

### 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".

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### 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?*

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