

Response by Authors: We agree with Professor Blizzard's comments. We wish to identify patients with potentially reversible GH secretion who could achieve catch-up growth without GH therapy. Eighty percent of our patients with hyperphagic short stature experienced occult physical, emotional, or sexual abuse. Treating such children with GH daily for many years, without recognizing child abuse, would add insult to injury.

There was no evidence of depression in our patients. GH reversibility was demonstrated in only 1 of 6 nonhyperphagic children in the hospital-referred comparison group who were not anorexic. Two patients had no reversibility of GH secretion.

We understand the point of view that a new syndrome has not been described, but rather a more specific subtype within type II classification of PSS. Nevertheless, considerable evidence of the syndrome's distinctive nature has been gathered. This includes evaluation of a new series of patients. The syndrome is not apparently on a qualitatively similar continuum with other types of PSS, as our data strongly indicate only some children are predisposed to develop it, even within a sibling group. We agree that if classified within Blizzard and Bulatovic's scheme, hyperphagic short stature will fall into category type II, or possibly type IIA. In this condition, GH deficiency reverses spontaneously with environmental manipulation, and such patients often are resistant to GH treatment. Our nonhyperphagic subjects without an eating disorder, which in our experience is rarely associated with GH deficiency, could possibly be classified as type IIB. Patients in this group only occasionally respond to GH treatment.

As induced injury can be considered as a spectrum of disorders, ranging from factitious injury to the Munchausen by Proxy syndrome, PSS also is a spectrum of morbidity ranging from environmentally induced growth failure due to chronic undernutrition to growth failure caused by the endo-

crinopathy originally described by Powell and colleagues in 1967. Our work has not only confirmed these findings in that hyperphagia and polydipsia [were part of the clinical picture of their cases, but we also have shown that hyperphagia and polydipsia] are very sensitive markers that suggest the patient probably has reversibility of GH deficiency. The syndrome is a remarkable example of the potential responsiveness of a neuroendocrinologic system to stress.

Our clinical impression is that many children with hyperphagic short stature are labeled as having true GH deficiency following a day-case evaluation of GH secretion. The true diagnosis is missed. We emphasize the importance of asking the appropriate questions in order to make the correct diagnosis and to reveal that occult child abuse is probable in children with the disorder. The consistency of the symptom constellation in affected children is remarkable. The physician should routinely ask whether a child with growth failure and GH deficiency eats excessively; gorges and vomits if given unlimited access to food; steals food at home and school; hoards food; has polydipsia or pica; scavenges from trash cans; or searches for food at night. We wish to emphasize that among children with GH deficiency, the syndrome of hyperphagic short stature is not as rare as previously believed.

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Holoprosencephaly and Sonic Hedgehog

The "hedgehog" story is emerging rapidly. The hedgehogs are a family of developmentally important signaling proteins first discovered in the fruit fly, *Drosophila*. There are 3 human hedgehog genes known to date: *Sonic Hedgehog (SHH)*, *Indian Hedgehog (IHH)*, and *Desert Hedgehog (DHH)*. They encode secreted proteins that undergo autocatalytic cleavage to produce a carboxy-terminal fragment and a biologically active amino-terminal fragment that tends to remain near the cell of origin.

The hedgehog proteins have been shown to have effects on the developing embryo in many species, including patterning effects on the midline central nervous system (CNS) structures and on developing limbs. Indeed, genetic inactivation of *SHH* in mice produced cyclopia and other CNS abnormalities, raising the possibility that mutations of *SHH* could be responsible for some human birth defects involving these structures.

These latter observations prompted groups headed by Muenke and Tsui to consider *SHH* as a candidate for alobar holoprosencephaly type 3 (HPE3), which behaves as a dominant trait with wide clinical variability in some families. It had been previously mapped to chromosome 7q36. This form of holoprosencephaly involves failure of the forebrain to divide into right and left hemispheres. At the severe end of the spectrum, it is typically associated with midline facial abnormalities, including cyclopia, a primitive nasal structure (proboscis), and clefting. Manifestations at the mild end of the spectrum may be limited to microcephaly, mild hypotelorism, midline facial clefts, and a single maxillary central incisor.

In the first paper, Belloni et al defined a critical region of about 500 kb for *HPE3*. This was done from physical mapping of breakpoints for chromosomal rearrangements in several HPE3 patients. Next, they mapped *SHH* to this interval. Interestingly, none of the breakpoints disrupted *SHH*.

