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AIDS RESEARCH

Researchers Urged Not to Inject Virulent HIV Strain Into Chimps

An unusual coalition of prominent AIDS researchers, primatologists, and animal conservationists is urging vaccine developers not to inject chimpanzees with recently isolated strains of HIV that can cause AIDS-like disease in the animals. In a letter published on page 1117, virologist Alfred Prince of the New York Blood Center, chimpanzee advocate Jane Goodall, and nine others raise scientific and ethical objections to such experiments, but stop short of calling for a ban on them. "Before we jump off the diving board and use a virulent strain, we should stop and reassess this," says co-signer Jonathan Allan, an AIDS researcher at the Southwest Foundation for Biomedical Research in San Antonio, Texas. "We're redefining what the ethical limits are for chimp studies."

The letter is the latest twist in a long-running debate about the value of various animal "models" for studying AIDS. Behind that debate are vehement disagreements among leading researchers about the most fundamental aspects of what, exactly, a vaccine designed to thwart HIV should do. Now, the prospect of conducting potentially lethal experiments on chimps has sharpened those disagreements.

The spark that rekindled this debate came from one paragraph in a review article about AIDS vaccine progress that Norman Letvin of Harvard's Beth Israel Deaconess Medical Center published in the 19 June 1998 *Science* (p. 1875). The great apes, Letvin noted, are the only animals other than humans that can be infected by HIV-1. But chimps have been poor models for testing vaccines, he argued, because HIV doesn't replicate well in the animals or appear to make them sick. Inoculating a chimp with a candidate vaccine and "challenging" it with HIV has not provided a rigorous test of whether the vaccine is likely to help humans, Letvin argued. But, he suggested, that may be about to change: A year earlier, researchers at Emory University's Yerkes Regional Primate Research Center in Atlanta, Georgia, reported that an HIV-infected chimpanzee named Jerome had developed an AIDS-like illness.

Unlike nearly 200 other chimps that researchers had infected with HIV, Jerome had a steep drop in CD4 cells—the main immune system warriors that HIV targets and destroys—and a coincident increase of virus in his blood. When Emory's Frank Novembre transfused another chimp, Nathan, with blood from Jerome, the virus again replicated well and in 6 months depleted his CD4s. An HIV isolate subsequently isolated from Nathan, whose health Novembre says is now "going downhill," also decimated the immune systems of two other chimps. Patricia Fultz of the University of Alabama at Birmingham has seen similar results in three chimps she infected with HIV derived from Jerome.

In Letvin's *Science* review, he wrote that a stock of this strain "would provide an important new tool for testing vaccine approaches." Letvin pointed out that scarcity of chimps and the steep fees primate centers charge researchers to use them in HIV experiments—at least $50,000 per animal—would limit their use compared with monkeys, which develop AIDS when infected with either SIV, HIV's simian relative, or a lab-made hybrid of the two viruses called SHIV. Still, a pathogenic strain of HIV adapted to chimps might allow researchers to conduct critical tests to determine whether candidate vaccines could foil infection by an aggressive virus or, failing that, prevent or delay disease.

Many AIDS researchers emphatically agree with Letvin's point of view. "In order to really test the efficacy of an HIV vaccine, we really need a disease endpoint in an animal as close as possible to man," says Malcolm Martin of the National Institute of Allergy and Infectious Diseases (NIAID), who himself has attempted to find an HIV that would cause disease in chimps. Although no vaccine tests are currently planned with the virus, Letvin's suggestion drew a sharp response from Prince, who runs a chimp colony in Liberia, and his co-worker Linda Andrus. In an initial letter, published in the 18 December 1998 *Science* (p. 2195), they said "the prospect of causing a rapidly progressive and fatal disease in this near-human species is abhorrent."

A more acceptable test of a vaccine, Prince and Andrus wrote, is whether it can prevent a virus from establishing a chronic infection. They pointed out that if a vaccine can block chronic infection, then disease would not occur. "Prevention of disease is not relevant," they wrote. And, they argued, several nonvirulent strains appear to replicate well enough in chimps to provide a realistic challenge.

Now, Prince, Andrus, and their nine new co-authors have taken the argument a step further. In the letter published today, they contend that the virulent strain may be too "hot": It destroys a chimp's immune system in a few weeks, while in humans the same process typically takes years. This could "seriously jeopardize the HIV vaccine effort" by ruling out vaccines that fail to protect against this strain, but which might be effective against wild-type HIV, they write. And they suggest yet another alternative "challenge" virus: a strain called Han-2, recently described by European researchers, that replicates well in chimps but does not appear to cause disease. This virus should provide a good test of a vaccine's ability to stave off chronic infection, Prince says.

New model? HIV-infected chimps like this one do not show symptoms, but new strains now make the animals sick.

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Fultz argues, however, that if Han-2 does replicate to high levels in chimps, it will cause disease. She also does not believe that the Jerome-derived strains of HIV are too hot, stressing that infected animals have lived up to 4 years even though their immune systems are damaged. "They're not as lethal as Prince is implying," says Fultz of the strains. And if Jerome-derived strains do cause disease somewhat faster in chimps than HIV normally does in humans, says Novembre, that has an advantage: "This virus will tell you a lot quicker" whether a vaccine is work-

ing. "You don't want to wait 10 years."

Fultz also takes strong exception to Prince and Andrus's statement that preventing disease in the chimp model is not a relevant criterion for judging vaccines. Says Fultz, "That's one of the stupidest statements I've ever heard." Letvin, too, dismisses the contention. Focusing only on chronic infection might lead researchers to overlook a useful vaccine, he argues. "If we have a vaccine that can make people live decades longer, we need to know that," says Letvin.

