

**Letter to the Editor: Misconceptions - Epiphyseal Fusion Causes Cessation of Growth**

Dr. A. Michael Parfitt brought to the attention of the Editorial Board his article published in a journal not often reviewed by *Growth, Genetics & Hormones*. I have summarized some of the highlights of this very interesting article and recommend that the readership review the full paper, as it is of great interest.

Parfitt AM. Misconceptions: Epiphyseal Fusion Causes Cessation of Growth. *Bone* 30:2002;337-339.

This paper brings to light the fact that when the bone reaches its appointed genetically determined length, the following takes place: the longitudinal growth ceases, the epiphysis fuses with the metaphysis, and the growth plate disappears. Pediatric endocrinologists have always believed that growth stops because the epiphysis fuses, and that short adult stature could result from early fusion of the epiphyseal growth plate. The reverse is also true - a sustained linear growth through puberty could be a consequence of failure of epiphyseal fusion. However, Dr. Parfitt suggests that the epiphysis fuses because growth stops. In other words, fusion is the marker of growth cessation, not a determinant of it.

Epiphyseal fusion is an active process that might not necessarily be preceded by, nor automatically follow, the cessation of growth. Endochondral ossification represents the culmination of a sequence of changes in the cartilage cells and their associated matrix. These events must always occur in the same order, requiring a minimum period of time. It has been shown that the growth plate narrows, not because cartilage replacement occurs earlier, but because cartilage addition occurs more slowly as the rate of chondroblast proliferation declines. The growth plate

does not begin to disappear until proliferation has stopped altogether. Collectively, the data demonstrate that epiphyseal fusion does not precede, but rather follows the cessation of growth. Nevertheless, fusion is not simply the result of continued cartilage replacement with no further cartilage addition; this is an active process with its own hormonal controls, cellular mechanisms and structural features. For example, if there is estrogen deficiency, the epiphyses may remain unfused long after growth has stopped, with resumption of the normal timetable of fusion after replacement of the missing hormone. However the complexity of estrogen action at the growth plate has contributed to the current confusion. Estrogen has separate and independent effects on chondroblast proliferation and on active epiphyseal fusion. It has a biphasic effect on proliferation, which is stimulated by low levels and inhibited by high levels. The latter predominate in late adolescence in both sexes, leading initially to growth cessation and subsequently to active fusion. Dr. Parfitt concludes that recognizing the correct temporal relationship between growth cessation and fusion is an essential first step to understanding the complexities of growth plate function, but evidently a great deal more work is needed to clarify all the sequences.

**Editor's Comment:** *The effects of the high levels of estrogens found in sexual precocity may account for the early fusion of the epiphyses and the reduced height of the patients. The biphasic effect of estrogen on chondroblast proliferation as stated by Dr. Parfitt would account for these findings.*

Fima Lifshitz, MD

**Gastrointestinal Complications of Russell-Silver Syndrome**

A survey was conducted among members of the support group MAGIC, which includes individuals with Russell-Silver Syndrome (RSS) and their families. Completed surveys were returned from 135 individuals. Of those, 65 were determined to have clear-cut RSS on the basis of the criteria of: small for gestational age (IUGR), small for age during childhood, and having preservation of head circumference. Asymmetry is often seen in RSS as well. To be included in the study, it was necessary for the subjects to have at least three of four findings. If they had only three distinctive minor clinical features, other features were sought, including hypospadias, clinodactyly, triangular face and hypoglycemia to confirm the affected individual as a "clear cut" case.

In carefully reviewing these "typical" RSS cases, a surprisingly high frequency of gastrointestinal (GI) symptoms were found. Among the many areas of complications surveyed, GI problems stood out. Out of 65 subjects with typical RSS, 77% (50 subjects) had gastrointestinal symptoms. The major symptoms included gastroesophageal reflux disease (34%), food aversion (32%), and esophagitis (25%). The latter two are often a result of gastroesophageal reflux.

These observations suggest that the GI problems are often significant components of typical, "clear cut" RSS. The high incidence of reflux and esophagitis resulted in Nissen funduplications in many affected individuals (18%). The group with GI complications also showed a high frequency of hypoglycemia (36%) as

compared to the overall group (25%). Blue sclera and kidney abnormalities were also more common among those with GI complaints.

These findings have important implications for management. In IUGR children with failure to thrive and presenting with severe GI symptoms the diagnosis of RSS should be considered.

Anderson J, et al. *Am J Med Genet* 2002;113:15-19.

**First Editor's Comment:** Among children with RSS, about 10% have uniparental maternal disomy for chromosome 7. It is not yet clear whether they also have this very high frequency of GI symptoms. This type of

*phenotype/genotype associations needs to continue to be explored since they are so important for natural history and management.*

Judith G. Hall, OC, MD

**Second Editor's Comment:** The association of failure to thrive, gastroesophageal reflux disease, and hypoglycemia is important. Inadequate nutrient intake increases the risks of hypoglycemia. This complication must be considered and hopefully prevented in these patients.

Fima Lifshitz, MD

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## Growth Hormone Deficiency in Salt-Losing Congenital Adrenal Hyperplasia

This short report describes the identification of 4 children with 21-hydroxylase deficiency with defects in the CYP21 gene who presented with growth hormone deficiency between ages 2.1 and 12.9 years of age. These children were receiving steroid replacement at traditional doses of hydrocortisone (12 – 15 mg/m<sup>2</sup>/d) and fludrocortisone (100 – 150 mcg/m<sup>2</sup>/d) and were compliant with their treatment. Neuroimaging in two of the children revealed small, but present pituitary glands. All four grew well with growth hormone (GH) therapy. The authors speculate that these children may have sustained pituitary damage during salt-losing crises with associated hypotension and suggest that GH deficiency be considered in children with 21-hydroxylase deficiency who are growing poorly on traditional glucocorticoid and mineralocorticoid replacement doses.

Tirendi A, et al. *Eur J Pediatr* 2002;161:556-558.

**Editor's Comment:** Unfortunately these authors do not present the denominator. How many children, out of a population of what size with 21-hydroxylase deficiency and poor growth, is the question to be answered. How many children with adrenal crises have poor growth? Despite these obvious and important questions, the take home message remains clear. Twenty-one-hydroxylase deficiency need not occur as an isolated disorder. Children with 21-hydroxylase deficiency, as pointed out in the manuscript, are not necessarily short. It is important to carefully consider all possible causes when evaluating growth failure in any child.

William L. Clarke, MD

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