SIV TRANSMISSION

Monkey Study Prompts High-Level Public Health Response

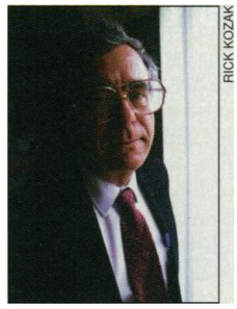
Tim Westmoreland, a former influential congressional staffer who until 1995 handled AIDS legislation for Representative Henry Waxman (D–CA), knows a public health issue when he hears one. And when he attended a board meeting of New York's Aaron Diamond AIDS Research Center on 15 April, he heard what sounded like a sure-fire public health concern. The board was briefed on a study indicating that monkeys treated with the hormone progesterone are at an increased risk of infection with SIV, the simian form of the AIDS virus. That finding raises the alarming possibility that women who use the progestin-containing contraceptives Depo-Provera and Norplant might—and that's a big might—be at an increased risk of becoming infected with HIV. Westmoreland decided to set the health policy wheels moving.

He called top officials at the Food and Drug Administration, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the United Nations Programme on HIV/AIDS. His calls started a cascade of events that led to high-level meetings of health officials, a last-minute presentation of the data at a scientific conference, a press release outlining the findings, and a request to *Science* for an expedited review of a paper detailing the work. "I agonized over whether this was the right thing to do," says Westmoreland, now a senior policy fellow at Georgetown University Law Center. He stresses that he is not a scientist and did not want to judge the import of the work himself. "I wanted to make sure all the people who look at forests looked at the appropriate trees," he says.

Westmoreland was concerned because more than 2.5 million women in the United States alone use either Norplant or Depo-Provera, and tens of millions have used Depo-Provera worldwide since its introduction in the late 1960s. And many of these women already belong to groups that have a higher risk of becoming infected with HIV. "I knew people could misunderstand or misuse these data," he says.

Preston Marx, the Aaron Diamond primate researcher who headed the study, well knew the impact his work might have. "These are blow-you-away findings," says Marx. Yet he is somewhat flummoxed that so many people at so many levels have become involved in getting the data out as quickly as possible. "I've never had a manuscript so widely distributed and read by everybody prior to publication," says Marx of the paper he submitted to *Science*, which, at press time, was under review. "[The data] have been under a microscope since the beginning."

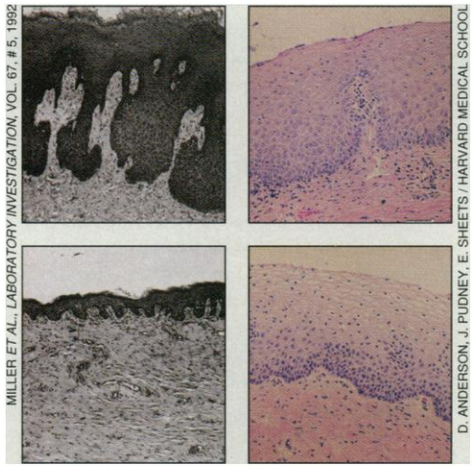
Marx's data, as he explained publicly on 6 May at a clinical research meeting in Washington, D.C.,* show that of 18 monkeys given progesterone implants, 14 became infected with SIV by vaginal inoculation. In comparison, only one of 10 untreated control animals became infected when given the same vaginal dose of SIV. This translates into a nearly eightfold higher risk of SIV infection for the treated monkeys. "I'm not used to data like this," Marx says.



RICK KOZAK

Weighing risk. Primatologist Preston Marx.

The data may be clear-cut, but Marx and other researchers are wrestling with what they mean. "It's an animal model and it has some predictive value, but you can't put a number on it," says Marx. And studies in humans are anything but clear-cut.



MILLER *ET AL.*, *LABORATORY INVESTIGATION*, VOL. 67, # 5, 1992

D. ANDERSON, J. PUDNEY, E. SHEETS / HARVARD MEDICAL SCHOOL

Progesterone's effects. Thick vaginal epithelium of monkey during follicular phase of menstrual cycle (*top left*) thins under influence of progesterone in luteal phase (*lower left*). But there is no apparent morphological difference in vaginal wall of a normal cycling woman (*top right*) and a woman on Norplant progestin contraception (*lower right*).

Ann Duerr, a CDC epidemiologist and coauthor of *HIV Infection in Women*, recently analyzed nine published studies that attempt to assess Depo-Provera use in women and risk of HIV infection. "The results from these studies are not consistent with a big increase in HIV infection for Depo use," says Duerr. Although some of the studies showed a slight increase in risk of infection, others, including an ongoing project Duerr is conducting in Thailand, do not. "We need to do more studies, but the data we have on hand don't support a change in any of our policies," she says. Duerr adds that researchers are "quite sure" that Depo-Provera and Norplant don't offer any significant protection against HIV. "So it underscores that women at risk of HIV infection should be using condoms."

Deborah Anderson of Harvard's Brigham and Women's Hospital has human data that also differ from what Marx found in monkeys. The progesterone-treated monkeys had marked thinning of the vaginal epithelium—possibly making it easier for SIV infection to occur. This builds on a previously published monkey study by Christopher Miller and colleagues at the University of California, Davis, that shows dramatic thinning at the point of the menstrual cycle when natural progesterone levels peak. Yet Anderson, a specialist in the immunology of the reproductive tract, recently analyzed vaginal biopsies from a dozen humans and found no increased thinning in those who used Norplant. Although she stresses that her study is uncontrolled and needs to be followed up, Anderson says she is very concerned that people will extrapolate from the monkey data. "I'd just hate to see women change their contraception and be at risk of pregnancy," she says.

The National Institute of Child Health and Human Development (NICHD), a prime funder of the study, said in a press release accompanying Marx's presentation at the clinical meeting that the work "does not change any U.S. Public Health Service recommendations." Why, then, the urgency surrounding these data? "Too many people knew about it," says Nancy Alexander, who heads contraceptive development at NICHD and worked with Marx on the study. "We thought that a whisper story would be worse than putting out the facts." If so, the strategy seems to have worked: Press coverage of Marx's presentation was light and measured.

NICHD and other NIH branches plan to hold a "research planning workshop" at NIH on 6 June to review related epidemiologic studies and plan future ones to establish what relevance, if any, the monkey data have to humans. "I feel like they reacted in a conscientious way," says Westmoreland. "That's the appropriate scientific discussion, and I hope it goes on."

–Jon Cohen

*Annual meeting of the American Society for Clinical Investigation and the American Federation for Clinical Research, Washington, D.C.