From analysis of *SHH* in 30 families, Roessler et al subsequently detected heterozygous mutations, which segregated with *HEP3* phenotype, in 5 families. Two mutations were nonsense mutations predicted to cause premature termination of the *SHH* protein. Another predicted disruption of the autocatalytic cleavage site. All 3 would be expected to produce loss of function of one of the *SHH* alleles, haploinsufficiency. The paper, as well as invited comments, speculated about how such mutations could cause such profound effects on craniofacial development.

Belloni E, et al. Identification of *Sonic hedgehog* as a candidate gene responsible for holoprosencephaly. *Nature Genet* 1996;13:353-356. Letter.

Dean M. Polarity, proliferation and the *hedgehog* pathway. *Nature Genet* 1996;14:245-247. News and Views.

Roessler E, et al. Mutations in the human *Sonic Hedgehog* gene cause holoprosencephaly. *Nature Genet* 1996;13:357-360. Letter.

Editor's comment: Signaling through the hedgehog family of proteins is becoming very interesting. In the past year, IHH has been implicated in a negative feedback loop controlling the rate of endochondral bone growth. Mutations of the hedgehog receptor, patched, have been found in the Gorlin syndrome and in sporadic basal cell carcinoma; and now mutations of *SHH* appear to cause some forms of holoprosencephaly. Given the apparent importance of hedgehog signaling in so many regulatory circuits, one wonders how many other sporadic disorders, especially those involved in craniofacial and limb development, might also be due to defects in hedgehog signaling.

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Constitutively Activated Receptors for Parathyroid Hormone and Parathyroid Hormone-Related Peptide in Jansen's Metaphyseal Chondrodysplasia

Jansen's metaphyseal chondrodysplasia is a rare form of short-limbed dwarfism associated with hypercalcemia and normal or low serum concentrations of parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP). It is an autosomal dominant genetic disorder. Most cases are due to new mutations. Jansen's metaphyseal chondrodysplasia is recognized in the newborn period by rhizomelic short stature, severe bowing of the legs, fronto-orbital asymmetry, hypertelorism, and hypoplasia of the mandible. X-ray films show cupping and irregularity of the growth plates. All metaphyses are severely involved and appear markedly enlarged, wide, irregular, and cystic. Laboratory findings include increased serum calcium and alkaline phosphatase, with normal or low PTH and PTHrP.

The actions of both PTH and PTH-related hormones are mediated through PTH-PTHrP receptors, and their intracellular signaling is mediated by both cyclic AMP (cAMP) and calcium. PTH-PTHrP receptors belong to the family of G protein-coupled receptors, which have dual signaling properties. They are expressed in many fetal and adult tissues and found in abundance in kidney, bone, and growth-plate cartilage.

Schipani et al have confirmed the presence of a mutation in the gene for PTH-PTHrP receptors in 4 of 6 additional individuals with Jansen's metaphyseal chondrodysplasia. A similar mutation has previously been identified by Schipani et al in an individual with Jansen's metaphyseal chondrodysplasia.

Three of the mutations found had the histidine changed to arginine at position 223 (H223R). One had a novel missense mutation that changed a threonine in the receptor's sixth membrane-spanning region to proline (T410P). None of these mutations were found in the healthy relatives. In one family, the H223R mutation was found in the affected mother and her affected daughter but not in the healthy father.

Mutations cause activation of PTH-PTHrP receptors, resulting in hypercalcemia and hypophosphatemia resembling that of humoral hypercalcemia of malignancy seen in some breast cancer tissues and some hematologic cancers such as adult T-cell leukemia. The mutant receptor seems to be constitutively active in Jansen's metaphyseal chondrodysplasia and its actions appear to be independent of PTH and PTHrP. When the authors compared the PTH and PTHrP receptors containing the H223R mutation with those containing the T410P mutation, they found that receptors containing the T410P mutation had significantly higher ligand-stimulated accumulation of AMP and inositol phosphate and that receptor activation (receptor function) was independent of PTH and PTHrP. Although there were differences in receptor functions between the 2 types of mutations, the manifestations of the disease were similar with both types of mutations in affected individuals. The 2 individuals without identifiable mutations had somewhat milder disease, with less severe hypocalcemia, normal serum phosphorus and alkaline phosphatase activity, normal serum PTH concentrations, and normal urinary cAMP excretion.

Schipani E, et al. *N Engl J Med* 1996;335:708-714.

Editor's comment: The discovery of this constitutively activating mutation has brought to light yet another physiologically important role of PTHrP in fetal bone growth and cellular differentiation. With recent advances in molecular biology as well as in tissue engineering, perhaps it may be possible to correct the abnormality during embryonic and fetal development by in utero gene manipulation and thus eliminate the disorder. This also may be true for some other activating receptors in disorders of growth and other metaphyseal dysplasias.

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