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Transgenic Mice

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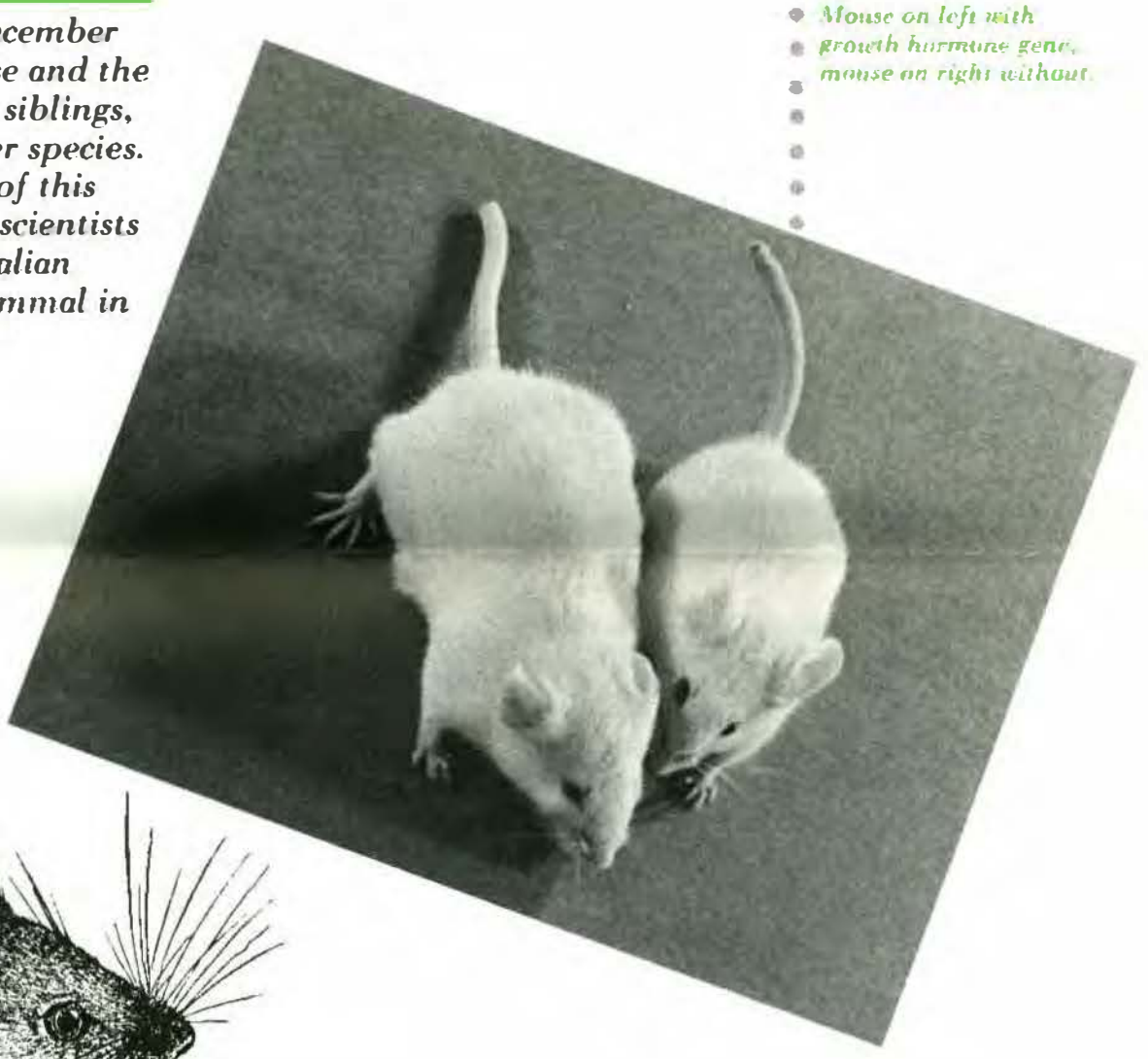
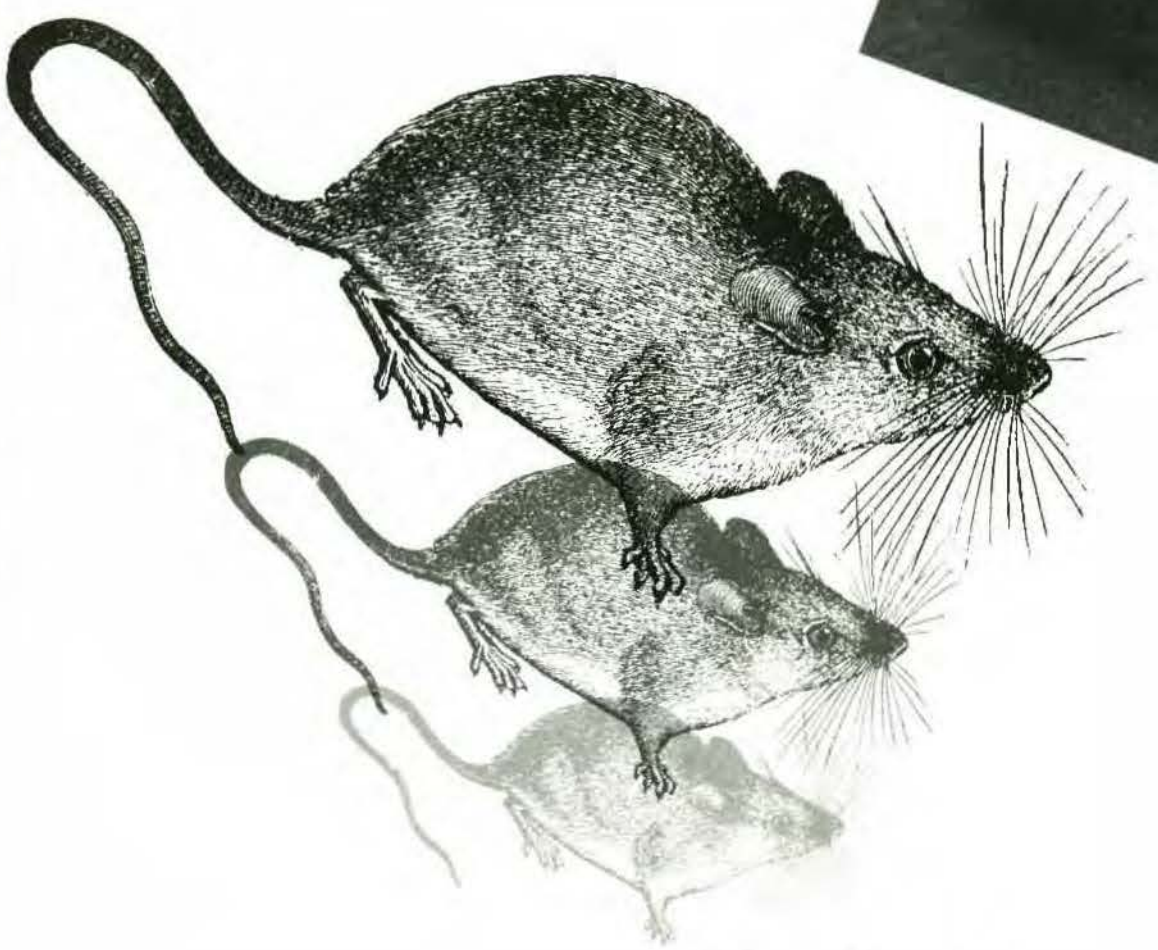
Transgenic Mice

