First Mutant Mice Infected With AIDS

Three research teams this week reported long-awaited successes in the use of mice as animal models to investigate AIDS and other fatal human diseases.

Among the accomplishments, all of which appear in the Dec. 23 SCIENCE, two U.S. teams managed for the first time to infect mice with the AIDS-causing virus, HIV. In one case, some of the mice showed symptoms resembling AIDS in humans – the first time any animal has developed an HIV-induced fatal syndrome. But in a major setback, workers performing routine maintenance in that laboratory on Dec. 3 inadvertently killed nearly all of the 130 uniquely engineered mice.

Following HIV's discovery five years ago, AIDS researchers could find only two animal species – humans and chimpanzees – susceptible to HIV infection, and only humans actually develop AIDS. Mice, the most popular animal models for studying human disease, lack on their cell surfaces the so-called CD4 receptors that HIV must bind in order to cause infection. Malcolm A. Martin, Abner L. Notkins, Jan W. Abramczuk and their colleagues at the National Institutes of Health (NIH) in Bethesda, Md., bypassed that obstacle by injecting multiple copies of HIV's entire genetic code into fertilized mouse eggs. The researchers implanted the HIV-laden embryos into surrogate-mother mice, where the embryos developed normally but with ready-made AIDS infections in many of their dividing cells.

None of the 13 transgenic "founder" mice thus created showed symptoms of AIDS. But when these founders mated with normal laboratory mice, some of the offspring developed a fatal illness. In particular, nearly half the progeny of one mother were runts and developed a skin disease resembling psoriasis, common in about one-quarter of AIDS patients. The offspring also contracted a pneumonia similar to that seen in many AIDS patients and had enlarged spleens and enlarged lymph glands, or lymphadenopathy, before dying at the rodent adolescent age of 25 to 28 days.

Offspring from other founder mice showed a variety of lesser symptoms. Tests showed that sick mice had HIV DNA in their cells, while well mice did not.

"We don't really know why the founders themselves haven't come down with the disease, but there are several possible explanations," says Notkins. He says it's possible the offspring have HIV in a greater number of cells than do their parents. More likely, though, the HIV is integrated into different parts of the mouse genome in different offspring, which in turn may affect the virus' ability to trigger disease.

"The transgenic mouse model is definitely a very exciting model, because the mouse is much more amenable to laboratory study and because we know a lot about mouse genetics," says Yen Li, a researcher at the New England Regional Primate Research Center in Southborough, Mass., where researchers study the AIDS-like simian immunodeficiency virus in rhesus monkeys. "Definitely we can use this model to study certain aspects of the disease, but for the whole picture we may have to employ other animal models as well."

Martin agrees that because natural infection is bypassed in the mice, the model has little potential for elucidating the process of infection itself, and probably will not prove useful in vaccine studies. In addition, although modest reductions occurred in some lymphocyte functions, the mice did not suffer from extreme immunodeficiency as human AIDS patients do. However, he says, "this whole system may be important for understanding some of the mechanisms at work in HIV patients to see what causes lymphadenopathy, skin problems and so on," and for testing the effectiveness of new drugs.

In addition, the researchers hope to inject various portions of the HIV genome into mouse embryos to study the role of individual viral genes. They plan to begin their original experiments anew this week; only three mice survived the inadvertent air-supply cutoff by workers repairing an alarm system at the NIH laboratory. NIH biosafety officials had required researchers to keep the infected mice in an airtight, high-security "glovebox" facility to prevent them from escaping.

Working in a similar facility in California, Joseph McCune and his colleagues at the Stanford University School of Medicine injected HIV into a custom-designed strain of mice bearing human immune systems (SN: 9/24/88, p.198). They report the first successful spread of HIV infection in human thymus and lymph nodes in an animal model. Although they note no clinical symptoms after eight weeks of HIV replication in the mice, the researchers predict their model may "closely approximate the course of infection in man."

In related research, Suzanne Kamel-Reid and John E. Dick of the University of Toronto grafted human stem cells into immune-deficient mice. Stem cells are the undifferentiated progenitors of all human immune cells; the research will allow an unprecedented view of human blood-cell development in a living system. The scientists say that by adding genetic markers to various stem cells, or by altering the cells' genetic codes in ways that can lead to leukemia, AIDS and other blood-cell diseases, their mouse model will help researchers study the progression and treatment of those diseases. – *R. Weiss*

Diabetes and the dangers of pregnancy

Insulin-dependent diabetic women with high blood sugar levels have an increased chance of miscarriage during the first trimester of pregnancy, according to new research. "There is a risk of losing a pregnancy associated with maternal diabetes. It appears that the risk can be eliminated by achieving good metabolic control," says James L. Mills at the National Institute of Child Health and Human Development in Bethesda, Md.

Mills, Joe Leigh Simpson at Northwestern University in Chicago and colleagues from a multicenter research team studied 386 diabetic women who required insulin injections to regulate their blood sugar levels and 432 nondiabetic controls. All women entered the study either before or within 21 days of conception. The researchers found that diabetic women who kept their blood glucose levels within a normal range had no greater risk of spontaneous abortion than controls. But for women with poor control, the threat of pregnancy loss rose as their blood sugar levels increased. The researchers report their findings in the Dec. 22 NEW ENGLAND JOURNAL OF MEDICINE.

"Diabetic women must be made aware that the time to prevent birth defects and spontaneous abortion is before conception, and contraceptive advice should be offered so that every pregnancy can be planned in advance," says Donald R. Coustan at Brown University in Providence, R.I., in an editorial accompanying the research report.

Achieving metabolic control of diabetes isn't always easy. "It's really more complicated than just taking insulin," Miller says. He recomends that diabetic women visit their doctors before pregnancy so that diet, exercise, and insulin can be coordinated to bring glucose into a normal range. – *K. A. Fackelmann*