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Update

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Transgenic Mice Develop AIDS-like Disease, Virus Recovered

Scientists at the National Institutes of Health have produced mice that may be a valuable model for understanding how the human immunodeficiency virus (HIV, the cause of AIDS) induces disease in infected humans. The mice contain the genetic information for the AIDS virus in every cell of their bodies and spontaneously develop disease with many of the features of AIDS. The disease observed is providing a way to examine pathogenic effects of individual HIV proteins in various tissues and organs, as well as early steps in the evolution of immune system destruction. "These transgenic mice are expected to be valuable not only for better understanding of HIV effects on tissue, but also for testing of therapeutics to prevent HIV-induced disease," said Anthony S. Fauci, Director, NIAID.

To study how HIV might affect tissues in a whole animal the researchers produced mice that contain complete copies of HIV genetic material in every cell of their bodies. Because the mice contain genetic material from another organism--HIV--in addition to their own, the mice are called transgenic. "Obtaining information about how HIV induces disease in infected people and ultimately destroys the immune system is a high priority of AIDS research. This can't be learned from the tissue culture systems currently available," said Dr. Malcolm A. Martin, Chief, NIAID Laboratory of Molecular Microbiology, and head of the research team.

To make the transgenic mice, Dr. Jan W. Abramczuk from the Laboratory of Oral Medicine (LOM), National Institute of Dental Research (NIDR), injected complete copies of HIV DNA into fertilized mouse eggs that were subsequently implanted into anesthetized adult female mice. Sixty-four mice were born; of these, the researchers identified seven (called "founders") that contained complete copies of HIV DNA in their chromosomes and later transmitted the copies to their transgenic offspring.

None of the seven founder mice showed any sign of disease, but about one-half of the offspring of one founder developed symptoms that were apparent 10 to 12 days after birth. The affected animals were easily identified by their smaller size (50 to 60% of the weight of unaffected littermates) and a skin condition characterized by dry and scaly tails, ears, and paws. All the diseased animals contained copies of HIV in their cells, while their healthy littermates did not. All affected animals died at about one month of age.

Several of the sick animals were sacrificed prior to natural death and their tissues examined microscopically to obtain information about how fatal HIV-induced disease evolves. All affected animals developed a lung disease characterized by accumulation of immune system cells called lymphocytes and macrophages around blood vessels in the lungs. This condition is similar to interstitial pneumonitis present in adult AIDS patients. Lymphadenopathy (swollen lymph nodes in the absence of tumors or other infection) existed in all of the diseased animals. The affected mice also developed a skin condition that had many of the abnormal features of human psoriasis, a disease frequently seen in adults with AIDS. Of

particular note was the recovery of infectious HIV particles from the skin, spleen, and lymph nodes of some affected animals. Dr. Abner L. Notkins, Chief, LOM, and Scientific Director, NIDR, who also participated in this work noted, "this is the first example of a transgenic mouse system in which the complete genetic information of an infectious human pathogen has been integrated into cells and the animals actually developed a disease."

The offspring of another founder mouse were also affected. These animals were smaller in size, became lethargic, and died spontaneously. Every affected animal from which DNA could be obtained was transgenic (contained HIV). Other founder animals, in comparison, did not give rise to offspring that spontaneously developed disease.

Because mouse cells do not contain the receptor by which HIV enters cells in humans, mouse cells cannot naturally become infected with the virus. The researchers believe that the disease observed in mice was due to the synthesis of viral proteins or progeny particles within particular mouse cells. For example, the production of HIV proteins or complete viral particles within macrophages residing in the lung or lymph nodes of the transgenic mice could have a direct toxic effect on these tissues, or could elicit the production of cellular proteins that could induce the disease observed.

Because of potential hazards associated with the production of mice capable of producing infectious HIV particles in their cells, the experiments are carried out in NIH Biosafety Level 4 (BL4) containment facilities--the highest level. Inside the laboratory the mice are in cages which in turn are placed in an approximately 3 x 4 x 30 foot plexiglass and steel containment area called a glovebox. This contained working area derives its name from the thick rubber gloves attached to its walls through which the researchers work with the mice. There are only two means of entry into the glovebox--through a 40 gallon tank of bleach, or through an autoclave (sterilizing equipment using scalding steam) that must be operated before the door will open. Chances that any of the transgenic mice will escape from the BL4 laboratory are extremely remote.

Before beginning the experiments, Dr. Martin and his colleagues presented their research plan to, among other experts, an NIH biosafety committee, and to the NIAID Recombinant DNA Advisory Committee. These groups decided that the potential benefit of the research outweighed the minute risks.

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This research was reported in the December 23, 1988 issue of Science in "Development of Disease and Recovery of Virus in Transgenic Mice Containing HIV Proviral DNA." The authors are John M. Leonard (1); Jan W. Abramczuk (2); David S. Pezen (1,3); Rosamond Rutledge (1); J. Harry Belcher (1); Frances Hakim (4); Gene M. Shearer (4); Lajos Lamperth (5); William Travis (6); Torgny Fredrickson (7); Abner L. Notkins (2); and Malcolm A. Martin (1).

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