

Pegvisomant also lowered IGF-I concentrations and ameliorated symptoms in acromegalic subjects resistant to treatment with octreotide. Whether this GHR antagonist or later generations of GH antagonists will be useful in children is a matter for study. One hopes that such agents will not be employed to alter the growth of normally tall children, but its

use in other overgrowth syndromes will be of interest to explore in controlled settings.

Allen W. Root, MD

Herman-Bonert VS, et al. Growth hormone receptor antagonist therapy in acromegalic patients resistant to somatostatin analogs. *J Clin Endocrinol Metab* 2000;85:2958-2961.

Normal Growth Velocity Before Diagnosis of Celiac Disease

Celiac disease has been shown to result in nutritional growth retardation even in asymptomatic patients. However, there are instances in which this disease does not alter normal physical growth.

To evaluate height velocity of patients with confirmed celiac disease before and after diagnosis, anthropometric measurements were taken in 23 patients aged 0.1 to 10.66 years of age. All patients studied during the first 6 months of life showed normal growth velocity, and 6 of 10 patients showed normal growth velocity during the second 6 months of life. Ten of 12 patients between 1 and 2 years of age showed normal growth velocity and 7 of 9 patients aged 2 to 10 years also showed normal height velocity. The authors concluded that celiac disease could be present in children who are growing at a normal rate and that appropriate height and growth should not be factors that exclude the possibility of celiac disease.

Lejarraga H, et al. *J Pediatr Gastroenterol Nutr* 2000;30:552-556.

Editor's comment: *This paper is interesting as patients with confirmed celiac disease were followed longitudinally with reliable anthropometric data. While most of us have stressed the pres-*

ence of short stature and delayed growth as 2 of the most important clinical manifestations of celiac disease, it is important to be aware of the existence of untreated patients who grow at normal rates. This paper clearly documents that this indeed occurs but is contrary to the usual clinical presentation. Normal growth found in patients with celiac disease requires an explanation. The length of the lesion in the small bowel could be a factor leading to normal or abnormal growth. In countries where the prevalence of celiac disease is high, clinicians should be alerted to the possibility of this disease in a normal, asymptomatic, short-statured child with a previous history of diarrhea or iron deficiency anemia.

Fima Lifshitz, MD

2nd Editor's comment: *Unfortunately, the authors made only a minimal statement regarding the weight-to-height relationship. Twelve of the 23 patients had normal height and height velocity at diagnosis. Of all the children, 6 also showed normal weight increments before diagnosis. We can only assume that the phenomenon described occurs in children of normal weight for height and in children of low weight for height.*

Robert M. Blizzard, MD

Nutritional Rickets in African-American Breast-Fed Infants

Kreiter and associates report the characteristics of infants and children diagnosed with nutritional rickets at 2 medical centers in North Carolina in the 1990s. Records of 30 children were reviewed; 57% of these presented in 1998 and 1999. All were black and all were breast-fed (average duration of breast-feeding, 12.5 months). Breast-feeding has increased significantly since 1988 (Figure) in North Carolina in both black and white women. Children older than 1 year had a history of poor intake of fortified cow's milk or other dairy products. The age of diagnosis ranged from 5 to 25 months, but one third presented at 12 months of age or younger. Sixty-three percent were diagnosed between April and October, some of the warmer spring/summer months in this southern area. As expected, presenting signs included skeletal abnormalities (n=16) such as bowing of the legs, flaring of the wrist, costochondral beading, fractures, failure to thrive (n=13), hypocalcemic tetany/seizures (n=2), and developmental delay (n=1). Length was <5th percentile in 17 of 26 of the infants (65%), and only 2 patients had a length >50th percentile. With the exception of 1 patient who had

recently begun vitamin D treatment, all patients had hypophosphatemia. Sixty percent had hypocalcemia, and 100% had elevations in alkaline phosphatase.

All of the children with rickets were breast-fed without vitamin D supplementation. A survey of 400 pediatricians in North Carolina revealed that 42% prescribed vitamin supplements for all breast-feeding infants, whereas 42% prescribed supplemental vitamins only for selected breast-feeding infants (ie, those with dark skin who are being exclusively breast-fed for more than 4 to 6 months or who are premature). The authors also note that the 1997 American Academy of Pediatric Policy Statement indicates that "vitamin D and iron need to be given before 6 months of age in selected groups of infants (vitamin D for infants whose mothers are vitamin D deficient or those infants not exposed to adequate sunlight)" but that no guidance is given as to how to test mothers for vitamin D deficiency.

