

humans and its likely importance in pubertal development. The influence of leptin on sympathetic tone is of interest, although the mechanism by which it exerts this effect is unknown at present. The finding of suboptimal GH secretion in the leptin-resistant subjects is unexpected, as patients with leptin deficiency reported to date have had normal linear growth patterns. The criteria employed for the diagnosis of GH deficiency in the leptin-resistant subjects seem reasonable, although the decline in growth rate appeared to coincide initially with a period of food restriction and weight loss. If the leptin receptor influences GH secretion in humans, it may be through regulation of hypothalamic GH-releasing hormone synthesis or secretion.

Allen W. Root, MD

2nd Editor's comment: The investigators of both papers are commended for performing very important studies.

While the data in the second paper pertaining to obesity, sexual infantilism, hyperinsulinemia, and leptin levels are interpreted correctly, I am reluctant to interpret the auxologic and/or biochemical data as being convincing evidence of GH deficiency. The growth curves are not the growth curves of GH-deficient children. The growth of the 3 affected children was never below the 3rd percentile. Two unaffected children (No. 412 and No. 419) were essentially of comparable heights at essentially the same ages as No. 413 and No. 417, who were affected; the latter 2 had not had sex steroids to enhance their growth. The low GH levels are compatible with those often seen in obese children. The IGF-1 levels are marginally low, but no sex steroids were present to stimulate GH production and, consequently, generation of IGF-1. In my opinion, further observations on similar patients are needed for the argument of GH insufficiency to be convincing.

Robert M. Blizzard, MD

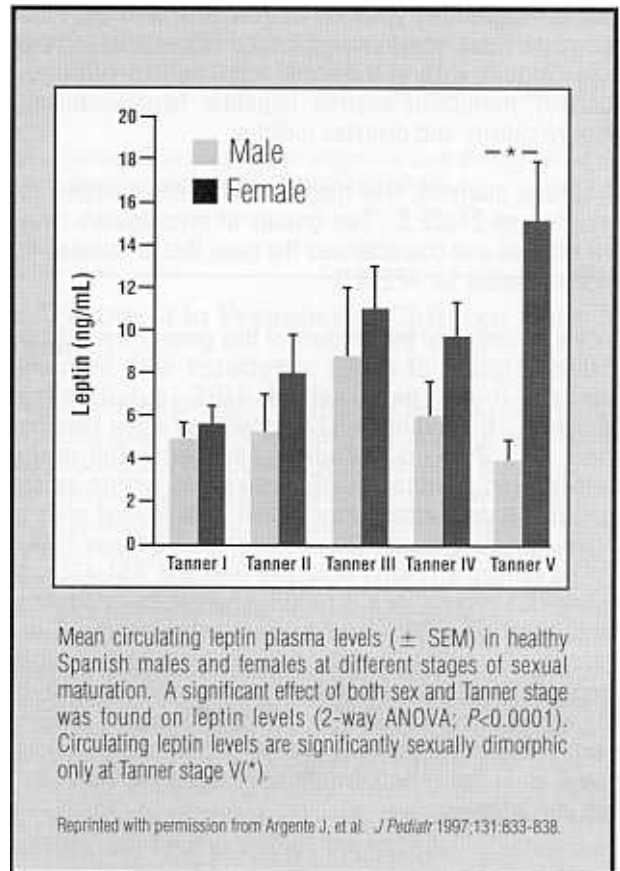
Leptin Plasma Levels in Healthy Spanish Children and Adolescents, Children With Obesity, and Adolescents With Anorexia Nervosa and Bulimia Nervosa

In order to determine normal circulating levels of leptin throughout adolescence as well as in children with eating disorders (obesity, anorexia nervosa, and bulimia nervosa), 100 normal children were prospectively included in this study. They were divided into 5 different groups, corresponding to each of the 5 Tanner stages. These children had height and growth velocities between ± 1 SD and body mass index (BMI) within ± 2 SD. Their bone ages were similar to their chronologic ages. These normal subjects were compared with 14 prepubertal obese children with BMI >2 SD. Fasting blood samples were taken in the morning. Leptin levels were measured at 6 and 12 months when 25% and 50% of BMI-SDS reduction was achieved by the obese group, respectively.

Eleven Tanner stage V females with anorexia nervosa also were included in the study. Leptin levels in these anorexic patients were measured after weight gains of 8% to 10% above their original weight. Bound and free leptin levels also were determined in 3 anorexic and 3 bulimic patients.

