

been validated in a population in which adult height is far less and there is a secular trend for increased adult stature compared with that of the (stable) Swedish population. If the validity of the Luo equations is further confirmed, they will be more widely utilized and could replace the corrected midparental height of Tanner. Those of you who are particularly interested and/or concerned

about the auxologic tools we use in clinical practice and in research will appreciate this article.

Allen W. Root, MD

Luo ZC, et al. *Pediatr Res* 1998;44:563-571.

Effects of Thyroxine as Compared With Thyroxine (T₄) Plus Triiodothyronine (T₃) in Patients With Hypothyroidism

The authors studied 33 patients receiving either replacement T₄ therapy for chronic lymphocytic thyroiditis (CLT) or suppressive therapy after near-total thyroidectomy because of thyroid cancer. Sixteen had CLT and 17 had thyroid cancer. Mean age was 46±13 years and mean T₄ dose was 175 ± 53 µg/d at baseline. After randomization, patients were assigned to receive T₄ alone for 5 weeks followed by T₄ + T₃ for 5 weeks or vice versa. On the last day of each 5-week period, thyrotropin, thyroid hormones, cholesterol, triglycerides, and sex hormone-binding protein (SHBP) were measured. Physiologic measurements, including pulse, blood pressure, electrocardiogram, sensory threshold, and Achilles tendon reflex, were recorded. Psychological assessment included cognitive function and psychological state.

Significant higher serum T₄ and free T₄ levels were found after T₄ treatment, compared with the combined treatment group. Significantly lower SHBP levels and heart rates also were observed during T₄ treatment. Conversely, after combined treatment, patients showed higher serum total SHBP levels and heart rates. However, those values remained within normal limits in both groups. Serum thyroid-stimulating hormone (TSH), cholesterol, triglycerides, blood pressure, sensory threshold, and Achilles tendon reflex relaxation half-time were similar with both treatment regimens. Significantly higher scores on the digit symbol test indicated better incidental learning, and the higher scores on the digit span test indicated improved mental flexibility and attention. After receiving T₄ + T₃, patients tended to be less depressed and experi-

enced less fatigue-inertia, depression-dejection, and anger-hostility. At the end of the study, 20 patients preferred T₄ + T₃ treatment, 2 preferred T₄ alone, and 11 had no preference.

The authors concluded that patients with hypothyroidism may benefit from partial substitution of T₃, improving their mood and neuropsychological function.

Bunevicius R et al. *N Engl J Med* 1999;340:424-429.

Editor's comment: Triiodothyronine treatment has been proven to be effective in several conditions, including myxedema coma and selective pituitary thyroid hormone resistance. In addition, Escobar-Morreale et al demonstrated that tissue euthyroidism and normal serum concentrations of T₃, T₄, and TSH were achieved in rats only with the administration of a combination of thyroid hormones (*Endocrinology* 1996;137:490-502). In the present study, Bunevicius et al add data to support the potential significance of adding T₃ to the conventional T₄ therapeutic regimen in hypothyroidism. The authors demonstrated not only increases in serum T₃ levels but also improvements in mood and neuropsychological function without total suppression of TSH concentrations. However, long-term studies are necessary to establish the effectiveness of combined treatment with T₄ and T₃, in particular the long-term effects on bone mineralization and cardiovascular function.

Fima Lifshitz, MD

Gene Mutations With Characteristic Deletions in Cord Blood T Lymphocytes Associated With Passive Maternal Exposure to Tobacco Smoke

The risks for cancer, heart disease, and other chronic illness are well known for adults who use tobacco, as are the risks for growth deficiency for fetuses exposed transplacentally to tobacco smoke. Now there is evidence that prenatal exposure to tobacco increases the risk for childhood malignancy. Finette et al used *HPRT* as a reporter gene to study the genetic consequences of tobacco exposure in utero. They analyzed *HPRT* mutations in cord blood T cells from newborn infants of mothers who had been exposed passively to tobacco smoke and of mothers with no known exposure. They searched especially for differences in types of mutations. The results showed the smoke-exposed infants harbored a higher frequency of a genomic deletion commonly associated with early childhood leukemias and lymphomas. The deletions are referred to as "illegitimate" mutational events because they are mediated by V(J)D recombinase activity, which normally mediates genomic rearrangements responsible for T-cell receptor and immunoglobulin diversity. The authors emphasized that the frequency of mutations was not statistically

different between the 2 patient groups; rather, it was the type of mutations that differed. They noted that tobacco-derived nitrosamine derivatives from O6-methylguanine adducts have been detected in fetal cord blood of leukocyte DNA of primates and raise the possibility that these adducts could be related mechanistically to the mutations.

Unfortunately, too few T-cell clones were isolated from infants whose mothers had smoked to be included in the analysis. The authors, as well as the authors of an accompanying editorial (Sozzi G, et al. *Nat Med* 1998;4:1119-1120) cautioned that the results need to be confirmed by other studies.

Finette BA, et al. *Nat Med* 1998;4:1144-1151.

