beyond the realm of vaccines. At the University of Wisconsin, David Pauza and co-workers found that four monkeys intrarectally infected with low doses of SIV did not develop a detectable immune response against the virus, nor could the scientists culture SIV from the monkeys' blood. Yet using the ultrasensitive PCR assay, the investigators could occasionally detect SIV sequences. And, sure enough, when blood taken from these healthy animals was injected intravenously into uninfected monkeys, it caused disease. Somehow, Pauza concluded, the first group of animals had developed an effective immune response.

To evaluate the strength of that response, Pauza next intrarectally challenged these four monkeys with high doses of SIV and all have remained virus-free and SIV-antibody free for more than 20 weeks. Two controls, in contrast, readily became viremic. Similar results come from Christopher Miller of the University of California, Davis, who recently found that a dozen mucosally infected monkeys showed SIV in their blood but then inexplicably cleared that virus. Uncovering what the immune system is doing to contain these infections could reveal important clues to designing an effective AIDS vaccine.

If researchers begin to reject the sterilizing immunity paradigm more widely, it also will give them a much better handle on selecting vaccines for efficacy trials. CAMR's Cranage advocates considering protection on a "sliding scale" ranging from high viral loads to no detection of virus. "Thus virus load reduction may provide a very useful means of comparing the efficacy of different vaccine preparations," he suggests, emphasizing that it still remains to be shown, definitively, that reducing the viral load can delay or prevent the onset of disease.

It now appears as though this "sliding scale of protection" will likely play a role in evaluating trials of vaccines in humans, too. Rodney Hoff, who heads the branch of the Division of AIDS that is planning vaccine efficacy trials for humans, says it may be possible to separate out everyone who becomes infected in such a trial and study their viral loads in detail. Perhaps some people will, as did some monkeys, only temporarily show virus in their blood. Others might have significantly lower amounts of virus than infected controls who received a placebo rather than a vaccine. "There are a spectrum of possible host-virus interactions," says Hoff. "It's not just an all or nothing phenomenon." And the challenge now is to define what happens when the result is in between.

–Jon Cohen

Additional Reading

A. Shafferman *et al.*, "Prevention of Transmission of Simian Immunodeficiency Virus From Vaccinated Macaques that Developed Transient Virus Infection Following Challenge," *Vaccine* **11**, 848 (1993).

V. Hirsch *et al.*, "Immunization With Inactivated, Human Cell-Culture-Derived SIV Vaccine Prolongs Survival of Monkeys Subsequently Infected with Simian Cell-associated SIV," *Vaccines* **93**, 63, Cold Spring Harbor Laboratory Press (1993).

A. Schultz and S.-L. Hu, "Primate Models for HIV Vaccines," *AIDS* **7** (supp. 1), (1993).