

### Editorial Comment:

Sotos syndrome and Weaver syndrome are both overgrowth syndromes beginning usually prenatally. Such overgrowth continues during childhood. These two syndromes are similar in many respects; in respect to overgrowth, mental retardation, large hands and feet, advanced bone age, and tall stature but, usually, adult height within the normal advanced percentiles. However, they do differ in certain subtle respects. The patient with Sotos syndrome (cerebral gigantism) has a head that is dolichocephalic. The occiput tends to be flat in the patients with Weaver syndrome. The face tends to be smaller. There are hypoplastic facial bones and

macrognathia in Weaver syndrome, but pointed chin and normal mandibular development prompts one to think more of Sotos syndrome. The joints are limited in motion often in Weaver syndrome with limited elbow, ankle, wrist, hip, and knee extension. The long bones are widened or splayed in Weaver syndrome and camptodactyly is frequent. Further details concerning these two syndromes can be pulled from the pediatric database, although the update listed is 1994 (<http://www.icndata.com/health/pedbase/files/sotosynd.htm> - or - [weaversy.htm](http://www.icndata.com/health/pedbase/files/weaversy.htm)). Comparable data can also be found on the web at <http://www.nlm.nih.gov>. At this web site you will have a choice to enter "Weaver".

Robert M. Blizzard, MD

### Abstracts from the Literature

## Circulating Levels of IGF-1 Directly Regulate Bone Growth and Density

Previous studies by LeRoith and co-workers and Ueki et al have demonstrated that selective loss of liver-derived insulin-like growth factor-1 (IGF-1) or of acid labile subunit (ALS) does not substantially impair murine growth and development despite marked decline in circulating levels of IGF-1.<sup>1,2</sup> This has led to the suggestion that only the IGF-1 produced locally by bone is necessary for linear growth.<sup>3</sup>

In order to explore this question further, LeRoith and his colleagues developed double "knock-out" animals which were deficient in both liver IGF-1 and ALS (LID-ALSKO), and compared these with animals deficient only in liver IGF-1 (LIDKO) or ALSKO. As anticipated, serum concentrations of IGF-1 were decreased markedly, -65% in ALSKO, -75% in LIDKO, and -90% in LID-ALSKO relative to control animals with normal hepatic IGF-1 and ALS production. However, the rate of IGF binding protein-3 (IGFBP-3) degradation was also increased in these animals; thus free IGF-1 values were increased modestly in LIDKO (+150%), minimally in ALSKO (+108%), and markedly in LID-ALSKO animals (+350%). Growth hormone and insulin concentrations were greatly increased in LID-ALSKO mice. The clearance of IGF-1 was markedly accelerated in ALSKO (32 minutes) and LID-ALSKO (18 minutes) as compared with control (69 minutes) and LIDKO (73 minutes) mice, reflective of lack of binding of IGF-1 to IGFBP-3/ALS.

Intrauterine growth of all animals was apparently normal. By 3 weeks and 4 weeks of post natal age (Figures), the length and weight of the LID-ALSKO mice were less than those of the intact animals. Linear growth of the LIDKO and ALSKO animals did not differ from controls. However, the rate of weight gain of ALSKO mice was impaired to the same extent as that of the LID-ALSKO group. Tibial length, and heights of germinal, proliferating, and hypertrophic zones of the proximal

tibial growth plate, were significantly diminished in the LID-ALSKO mice but not in the two single "knock-out" groups. On the other hand, femoral length, total and cortical bone density, periosteal circumference, and cortical and trabecular bone volume were diminished in all "knock-out" groups, but to a substantially greater degree in the LID-ALSKO animals. Administration of exogenous IGF-I increased linear growth, femoral length, and size of the proximal tibial growth plate, as well as IGFBP-3 concentrations, in all groups. IGF-1 mRNA levels in bone were similar in all groups.

The investigators concluded that *circulating* IGF-1 was important for linear and appositional bone growth and bone mineralization and that its effects were mediated through actions on periosteal osteoblasts as well as upon chondrocytes within the epiphyseal growth plates.

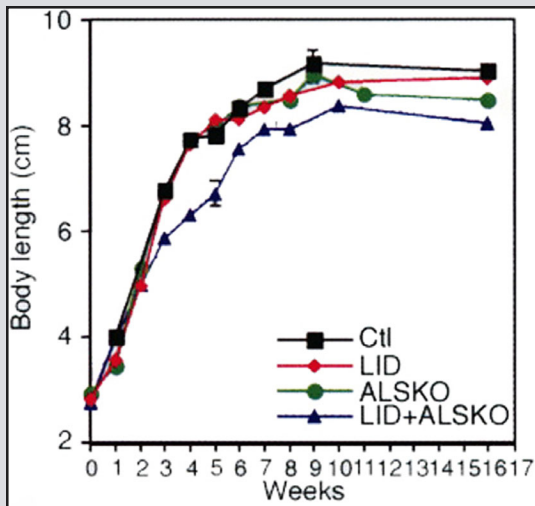
Yakar S, et al. *J Clin Invest* 2002;110:771-781.