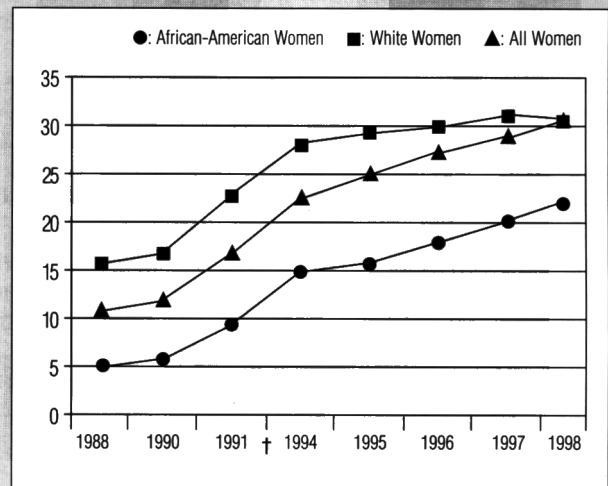
Kreiter S, et al. *J Pediatr* 2000;137(2):153-157.

Editor's comment: Although this is primarily a descriptive report, the information provided is of significant importance not just to pediatric endocrinologists but to all physicians. In this editor's personal experience, I have seen 2 such children in the past 6 months (1 who was 13 months of age and 1 who was 4 years old). Of interest, the 4 year old was referred for evaluation of short stature and failure to thrive. His lower limb bowing and metaphyseal flaring were obvious at cursory inspection.

With the significant increase in breast-feeding, accompanied by a significant increase in public health warnings regarding the effects of excessive sunlight and the subsequent use of sunscreen on many infants, it is important that all physicians be aware of the possibilities of vitamin D-deficient rickets and that children be supplemented appropriately. In addition, it is important that the community and physicians be reminded of the signs and symptoms of this easily treatable cause of short stature. A study of subclinical rickets in both white and black infants who are breast-feeding would very possibly determine that the incidence of clinical or subclinical rickets is very significant in the latter group.

William L. Clarke, MD

Figure



Incidence of breast-feeding in African-American women in North Carolina, 1988 to 1998. Information for women seen for the maternal postpartum WIC visit. †Data not available for years 1992 to 1993.

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The Central Melanocortin System Affects the Hypothalamo-Pituitary Thyroid Axis and May Mediate the Effects of Leptin

In the fasted rodent, in the genetically leptin-deficient mouse (*ob/ob*), and in the genetically leptin-resistant mouse (*db/db*), there is secondary hypothyroidism. Kim and collaborators hypothesize that leptin may act through the melanocortin system (MS) upon pituitary thyroid-stimulating hormone (TSH) secretion in adult rats. The basis for the hypothesis is that the MS is known to mediate the inhibitory actions of leptin on feeding. α MSH was administered by cannulae into the third intracerebroventricular (ICV) or into the intraparaventricular nucleus (IPVN), which regulate the secretion of pituitary TSH. Also, similarly injected was the *agouti*-related peptide (Agrp), which is an endogenous antagonist of melanocortin 3 and 4 receptors (MCR-3, MCR-4). When activated by α MSH, these receptors inhibit feeding.

In vitro, Agrp significantly decreases plasma TSH concentrations in the *fed* animal when injected into the ICVN or IPVN. In contrast, α MSH increased TSH levels in fasted rats. In vitro, α MSH increased the release of thyrotropin-releasing hormone (TRH) from hypothalamic slices (Figure), an effect blocked by Agrp. In this in vitro system, leptin increased and Agrp blocked the release of α MSH and TRH.

Therefore, the investigators concluded that leptin stimulates thyroid function by enhancing the production of α MSH from pro-opiomelanocortin and possibly by blocking the synthesis of Agrp. α MSH stimulates release of TRH, which increases TSH secretion. Consequently, the regulatory pathways for the

control of energy balance via food intake and food metabolism are linked.

Kim MS, et al. *J Clin Invest* 2000;105:1005-1011.

Editor's comment: In the starved state, the expression of TRH in the paraventricular nucleus is dramatically decreased, a response that can be reversed by the administration of leptin. In addition to the pathway through pro-opiomelanocortin and α MSH synthesized in the arcuate nucleus, leptin likely acts directly on transcription of the gene encoding TRH (Figure).¹ Thus, changes in leptin secretion mediate the metabolic responses characteristic of the fed or starved states. Interestingly, MCR-3 and MCR-4 mediate different aspects of leptin- α MSH actions: MCR-3 affects feed efficiency—that is, the quantity of weight gained per calorie ingested—while MCR-4 influences the quantity of food ingested (or appetite) and energy utilization.² Not only does leptin mediate feeding behavior and energy expenditure by its central action, this fat-derived protein also influences bone mass in this manner. ICV administration of leptin inhibits bone formation in *ob/ob* mice by unknown mechanisms, while patients with a loss-of-function mutation in MCR-4 are obese and have a high bone mass.³

Besides its effects on melanin synthesis and dispersal by keratinocytes and on feeding mediated primarily by MCR-4, α MSH, acting through 1 of 5 MCRs, reduces a number of