Concerns Raised About Mouse Models for AIDS

Interaction with mouse viruses may make the AIDS virus more dangerous and complicate interpretation of the model results

AIDS RESEARCHERS reacted with enthusiasm when they learned at the end of 1988 that mouse models for studying the AIDS virus had been developed. Lack of such models had been handicapping their efforts to understand how the virus destroys the immune system and to devise therapies for counteracting it.

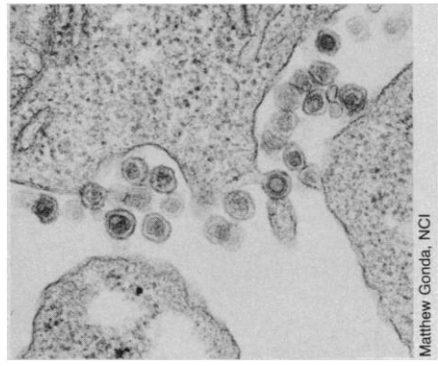
But the enthusiasm may have been premature. A paper in this issue of *Science* raises warning flags about the mouse models. Not only might they be biologically irrelevant, they might promote hazardous changes in the AIDS virus.

On page 848, Paolo Lusso, Robert Gallo, and their colleagues report that the AIDS virus can interact with a common mouse virus when the two come in contact in infected human cells. As a result, the AIDS virus, also known as HIV-1 (for human immunodeficiency virus 1), acquires some new biological characteristics, including the ability to reproduce much more rapidly than it normally does and to infect new kinds of cells. Similar findings are also being reported from other labs.

"The findings raise all kinds of questions about these mouse-human models," says virologist Howard Temin of the University of Wisconsin, Madison. So far the AIDS virus changes have been seen only in cultured cells. But if they occur in the mice, the animals might produce viral variants that can spread by novel routes, says Lusso, a member of Gallo's group at the National Cancer Institute. One of these novel routes might be transmission through the air.

Although that sounds alarming, the potential for disaster is limited because mice infected with HIV-1 already have to be kept in very strict containment. "The way we handle the mice would not change even if we knew that [the HIV changes] were occurring," says Donald Mosier of the Medical Biology Institute in La Jolla, who developed one of the mouse models.

Still, safety isn't the only concern. If the AIDS virus changes its properties by interacting with native mouse viruses, the results obtained from mouse models may not accurately represent the way the virus actually behaves in human beings. "The results in the mice can't be interpreted as easily after this paper comes out," Gallo maintains.



Budding mouse virus. *Infected human cells release mouse virus particles.*

He originally decided to investigate interactions between HIV and mouse viruses because he was thinking of adopting the mouse models for his AIDS research. The models are made from mice, designated SCID (for severe combined immunodeficiency), which have a genetic defect that has wiped out the animals' own immune systems. These animals are essentially engrafted with a human immune system, allowing researchers to observe what the AIDS virus does to human cells in living animals. Without the models they would be limited to studies in cultured cells only.

Researchers also want the models for studying potential AIDS drugs and vaccines. Just 2 weeks ago, for example, Mike McCune, who was also instrumental in mouse model development, and his colleagues at Systemix, Inc., in Palo Alto, reported progress in this area, showing that the AIDS virus in infected mice responds to the antiviral drug AZT much as it does in human patients (*Science*, 2 February, p. 564). The finding suggests that the animals can be used to assess AIDS drugs.

The models might be less valuable for such studies, however, if the AIDS virus behaves differently in the mice than in humans. And Gallo says there are reasons for thinking that that might happen if it came in contact with the viruses mice normally carry.

Virologists have known for years that if two viruses are reproducing in the same cell, they can exchange coat proteins. The coat proteins determine what kind of cells a virus can infect, so one result of this exchange, which goes by the name of pseudotyping, is that the viruses may acquire the ability to infect new types of cells. This could happen with HIV-1 in the mice, Gallo reasoned, because some mouse viruses can infect human cells, possibly giving them a chance to come in contact with the AIDS virus.

When Lusso, Gallo, and their colleagues checked to see whether human immune cells could be infected by a mouse virus, murine leukemia virus, in the animals, they found the answer was yes. The researchers then took cells from one of the infected lines and infected them, albeit in culture dishes, not mice, with HIV-1.

The HIV-1 produced by those cells reproduced faster than normal and infected cells, including the type that lines the respiratory tract, that the AIDS virus would not usually enter. The results indicated, Lusso says, that the changes in HIV-1 resulted from acquisition of mouse virus envelope proteins.

Other investigators, including Deborah Spector of the University of California, San Diego, and Bruce Chesebro of the Rocky Mountain Laboratories of the National Institute of Allergy and Infectious Diseases (NIAID) in Hamilton, Montana, have made similar observations when they infected cultured cells with both an appropriate mouse virus and HIV-1.

So there is no doubt that pseudotyping can occur with HIV-1 in cells growing in culture. But does it happen in the mouse models themselves?

Neither Mosier nor McCune has seen it so far. Both were aware of the possibility and looked for signs that the AIDS virus was infecting mouse cells in the animals. If it could do that, it would indicate that HIV-1 had picked up mouse virus proteins that would enable it to enter mouse cells. That did not appear to happen, however.

Nevertheless, both Mosier and McCune concede that they haven't absolutely ruled out pseudotyping of the AIDS virus in their models. "The question still remains about whether it could happen," McCune says. "Any test is subject to the limits of the detection methods." And Mosier told *Science*, "Hearing that [about the Gallo group's result] makes me want to go back and look more carefully in our animals."

While the issue remains to be sorted out, there is also the possibility that pseudotyping under some circumstances might be helpful to AIDS researchers. For example, Malcolm Martin of NIAID is attempting to produce HIV-1 pseudotypes that can be used to infect mice directly. If those efforts succeed, then the animals could be used as AIDS models without having to engraft them with human cells. ■ JEAN MARX