**First Editor's Comment:** *This important paper establishes the necessity of circulating IGF-I for normal growth and bone mineralization. It demonstrates that osseous synthesis of IGF-I alone is insufficient for normal linear growth of bone and mineral deposition. Thus, reexamination of the "somatomedin hypothesis" suggests that both liver derived and locally synthesized IGF-I are necessary for normal bone metabolism. Interestingly, "knock-out" of any of the IGFBPs has little effect upon the phenotype of the mutant mouse, but their over expression results in inhibition of growth.<sup>4</sup> One wonders what the phenotype of the mouse that lacks IGF-I, IGFBP-3, and ALS might be ... possibly lethal?*

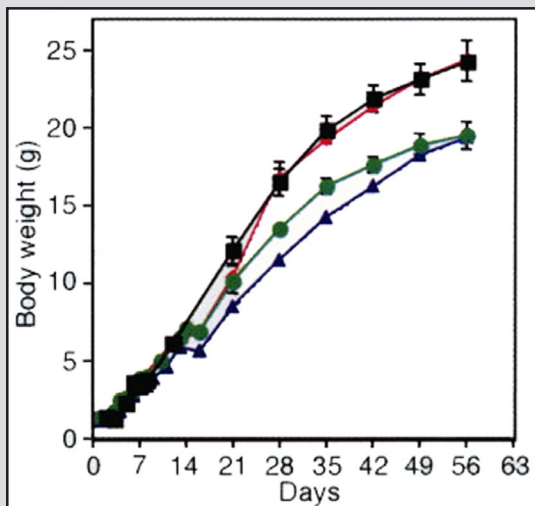
Allen W. Root, MD

Figures

Postnatal growth in LID+ALSKO mice



Body length was measured from nose to anus at weekly intervals ( $n = 20-30$  mice per group).



Body weight was measured at weekly intervals from birth to the age of 8 weeks ( $n = 30-60$  mice per group).

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References

1. LeRoith D, et al. *Endocrine Rev* 2001;22:53-74.
2. Ueki I, et al. *Proc Natl Acad Sci USA* 2000;97:6868-6873.
3. Kaplan SA. *Growth Genetics & Hormones* 2002;18:38-39.
4. Silha JV, Murphy LJ. *Endocrinology* 2002;143:3711-3714.

**Second Editor's Comment:** In *Growth, Genetics & Hormones* (Vol. 18, No. 3), an important lead article entitled *Somatomedin Hypothesis: Time for Reexamination* was written by Dr. Solomon Kaplan. He has been asked to write an editorial comment.

**Dr. Kaplan's Comment:** The paper by Yakar et al extends and amplifies the findings in a previous publication by the authors<sup>1</sup> on the role of circulating IGF-1 in promoting longitudinal growth in mice. They had already shown that despite inactivation of the IGF-1 gene in the liver, resulting in reduced concentrations of circulating IGF-1 by as much as 75%, the growth of the animals was not impaired. Their findings were consistent with the growing body of evidence against the validity of the somatomedin hypothesis, which holds that the effects of growth hormone on longitudinal growth are mediated through hepatic production of IGF-1.<sup>2</sup>

IGF-1 circulates in the serum largely as a 150-kDa complex comprised of the IGF-1 molecule, IGF binding proteins (mostly IGFBP-3), and the acid labile subunit (ALS). Others had previously shown that ALS knockout (ALSKO) mice experienced only mild growth retardation despite profound disruption of the circulating IGF system.

Yakar's current paper reported the effects of double gene disruption of the IGF system: inactivation of the hepatic gene for IGF-1 (LID) combined with ALSKO, on bone growth and density. In the mice carrying the double gene deletion, there was a reduction of circulating IGF-1 concentrations by as much as 85 to 90%; the animals also experienced significant growth impairment. There was a diminution in the amount of circulating IGFBP-3 protein and also in the free IGF-1 fraction. Loss of ALS led to more rapid disappearance of 125-I labeled IGF from the serum because absence of the ALS protein

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leads to proteolytic cleavage of IGF-1 and loss of its protective binding of IGF-1. The authors conclude that a minimum concentration of IGF-1 in the serum, higher than what they observed in the double gene-deletion mice, is necessary for normal bone and somatic growth.