Editor's comment: This is an intriguing article because of its clinical implications. The following is abstracted from the editorial by Sozzi et al appearing in the same issue:

"Although epidemiologic studies have suggested that maternal and paternal passive smoke exposure increases cancer risk in children, the Finette study is the first demonstration of smoking-induced genetic damage in utero. It is noteworthy that a recent study by Hecht and colleagues (presented in August at the American Chemical Society meeting) found that urine from 19 of 31 neonates born to mothers that smoked during pregnancy contained metabolites of NNK (4-methylnitrosamino-1-(3-pyridyl)-1-butanone), a carcinogen found only in tobacco smoke. Metabolites were not found in urine samples from any infants born to non-smoking mothers.

Given the small sample size of the Finette study, additional investigations of the transplacental effects of passive smoke in newborns are required. These studies should include analysis of transplacental exposure of preterm infants and newborns to 'active' as well as passive cigarette smoke. (In adults a similar spectrum of p53 mutations in lung tumors from passive and active smokers has been found.) In addition, measurement of the 'rate' of tobacco consumption in actively smoking mothers as well as a more precise

quantitation of passive smoke exposure in non-smoking mothers should be obtained. V(D)J-recombinase-mediated HPRT deletions also occur spontaneously, thus the comparison of these changes in exposed and in unexposed groups is critical.

This study provides incontrovertible genetic evidence of the devastating effects of tobacco smoke particularly among the young, who suffer a greater risk from environmental toxicants, such as tobacco smoke, not only because of their smaller size but also because of their physiological immaturity. The time has come to proclaim an end to the exposure of preterm infants, newborns, and children of all ages to tobacco smoke."

My opinion is possibly a little more cautious than that of Sozzi et al. I agree the results must be confirmed. The causative nature of the deletions needs to be established before drawing firm conclusions. If the risk turns out to be true, the article provides an additional reason not to expose fetuses to tobacco smoke.

William A. Horton, MD

Monthly Measurements of IGF-1 and IGFBP-3 In Healthy Prepubertal Children: Characterization and Relationship With Growth: The 1-Year Growth Study

Gelander et al studied 65 prepubertal healthy children (38 boys and 27 girls) between the ages of 8 and 11 years (mean, 9.1 ± 0.85 years) with monthly determinations of insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3). In addition, measurements of height, weight, and lower leg length (using a knemometer) were recorded monthly by the same person between 0800 and 1000 hours. All biochemical analyses for each child were performed in the same assay. Additional data, including recent illness, food intake, and the daily mean temperature and number of hours of sunshine, also were recorded. Since concentrations of IGF-1 and IGFBP-3 are age dependent, the values were converted to SDS using prepubertal reference values.

Mean levels of IGF-1 in the children were significantly higher for the girls than for the boys ($P < 0.05$). By multiple stepwise regression analysis, height SDS, gender, and height velocity were significant parameters that explained 45% of the variance in IGF-1 SDS. The mean coefficient of variation for IGF-1 adjusted for age for each child was 13.9%, with a mean difference between samples taken at 3 monthly intervals from -0.4 to +0.3. These changes were correlated with changes in body mass index, but also were influenced negatively by illness and positively by outdoor temperature. Maximum changes over 3 months were related only to changes in temperature. The mean serum concentration of IGFBP-3 was comparable in boys and girls and correlated with the height SDS, weight SDS, height velocity, and weight gain. By using multiple regression analysis, 33% of the level of IGFBP-3 could be explained by gender, height SDS, and weight gain. The mean coefficient of variation for IGFBP-3 was 9.7%, and changes in IGFBP-3 were not related to recent illnesses and changes in body mass index. However, the changes in IGFBP-3 over 1 and 3 months correlated with season, evaluated as either changes in the outdoor temperature or hours of sunshine.

The authors noted that their data demonstrate considerable monthly variation in both IGF-1 and IGFBP-3 of such a magnitude that it exceeds the analytical precision of the measurements. This infor-

mation needs to be carefully considered when evaluating a single IGF-1 or IGFBP-3 concentration in a child who is not growing or whose growth is being evaluated. If repeated IGF-1 concentrations are to be used to evaluate treatment, the changes must exceed -0.4 to +0.4 SDS, whereas the changes for IGFBP-3 must exceed -0.6 to +0.3 to reflect a significant treatment effect. The data also demonstrate the importance of following more than 1 auxologic or biochemical variable. The seasonal variation in growth also has been demonstrated with these changes in IGF-1 and IGFBP-3.

Gelander L, et al. *Pediatr Res* 1999;45:377-383.

Editor's comment: This is an interesting, well-conducted study. The type of carefully collected information that Gelander and colleagues have provided can be of significant use in interpreting biochemical growth variables in short children, even those not receiving exogenous growth hormone. Knowing the coefficient of variation around the child's IGF-1 or IGFBP-3 level enhances the physician's ability to determine whether changes in these parameters are of biologic significance. Finally, it is of interest to have verification of the frequently observed finding that children grow up better when the weather is warmer.

William L. Clarke, MD

GROWTH, Genetics, & Hormones is published under an educational grant from Genentech, Inc. The information reflects the views of the editors and/or contributors and not necessarily those of the sponsor, grantor, or the publisher.

Published by:
405 Trimmer Road
PO Box 458
Califon, NJ 07830

Gardiner-Caldwell
SynerMed

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