

## Effects of Chronic Overproduction of GH and IGF-I in Transgenic Mice

An animal model of gigantism was created a few years ago by developing a transgenic mouse that expressed high levels of growth hormone (GH). The animals exhibited a dramatic increase in size and weight as well as a variety of complications (*Nature* 1982;300:611-615). Because nonmurine GH genes were used and also because the GH was expressed in many organs, it was not known if the pathologic effects were due to chronically high levels of circulating GH or to other factors. To resolve this question, another transgenic mouse model was created in which hypothalamic growth hormone releasing factor (GRF) was overproduced. This caused hyperplasia and hypertrophy of pituitary somatotrophs with secretion of excessive amounts of endogenous GH in the transgenic mice (*Nature* 1985;315:413-416). Since many of the effects of GH are mediated by insulin-like growth factor I (IGF-I), Quaife et al produced another transgenic mouse in which IGF-I is overproduced. They also compared a number of parameters in the three transgenic mouse models and controls.

In general, animals with high levels of GH exhibited similar features regardless of the source of the "trans" GH gene (rat, human, bovine), the promoter that regulated its expression (metallothionein or albumin promoter), or whether the GH excess was endogenous from GRF overstimulation or from expression of a foreign GH gene. When these animals (high-GH animals) were compared to animals with high IGF-I levels that resulted from IGF-I transgene expression (high IGF-I animals), several differences were detected. Although both animals weighed much more than controls, linear skeletal growth was increased in the high-GH animals

but not in the high-IGF-I animals. In addition to GH, insulin levels were greatly increased in the high-GH animals, whereas both were subsequently reduced in the high-IGF-I animals. Hepatic and renal pathologic lesions were seen in the high-GH animals but not in the high-IGF-I animals. The lesions consisted of hyperplasia, hypertrophy, and sclerosis in the liver and increased glomerular size, mesangial hypercellularity, and glomerular sclerosis in the kidneys. The renal lesions resembled those found in diabetes. Thickening of the skin due to an increase in dermal and subdermal fat was observed only in the high-IGF-I animals. Cholesterol tended to be elevated in the high-GH animals, whereas triglycerides were elevated in the high-IGF-I animals. Finally, survival was reduced in the high-GH animals; 60% were alive at 6 months of age compared with 100% of controls. The deaths were attributed to renal disease. Survival was not examined in the high-IGF-I animals.

The authors concluded that chronically elevated GH has detrimental effects on a number of organ systems and that many of these effects are not mediated by IGF-I alone. They acknowledged many differences between transgenic models of GH elevation and the clinical administration of GH in humans but cautioned that the long term effects of GH treatment in children must be carefully evaluated.

Quaife CJ, Mathews LS, Pinkert CA, et al. *Endocrinology* 1989; 124:40-48.

**Editor's comment**—As the authors point out, the experimental models employed in this study of the effects of chronic GH and IGF-I stimulation differ both qualitatively and quantitatively from the clinical setting in which GH is administered to children. Nevertheless, as temptation grows to use higher and more frequent doses of GH to treat short stature, especially short stature not due to GH deficiency, the caution urged by the authors should be remembered.

One of the more interesting observations from the study is that even though IGF-I levels were increased 1.5-fold and body weight 1.4-fold over controls in the mice expressing the IGF-I transgene, linear skeletal growth was not increased. These results differ from those reported by Guler et al (*Proc Natl Acad Sci USA* 1988;85:4889-4893), who infused GH or IGF-I into hypophysectomized rats and found increased linear bone growth in both cases. Because of differences in design, the results of the two studies cannot be directly compared, but both sharpen the debate over how GH acts to promote linear skeletal growth.

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## Do Extracellular Matrix Proteins Exhibit Growth Factor Activity?

Historically, growth factors were identified as circulating proteins and peptides that influenced cell division and differentiation. It was later determined that many growth factors are generated and act locally, ie, paracrine and autocrine growth factors. There is now growing evidence that many extracellular matrix proteins contain func-

tional domains with growth factor activity.

Engel recently reviewed the situation with regard to epidermal growth factor (EGF) domains in several large matrix proteins. EGF is a small peptide (53 amino acid residues) that is known to promote mitosis in many cell types through interaction with a specific cell