Can One Type of HIV Protect Against Another Type?

Like fighting fire with fire, you can fight viruses with viruses. Take smallpox. The disease has been eradicated because vaccine pioneer Edward Jenner discovered the fighting-fire-with-fire principle in the 18th century. Jenner, a British country doctor, knew from folklore that milkmaids who developed the mild cowpox disease rarely suffered the ravages of smallpox. This formed the basis for his vaccine, which was no more than cowpox virus. Now an analogous phenomenon has been uncovered in Senegal that may help researchers develop an AIDS vaccine.

Researchers led by Phyllis Kanki of the Harvard School of Public Health in Boston report on page 1612 that for 9 years they followed the HIV status and health of 756 women who are registered as "commercial sex workers" in Dakar, Senegal. The researchers tracked the spread of HIV-1, the most common type of AIDS virus, as well as the spread of its less aggressive cousin HIV-2, in this cohort of prostitutes. They found that of 618 women who were initially uninfected with either type of HIV, 61 became infected with HIV-1 during the study. But of 187 women who became infected with HIV-2 before or during the study, only seven later became infected with HIV-1 as well. "I think it's protection," says Kanki, who collaborates with Harvard's Max Essex and Richard Marlink and with researchers at the University of Cheikh Anta Diop in Dakar.

Kanki is not arguing that HIV-2/HIV-1 is strictly analogous to cowpox/smallpox: HIV-2, after all, can cause AIDS. Yet the time lag before it causes full-blown disease is typically much longer than that for HIV-1. As Kanki, Marlink, Essex, and colleagues reported in *Science* last year (9 September 1994, p. 1587), HIV-2 on average takes at least 25 years to cripple the immune system and cause symptomatic AIDS—more than twice as long as the lag typically seen with HIV-1. Kanki's hope is that people infected with HIV-2 might live to a ripe old age, dying of other causes before AIDS has a chance to develop, and might benefit from the infection if it staves off the more lethal HIV-1.

Kanki is quick to note that she doesn't want this potential protection "to be taken too far, so that people run out and go get infected with HIV-2." But she does see parallels with cowpox/smallpox and other so-called "heterologous virus" systems, in which a weak cousin protects against its aggressive relative by stimulating immune molecules that recognize both strains. Kanki and her co-workers underscore this point by using a risk-assessment analysis which shows that in their study population, HIV-2 infection lowered the risk of becoming infected with HIV-1 by about 70%.

Firefighters. Phyllis Kanki and the Senegalese team she collaborated with in the HIV-2 studies. To her right is Souleymane Mboup, leader of the Senegalese team.

If there were a vaccine against HIV that had 70% efficacy, the world would rejoice, and some researchers are cheering Kanki's findings. "I think it's extremely important data, and it's important that people think about it," says Frances Gotch, an immunologist at the University of Oxford who published a study in the January issue of *Nature Medicine* analyzing immune responses of prostitutes in The Gambia who appear protected from both HIV-1 and HIV-2. "I'm not advocating that we go into people with pathogenic HIV-2," says Gotch, but she says, "if we look hard enough one might come across a [weakened] strain of HIV-2" that protects against HIV-1 with minimal risks.

AIDS vaccine developer Ronald Desrosiers of Harvard's New England Regional Primate Research Center is also enthusiastic. "I'm very excited by these results," Desrosiers says. To Desrosiers, Kanki's work offers support for a strategy he has been struggling to convince his colleagues to consider: making an AIDS vaccine from a live version of HIV-1 rendered harmless by deleting key viral genes. The theory behind this "attenuated" vaccine approach is similar to Kanki's theory about HIV-2: The wimpy, attenuated virus causes an infection that teaches the immune system how to thwart related viruses that are more aggressive. Desrosiers raised hopes when he showed that, in monkey experiments, such an attenuated AIDS vaccine offers solid protection against subsequent infection (*Science*, 18 December 1992, p. 1880).

Despite his enthusiasm, Desrosiers says he does have a serious concern about the Kanki study: Did women who became infected with HIV-2 then begin practicing safer sex by using condoms and the like, lowering their risk of HIV-1 infection? Kanki and co-workers have attempted to address this confounding variable by showing that rates of gonorrhea, another sexually transmitted disease, were significantly higher in these women, implying that they hadn't used condoms.

Other AIDS vaccine researchers who have strong reservations about attenuated AIDS vaccines are much more circumspect than Desrosiers is about Kanki's study. "It leaves me hanging in about 18 different directions," Duke University's Dani Bolognesi says of the Kanki paper. Bolognesi says he would have serious reservations about giving someone any live retrovirus (the category that all HIVs belong to), even one that's been attenuated in the lab. "I don't know any retrovirus that's a safe strain," says Bolognesi. "I wish we had a vaccine that would do [what the attenuated virus] does, but ... I keep looking for a way of getting the same answer that doesn't involve those risks." One risk is that some retroviruses can trigger cancer when they insert their genetic material into the DNA of the host cell they are infecting. Retroviruses also mutate at a notoriously high rate, which means a "harmless" virus might become an AIDS killer over time.

Add to those fears data from Ruth Ruprecht of Harvard's Dana-Farber Cancer Institute in Boston, who recently reported sobering evidence that a monkey AIDS vaccine made from an attenuated virus was safe and protective in adult animals but caused AIDS in newborns (*Science*, 24 March, p. 1820). To make the picture more disturbing, adds Ruprecht, retroviral diseases take years to develop. "How are you going to determine that the virus is nonpathogenic?" she asks.

Although Harvard's Essex also worries about an attenuated HIV vaccine, he says he hopes this work generally "renews people's optimism about the possibility of making an AIDS vaccine"—which, he notes, skyrocketed after Desrosiers reported his success with an attenuated monkey AIDS vaccine but nose-dived following Ruprecht's findings. Kanki says her group now has immunologic studies under way to tease out precisely which immune responses protected these women from HIV-1. If such responses can be found, then researchers developing HIV-1 vaccines dream that they may at long last have a clear view of the target.

–Jon Cohen