Following administration of IGF-1 by injection, the animals with the double gene deletion experienced increased serum IGF and IGF-1 concentrations accompanied by restoration of normal bone growth and modeling, as well as increased somatic growth. These findings are consistent with their observation that the restoration of normal growth can be accounted for by increased serum IGF-1 concentrations above the minimal levels necessary for normal growth to occur.

This paper provides confirmatory evidence that hepatic derived IGF-1 and acid labile subunit are not necessary for normal growth provided minimal serum levels are maintained from non-hepatic sources including autocrine/paracrine production by target tissues.

Solomon A. Kaplan, MD

## References

1. Yakar S, et al. *Proc Natl Acad Sci USA* 1999;96:7324-9.
2. Daughaday WH, et al. *Nature* 1972;235:107.

## The BRCA2 Gene's Role in Fanconi Anemia and Various Cancers

Fanconi anemia (FA) is an autosomal recessive disorder in which affected subjects have great susceptibility to neoplasia early in life, including acute myeloid leukemia and squamous cell carcinoma. Bone marrow failure is also frequent, as well as mutations in at least 8 groups of FA patients (A, B, C, D<sub>1</sub>, D<sub>2</sub>, E, F and G) and germline mutations in six of these have been identified in 6 genes (A, C, D<sub>2</sub>, E, F and G). The FA cells manifest many broken and misshapen chromosomes reflecting that FA proteins participate in the repair of DNA damage, either stimulating or inhibiting normal repairs. Five of the 6 genes previously described combine in a multi-subunit nuclear complex which activates by ubiquitination of the protein product of a sixth gene (FANCD2) which is involved in the process of DNA repair. Howlett et al<sup>1</sup> identified a 7th gene by demonstrating that homozygous "loss of function" mutations occurring in the BRCA2 gene (causing breast cancer as does the BRCA1 gene) occurs in a subset of patients with FA.

Witt and Ashworth<sup>2</sup> stated in the introduction of their commentary; "Important discoveries are so neat and satisfying that, in retrospect, they seem obvious. Howlett et al disclosed that the inheritance of two defective copies of the BRCA2 breast cancer susceptibility gene can lead to FA. The BRCA2 protein is thought to be important in the repair of DNA damage. Cells lacking BRCA2 inaccurately repair damaged DNA leading to gene mutation and progression of tumors and are particularly sensitive to DNA cross-linking agents. Howlett et al demonstrated that one of the previously unidentified FA genes (FANCD1) is BRCA2." No BRCA1 mutations were found in the patients studied by Howlett et al. However, all the authors of all three papers speculatively agreed that the 6 previously cloned genes are linked in a common pathway with BRCA1 and BRCA2 genes.<sup>1-3</sup>

Venkitaraman<sup>3</sup> in his closing comments stated; "The network which connects BRCA and FA proteins in DNA

repair includes at least two other molecules - ATM (mutated in ataxia telangiectasia) and CHEK2 - whose inactivation is also associated with carcinogenesis in several tissues. Although the precise functional connections between the molecules in this network remain obscure, it is clear we are glimpsing an important tumour suppressor pathway whose disruption may underlie many different types of human cancer."

1. Howlett NG, et al. *Science* 2002;297:606-609.
2. Witt E, Ashworth A. *Science* 2002;297:534.
3. Venkitaraman AR. *Lancet* 2002;369:1343-1345.

**First Editor's Comment:** *Heterozygous inactivating germline mutations in BRCA1 and BRCA2 have been linked to increased susceptibility to breast and ovarian cancer in women.<sup>1</sup> In the tumors that develop in these patients, there is loss of heterozygosity of BRCA1 or BRCA2. Both BRCA1 and BRCA2 are important for repair of DNA damaged by exposure to ionizing radiation and cross-linking, and do so by interrupting the cell cycle while promoting repair of the damaged DNA strands.<sup>1-3</sup> The carboxyl-terminal domain of BRCA2 likely binds to single strands of DNA at the site(s) of a double stranded DNA break and facilitates the binding of other repair factors such as RAD51, an important member of this family. This article is of interest because it demonstrates the difference in phenotypes that result from heterozygous as compared to homozygous germline mutations in BRCA2. How this mutation affects somatic growth and the reproductive endocrine system is unclear. However, Wajnrajch et al<sup>4</sup> found aberrations of endocrine function in 44/54 primarily prepubertal patients with FA.<sup>4</sup> Abnormalities included short stature with mean height SDS -2.35 (due to growth hormone insufficiency in 44%), hypothyroidism (36%), hyperinsulinemia (72%), impaired glucose tolerance (25%), and diabetes mellitus (2%). Skeletal maturation*