# Giant mice grow from rat hormone gene transplant

Transfer of the gene for rat growth hormone into fertilized mouse eggs has provided the first dramatic effects of genetic engineering in mammals. A collaborative effort by scientists at four institutions produced six extra-large mice, some almost twice the normal size. Matings of large male mice with normal females gave both large and normal sized offspring, indicating the rat gene is permanently incorporated into the mouse DNA.

These results indicate for the first time that genes transferred from one animal to another can function appreciably. Previous experiments by several teams have demonstrated that genes can be successfully transferred and even made to produce low levels of protein (SN: 10/16/82, p. 252; 9/12/81, p. 164), but none had been shown to function "in a manner that was meaningful for the life of the host animal," the scientists say.

The reason the mice with the transplanted rat growth hormone gene are larger than normal mice is not because rats are larger than mice. Instead it is because the rat gene which was transferred is unusually active and because it is expressed in an unusual location. Before inserting the rat gene the scientists removed its control region and attached the control region of an unrelated mouse gene called metallothionein. Therefore once inserted in the mouse, the rat gene was not turned off by the mechanisms that naturally regulate growth hormone production. And instead of being made in the pituitary gland, much of the rat growth hormone was produced by the mouse liver, a major site of action for the metallothionein gene.

In the blood of the largest genetically engineered mice, the scientists measured growth hormone at 800 times the normal amount, they report in the Dec. 16 NATURE. This situation of continuously high levels of hormone parallels the human clinical condition called gigantism. These experiments may lead to work to mimic for experimental purposes, or to correct, various genetic diseases.

The recent experiments "point the way to a new era in genetic engineering," say the scientists in an announcement released by the four institutions. They see new possibilities for obtaining important biological products, such as hormones, and for studying their effects. They also envision more powerful approaches to the study of gene regulation and the genetic basis of development, work that could lead to a better understanding of congenital diseases and cancer. Finally, they suggest agricultural applications—for example, accelerating growth rates in farm animals to increase yield of milk and meat. The scientists state, however, that it is "impractical" to apply this technology directly to humans.

UPI

*High amounts of growth hormone, produced by a rat gene attached to the control element of an unrelated mouse gene, caused this mouse (bottom) to grow to almost twice normal size (top). This is the first example of an experimental gene transfer between species noticeably influencing an animal's physiology.*

The scientists collaborating in the transfer of the rat gene to mice are Richard D. Palmiter of the University of Washington in Seattle; Ralph L. Brinster, Robert E. Hammer and Myrna E. Trumbauer of the University of Pennsylvania School of Veterinary Medicine in Philadelphia; Michael G. Rosenfeld of the University of California School of Medicine in San Diego; and Neal C. Birnberg and Ronald M. Evans of the Salk Institute in San Diego.

The key to their success is the fusion of the rat gene to a strong regulating element. Many copies of the fused gene were injected into each of 170 fertilized mouse eggs, which were then inserted into female mice serving as foster mothers. From these eggs, 21 mice were born. They appeared normal, but within a few weeks some began to grow more rapidly than their littermates.

Analysis of the DNA of the young mice showed that seven animals carried the rat growth hormone genes, in one to 35 copies per cell. Further biochemical studies revealed that the highest numbers of gene copies corresponded to the greatest amounts of messenger RNA molecules from these genes in the cells. The mouse cells correctly processed the messenger RNA molecules derived from the rat gene, removing four non-coding, intervening sequences. The largest of the animals had the highest levels of growth hormone in the blood and the greatest numbers of gene copies.

The mouse with the most copies of the rat gene died after 7 weeks of rapid growth. Some of the biggest of the genetically engineered mice are partially sterile, but some were able to mate. One male mouse transmitted the rat growth hormone gene to 10 out of 19 offspring. In this case the genes appear to be stably integrated into one of the mouse's chromosomes, but the scientists need to do further studies to determine their exact locations.

In its natural setting, the metallothionein gene product helps clear the body of heavy metals. The gene's control element switches it on in the presence of metal. Whether heavy metals can influence production of rat growth hormone by the hybrid gene containing a metallothionein control region in mice is still uncertain. The scientists put mice carrying the hybrid gene on a zinc diet after they were weaned, but at that time they were already larger than normal, and one animal removed from the diet continued to grow at an accelerated rate. The scientists suggest that mice carrying several copies of the gene may produce growth hormone all the time without requiring heavy metal. They plan to look at the question again in offspring, which are expected to carry fewer copies of the gene. —*J. A. Miller*

## Sea treaty signed by 117

Delegates of 117 nations signed the United Nations Law of the Sea Convention in Montego Bay, Jamaica last week. The international sea law treaty establishes a code for all uses of the oceans and their resources. The United States, along with Britain, Belgium, Italy, Japan, Venezuela and West Germany, was one of 22 nations that did not sign the treaty. The treaty remains open for two years and will not take effect until 12 months after it is ratified by 60 nations. Its provisions will be binding only to those nations that ratify it.

President Reagan announced in July that the United States would not sign the treaty (SN: 7/17/82, p. 38), mainly because many provisions regarding deep seabed mining were perceived as unacceptable, including the creation of a global authority that would determine who mines the metals. Contracts for seabed mining would be awarded to mining consortiums, including concerns from America, France, Japan, the Soviet Union and India. For each site mined, a private or national mining enterprise would be required to give to the global mining authority a site equal in size or value. The treaty also stipulates that the sovereign territory of each nation extends 12 miles beyond its coast, and sets criteria for rights to fishery and oil and gas resources. □