Significant changes in leptin level were observed throughout puberty at different Tanner stages. Normal males exhibited only 1 peak level at Tanner stage III, while normal females revealed 2 peaks at Tanner stages III and V. Linear correlation between leptin and BMI-SDS was found in lean normal subjects. Mean leptin levels for obese prepubertal children were significantly elevated compared with age- and sex-matched controls. Normal leptin levels were reached after 1 year on a low-calorie diet and weight loss of at least 50% of the initial BMI-SDS. No direct correlation was found between BMI-SDS and leptin levels in the obese group.

Patients with anorexia nervosa exhibited lower plasma leptin levels compared with age- and sex-matched controls. Those patients with bulimia have higher leptin levels than patients with anorexia nervosa and do



not differ significantly from controls. Total and free leptin levels were higher in bulimic patients than in anorexic patients, but no differences were found in levels of the bound form.

Argente J, et al. *J Pediatr* 1997;131:833-838.

Editor's comment: This paper reports new leptin level data throughout normal developmental stages and its correlation with body weight in 2 different pathologic states, as well as after a phase of weight recovery in obese and anorexic patients. The data presented in this article confirm previous findings during adulthood reported by Ferron et al (*Clin Endocrinol [Oxford]* 1997;46:289).

The authors also demonstrated differences between different leptin fraction levels in those patients with anorexia and bulimia; however, these values were not compared with those of normal subjects. Previous

reports in adult populations already have described the biokinetics of the different leptin fractions in normal and obese subjects. Thus, it would have been interesting to see in this particular study not only how the leptin profiles change throughout the normal development stages but also the kinetics of different leptin fractions in normal subjects throughout childhood. Although determination of leptin values may be helpful to assess adipose tissue stores, it still is not clear what their clinical role is in the diagnosis or prognosis of severe eating disorders.

Zhang et al recently contributed an outstanding lead article concerning leptin physiology in GGH (1998;14[2]:17-26), which readers will find most enlightening.

Fima Lifshitz, MD

J Clin Invest 1998;98:1277-1282.

Diabetes 1996;45:1638-1643.

The APECED Gene and Its Products and Polyglandular Autoimmune Disease I

Autoimmune polyglandular syndrome type 1, also termed autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a monogenic, autosomal recessive disorder associated primarily with autoimmune hypoadrenalism, hypoparathyroidism, and chronic mucocutaneous candidiasis; it also is associated to a lesser extent with ectodermal dystrophies (vitiligo, alopecia), pernicious anemia, hepatitis, hypogonadism, hypothyroidism, and diabetes mellitus.

By linkage analysis, this disorder has been mapped to chromosome 21q22.3. Two groups of investigators have now isolated and characterized the gene that is mutated in and responsible for APECED.

Since it is likely that the product of this gene is a regulator of transcription of genes associated with immune function, it has been named *AIRE* (autoimmune regulator). It contains 2,027 bp with an open reading frame of 1,763 bp encoding 14 exons; the main transcription product (*AIRE-1*) has 545 amino acids without a transmembrane or signal peptide, but with a nuclear targeting signal, 2 cysteine-rich zinc-finger DNA-binding domains (amino acid 299-340 and 434-475), a proline-rich region, and 3 LXXLL sequences—domains associated with DNA and protein interaction. Two alternatively spliced products also have been found composed of a separate first exon and exons 8-14: *AIRE-2* (348 amino acids) and *AIRE-3* (254 amino acids). *AIRE-1* is expressed in the thymus, adrenal cortex, and pancreas as well as in the spleen, lymph node, bone marrow, fetal liver, and testis.

Homozygous and compound heterozygous mutations in *AIRE* have been found in Finnish, Swiss, Dutch, and German families with APECED, including 5 mutations resulting in frameshifts and truncated proteins and loss of the zinc-finger domains. No mutations in *AIRE-2* or *AIRE-3* have been found to date in patients with APECED.

Nagamine K, et al. *Nature Genet* 1997;17:393-398.
Finnish-German APECED Consortium. *Nature Genet* 1997;17:399-403.

Editor's comment: Autoimmune polyglandular syndrome type 2 (primarily autoimmune hypoadrenalism, diabetes mellitus, and thyroid disease) and other polyglandular syndromes such as pernicious anemia and autoimmune thyroid disease are clearly linked to the HLA system (chromosome 6p) and presumably result from an aberration in immune surveillance related to antigen presentation or recognition. Since APECED is not linked to HLA, the protein product of *AIRE* (which has many characteristics of a regulator of gene transcription) introduces another potential pathway of immune regulation. As the genes regulated by *AIRE* are identified and the biologic functions of the products of these genes determined, our understanding of the mechanisms of immunity and disorders thereof will increase. Parenthetically, it is interesting to note that the Down syndrome critical region also is assigned to chromosome 21q22.3. It is possible that the propensity for autoimmune thyroid disease characteristic of the Down syndrome patient may be related to *AIRE*.

Allen W. Root, MD