Two mice were the stars of a press briefing in December 1982. One looked like any other laboratory mouse and the other was almost twice as big. Though they were siblings, the big one carried genetic material from another species. It had genes for rat growth hormone. The birth of this mouse and six others marked the first time that scientists had succeeded in making DNA from one mammalian species function and be expressed in another mammal in such a dramatic manner.



Mouse on left with growth hormone gene, mouse on right without.



These mice were the culmination of several years of research by Ralph L. Brinster, V.M.D., Ph.D., Richard King Mellon Professor of Reproductive Physiology, School of Veterinary Medicine, University of Pennsylvania, a principal investigator in these studies which were supported by grants from the National Science Foundation and the National Institutes of Health. The co-investigators were Dr. Richard P. Palmiter, Howard Hughes Medical Institute, University of Washington, Seattle; Michael G. Rosenfeld, University of California, San Diego; Neal C. Birnberg and Ronald M. Evans, Salk Institute for Biological Studies, La Jolla, California; Robert E. Hammer and Myrna E. Trumbauer, Laboratory of Physiology, School of Veterinary Medicine, University of Pennsylvania.

Dr. Brinster and his colleagues have been conducting basic research to study gene regulation and the genetic basis of development. In their experiments they introduced foreign

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Transgenic Mice

(continued from cover)

genes into mammalian embryos at the earliest stage of gestation. The technique utilized was gene-splicing where DNA from one species was attached to the mouse metallithionein (MT) gene and then micro-injected into fertilized mouse eggs which were implanted into foster mother mice.

The MT gene enables the body to bind heavy metals and have resistance to these substances. It is present in most tissues and most prominently found in the liver. The gene is activated when the organism ingests heavy metals, then messenger RNA is produced which enables the cells to bind heavy metals.