The next step in this debate could be a meeting to hash out these issues. Alan Schultz, who oversees AIDS vaccine research at NIAID, says he will do his "public servant best" to organize one. **–JON COHEN**

SCIENTIFIC MISCONDUCT

Baylor Saga Comes To an End

Molecular physiologist Kimon Angelides last week ended a long, costly battle against his former employer, Baylor College of Medicine, which had found him guilty of fabricating data, stripped him of tenure, and evicted him from his lab. On 10 February, Angelides settled a civil suit filed against Baylor and 14 individuals at the university, just hours after a federal appeals board had released a report backing Baylor's findings that Angelides had "committed scientific misconduct." Angelides has agreed to accept the appeals board's decision and will receive no payment, although Baylor will pay his attorneys $500,000.

"We're quite pleased with the result," says Baylor lead trial counsel Gerard G. Pecht of the Houston-based firm Fulbright & Jaworski LLP, who says those sued "have been totally vindicated." The settlement also may bring a measure of relief to officials at other universities, who have worried about being sued simply for following the federal government's requirements to investigate misconduct allegations (*Science*, 12 February, p. 913). "This kind of suit shouldn't have gotten to this point at all, in our view," says Allan Shipp of the Association of American Medical Colleges (AAMC).

The saga began in 1992, when a Baylor department chief questioned data in Angelides's grant applications for research on the transmission of nerve impulses through sodium channels. After a 2-year investigation, a Baylor panel found that Angelides had falsified and fabricated figures in five journal articles and five grant applications. In 1997, the Office of Research Integrity (ORI) of the Department of Health and Human Services (HHS) concurred with Baylor's findings and barred Angelides from receiving federal grants for 5 years.

Angelides, who claimed that other scientists in his lab were the ones who had falsified data, appealed the ORI ruling. He also sued Baylor, its president, the seven panelists who examined his case, two former members of his lab, and four others for slander and denial of due process.

A jury had listened to more than a week's worth of plaintiff's testimony when the HHS appeals board released its 171-page report on 10 February. The board, which conducted its own investigation, found that Angelides's "accusations against other researchers were unsubstantiated." The evidence, the board concluded, showed "not honest error, not disputes in interpretation of data, not preliminary results that later proved overly optimistic, not even carelessness, but rather intentional and conscious fraud."

According to Angelides's attorney, James Pianelli of McGehee and Pianelli LLP in Houston, "the timing of the [appeals board report] influenced our decision to settle the litigation." Under the 10 February agreement, Angelides accepts the appeals decision and ORI debarment and will neither appeal nor criticize the decision publicly, will not claim "he has been exonerated or vindicated," and dismisses all claims against the defendants.

The appeals board's validation of Baylor's findings "certainly says that the system is working properly," says Barbara Mishkin, a Washington, D.C.–based attorney who specializes in scientific misconduct. But while Baylor came out ahead, the Angelides case may still discourage universities from pursuing misconduct cases—and scientists from serving on review panels, experts say. "It's not reasonable for people to make this very difficult, painful decision and expose their personal assets to risk," says C. K. Gunsalus, associate vice chancellor for academic affairs at the University of Illinois.

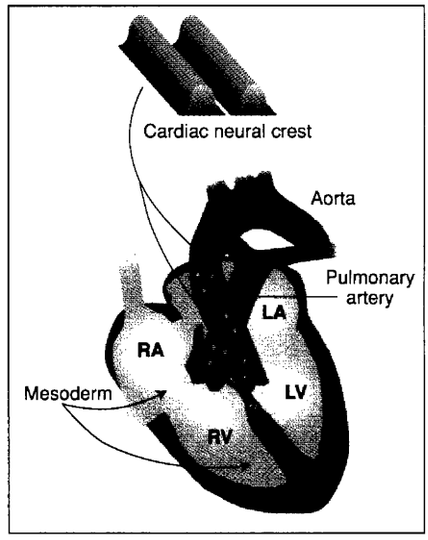
The case may yet leave a positive legacy for researchers. In response to the Angelides affair, the AAMC and ORI have argued that universities and faculty who conduct proper scientific misconduct investigations should be shielded legally from lawsuits. At least, argues Pecht, any civil action should be delayed until the case has been through appeal at HHS. ORI acting director Chris Pascal says HHS "is considering whether additional legal protections are needed in this area," via legislation or regulation. "Otherwise," says Pecht, "the inclination may be for some institutions to sweep the problem under the rug."

–JOCELYN KAISER

HUMAN GENETICS

A Gene That Scrambles Your Heart

Building the perfect heart is hard. Each year about 30,000 babies are born with one of the more than 30 different types of congenital heart defects (CHDs), making these the most common of all human birth defects. Despite much searching, until now the genes behind only three rare disorders had been found. But on page 1158, researchers identify a gene that appears to be key to a widespread form of CHD associated with DiGeorge syndrome, which is second only to Down syndrome in causing malformations of the heart.



The heart of the problem. Parts of the heart's outflow tract and its vessels are derived from neural crest cells (green), which rely on the *Ufd1* gene.

The findings may finally end a frantic hunt for the DiGeorge gene, which when damaged or missing prevents a proper connection between the outflow of the heart and the main blood vessels and also causes malformations in the facial bones and thymus gland. Surprisingly, the gene encodes a component of the cell's protein degradation machinery, support-

SOURCE: SRIVASTAVA *ET AL.*, *NATURE MEDICINE*, 12, 10, P. 1069 (OCTOBER 1996)