

**Editor's comment:** *The implications of the 2 different models of growth—continuous versus saltatory—for the regulation of mitogenesis and growth are significant. This writer finds it difficult to conceptualize a regulatory system in which cellular growth completely ceases and then resumes. On the other hand, a system that modifies the rates of cellular growth (but not to zero) is less difficult to conceptualize because this is observed clinically in the growth of normal infants, children, and adolescents, as well as during and after intervals*

*of illness or suboptimal nutrition. I would prefer to consider the periods of absent growth observed by Lampl et al<sup>1</sup> as intervals of such slow cellular replication that the measurement instruments utilized to record growth were too insensitive to recognize them—thus merging the concepts of continuous and saltatory growth.*

Allen W. Root, MD

## A Novel Transcriptional Activator Originating From an Upstream Promoter in the Human Growth Hormone Gene

**Editor's comment:** *The finding of a "gene within a gene" is intriguing. By analogy to large proteins that may be precursors for several peptides, eg, proopiomelanocortin, it is likely that other genes will be identified with similar construction. It is of interest to speculate that growth hormone-derived transcriptional activator (GHDTA) may be a transcription-activating factor for proopiomelanocortin; alternatively, it might serve as a repressor of human growth hormone (hGH) gene transcription in corticotropes. Now that you have read this comment, please read the abstract that follows.*

Allen W. Root, MD

Labarrière and coworkers identified a second gene product that begins in the upstream promoter region of the hGH gene and includes all of the first and part of the second exon of the hGH gene. The major transcription-activating factor for the hGH gene is Pit-1; this factor binds to upstream bases -130 to -105 and -92 to -65 to initiate gene transcription for hGH mRNA. Between bases -294 and -177 is a sequence that also has the structure of a transcription-promoting region. These investigators cloned the mRNA transcribed from this

secondary promoter region, which begins at base -151 in the hGH gene and ends in the middle of exon 2 of the hGH gene at a stop codon, the result of a frameshift. This mRNA encodes a protein of 107 amino acids (molecular weight = 11.4 kd). Expression of mRNA for hGH is confined to the pituitary somatotrope, whereas the protein product of the secondary mRNA is detectable in pituitary corticotropes and placenta. The second protein has been termed GHDTA because it acts as a transcription-activating factor in cells transfected with reporter genes. GHDTA has homology with a liver-specific transcription factor and contains potential protein kinase C-dependent phosphorylation sites. The investigators suggest that GHDTA might be a DNA-binding transcription factor or an activator of a transcription factor.

Labarrière N, et al. *J Biol Chem* 1995;270:19205-19208.

**2nd Editor's comment:** *A change in GGH's usual format was made for this abstract and the editor's comment precedes the abstract. This was done so that readers may better interpret the abstract.*

Robert M. Blizzard, MD

## Insensitivity to Anti-Müllerian Hormone Due to a Mutation in the Human Anti-Müllerian Hormone Receptor

Müllerian-inhibiting substance (MIS), a product of the Sertoli cell, causes regression of müllerian duct development and prevents formation of the fallopian tubes, uterus, and upper third of the vagina in the normal male. Abnormalities in the production of MIS lead to the persistent müllerian duct syndrome (PMDS) of müllerian duct structures in phenotypic and genetic males. The present investigators have isolated and characterized the human MIS receptor and have identified a patient with PMDS due to an abnormality in the gene for this receptor. This patient thus has end-organ insensitivity to MIS. This gene is situated on chromosome 12q13 and is composed of 11 exons that encode a mature protein of 573 amino acids. Exons 1 through 3 encode the signal sequence (17 amino acids) and extracellular domain (127 amino acids); exon 4

encodes the single transmembrane domain (26 amino acids); and exons 5 through 11 encode the intracellular domain (403 amino acids), which has serine/threonine kinase activity. The human MIS receptor is homologous to that of the rat (78.5%) and rabbit (82%). In addition to the testicular Sertoli cell, RNA for MIS and its receptor is expressed in the normal ovary and some granulosa cell tumors.

In a 3-month-old boy with PMDS, the AMH gene was normal, and serum AMH was easily measurable. Analysis of the MIS receptor gene revealed a guanine to adenine (G→A) transition at a guanine-thymine (GT) dinucleotide at the splicing donor site of the 5' end of the second intron. This led to 2 abnormalities of gene transcription: (1) loss of exon 2 (exon skipping); and (2) substitution of aspartate for glycine at amino