In earlier experiments Dr. Brinster, *et al.* had fused the mouse MT gene with a virus gene to measure specific viral enzymatic activity in the cell. The altered genes were micro-injected into fertilized mouse eggs which were implanted into female mice. Some of the offspring showed the enzyme activity, generated by the virus gene, when they were given heavy metals. This experiment helped the researchers to identify the sequence responsible for heavy metal inducibility on the mouse MT gene. It was this sequence that was attached to the rat growth hormone gene.

In the latest experiment Dr. Brinster and his colleagues modified the rat growth hormone gene by removing its regulatory sequences and replacing these with the regulating part of the mouse MT gene. The section of the MT gene used was the sequence which contains the MT promoter that helps control expression of the gene in the cells of the organism. The altered gene was cloned, and the new gene was placed into fertilized mouse eggs by micro-injection. The researchers modified 170 eggs and these were implanted into foster mother mice.

Some gave birth and twenty-one offspring resulted. Tests showed that seven of these had inherited the altered gene. After weaning, these mice were fed a regular diet and small quantities of zinc, a heavy metal, were added to their water to activate the altered gene. Six of the mice showed an accelerated growth rate prior to the addition of zinc to their diet. One of these was removed from the zinc supplement after two weeks and continued to grow faster than normal.

Studies on the mice found that growth hormone was produced in the liver and other tissues. Normally this hormone is produced in the pituitary gland. Some of the mice had up to 800 times more growth hormone than normally expected in mouse blood. It appears that the overproduction is due to a lack of feedback, a mechanism which regulates the production of the hormone when it is produced by the pituitary gland. It was found that mice with the greatest amount of growth hormone had the largest quantity of the altered gene in their tissues. The experiment was carried further. Mice possessing the altered gene were mated to normal mice and of the nineteen offspring, ten carried the gene. The offspring with the new gene also grew larger than normal.

These mice demonstrate for the first time that genes can be transplanted from one mammalian species to another and can be expressed phenotypically in such a manner as to affect basic metabolic function. This has great implications for research. These mice can serve as a model to study gigantism, a human genetic disease. It was found that the amount of growth hormone produced by the mice far exceeded the amount which can be produced by conventional methods. Thus, the technique of fusing the MT gene to other genes controlling protein production in mammals may lead to "genetic farming" where such altered genes are utilized to produce protein substances such as blood clotting factors used for hemophilia.

The use of growth hormone may also have agricultural application; perhaps one day it may be possible to alter the growth pattern of animals produced for food so they can reach the market in a shorter time. The fusion technique may also be utilized in development of cows with greater capabilities of milk production.

The research by Dr. Brinster and his colleagues opens important new avenues of study and will provide insight into gene regulation and the basis of development.

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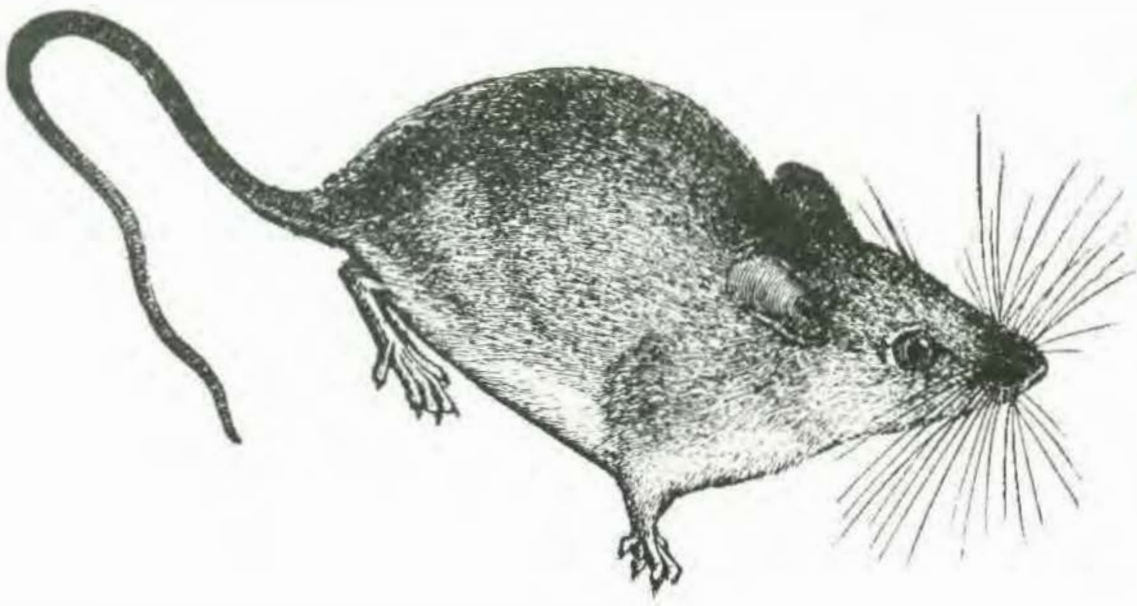

DNA + MT