

Growth Hormone in Short Children: Beyond Medicine?

The increasing use of rhGH in short children with non-GH deficient (GHD) short stature, whether or not data support the efficacy of such treatment, may lead to its use being perceived as a cosmetic “enhancement”. Drs. Bolt and Mul discuss the merits of the use of rhGH in such children and whether such treatment is “in the medical realm”. Employing a disease-oriented model, rhGH would be administered only to patients with documented GHD or identified abnormal state (e.g., Turner syndrome) to restore health and normal functioning. The authors reject this approach because the differences between normal and abnormal growth and function are often indistinct. On the other hand, they also reject the “client approach” to prescribing of rhGH in which one would administer it “on demand” for any and all types of short stature including familial and idiopathic, because this approach might lead to “medicalization” of many perceived and apparent differences between individuals and make patients of otherwise healthy persons. Bolt and Mul believe the proper goal of medicine is to prevent or relieve suffering, both demonstrable and subjective, and advocate this approach to deciding when the administration of rhGH is or is not warranted. Suffering, while perhaps not always quantifiable, can be perceived by the family and physician. Thus, children with non-GHD short stature may be eligible for treatment with rhGH if s/he demonstrates present suffering or the potential for future suffering. They conclude that because the impact of short stature upon the functional status of normal adults is minor, treatment with rhGH “should take place in a research setting”.

Bolt LLE and Mul D. *Acta Paediatr* 90:69-73,2001.

Editor’s Comment: *The suffering individual is anguished, tortured, bitter and sad. However, it may not always be easy to identify the suffering short child.*

Firstly, the majority of short, otherwise normal children are brought to the office of the pediatric endocrinologist by their parents who are often more concerned about the height of their child than is the child himself. Thus, it is likely that it is the parent who is “suffering” rather than the child. Drs. Bolt and Mul do not address the issue of whether rhGH should be administered to a short child to alleviate parental suffering. Secondly, suffering related to short stature is seldom due exclusively to height, but reflects a constellation of behavioral, learning and social problems. As Macklin¹ points out in a companion commentary, the discomfort of the short-statured child may pale when compared to the physical suffering imposed by the numerous medical procedures that accompany treatment with, and the administration of rhGH. Although the “goal of medicine” involves all of the interrelated components delineated by the authors - disease-oriented, client-related, relief of suffering - this reviewer adheres to the precept that medicine is primarily a science and that medical decision making should be based upon valid scientific data. To date, there are limited and conflicting data relative to the growth promoting efficacy of rhGH therapy of the non-GHD short child and even fewer data concerning any psychosocial benefits of treatment.² Thus, I concur with the recommendation of Drs. Bolt and Mul that such treatment be undertaken in the context of a research environment.

References

1. Macklin R. Growth hormone in short children: medically appropriate treatment. *Acta Paediatr* 90:5-6,2001.
2. Guyda HJ. Four decades of growth hormone therapy for short children: what have we achieved? *J Clin Endocrinol Metab* 84:4307-4316,1999.

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Extended Life-Span Conferred by Cotransporter Gene Mutations in *Drosophila*

These investigators demonstrate that in the adult fruit fly, *Drosophila melanogaster*, heterozygous inactivating mutations in a newly identified gene *Indy* (for *I’m not dead yet* from the film “Monty Python and the Holy Grail”) double the active, fertile, and fecund life span of this insect. *Indy* encodes a 572 amino acid sodium dicarboxylate cotransporter, a membrane protein that shepherds the uptake and re-uptake of di- and tricarboxylic acid intermediate metabolites (e.g., succinate, citrate) of the Krebs cycle across cell membranes of organs responsible for metabolism and storage of fat, glycogen, and protein (e.g., the liver in

mammals). The investigators suggest that heterozygous loss-of-function mutations in *Indy* decrease the rate of absorption and utilization of metabolites, thus acting functionally to extend life span in a manner similar to that of partial caloric restriction.

Rogina B, et al. *Science* 290:2137-2140, 2000.

Editor’s Comment: *Energy restriction has been demonstrated to extend life span in worms, mammals, and insects, but the mechanism(s) by which decreased calories does (do) so have not been identified. It may*

be that caloric restriction down regulates the expression of sodium dicarboxylate cotransporter(s) genes thus decreasing the rate of intracellular metabolism and consequently increasing cellular life. These observations suggest that perhaps some obese subjects possibly have gain-of-function mutations in one or another sodium dicarboxylate cotransporter that enhance intracellular intermediary metabolism leading to accumulation of fat, while other individuals (who can

“eat a tone and never gain an ounce”) may have a variant that impedes metabolism. The data also suggest that it may be possible to modify the activity of these cotransporter molecules chemically - opening a portal for treatment of a group of obese subjects.

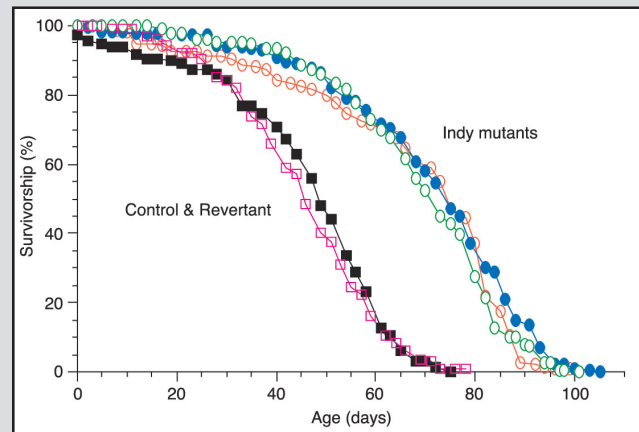
Pennisi E. Old files may hold secrets of aging. *Science* 290:2048, 2000.

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Figure

Life-span extension in *Indy* mutants. Survival curves of males heterozygous for three different *Indy* mutations, a precise excision of the P-element from *Indy* 302 (revertant), and an enhancer-trap control are shown. All flies were tested as heterozygotes over a wild-type Canton-S strain. The *Indy* mutants are *Indy*302 (open white circles), *Indy*206 (solid gray circles), and *Indy*159 (strikethrough circles). The excision line (strikethrough squares) is one of four exact excisions (sequence confirmed) of the P element obtained by mobilizing the P element from either the *Indy*302 or *Indy*206 line, using delta 2-3 transposase. The control (solid black squares) is one of four other enhancertrap control lines from the same mutagenesis that generated *Indy*302 and *Indy*206, tested as a heterozygote over Canton-S.

From Rogina B, et al. *Science* 290:2137-2140, 2000.



Insulin Resistance and Insulin-Like Growth Factors in Children with Intrauterine Growth Retardation

The authors recently proposed that when tissues in utero are chronically depleted of insulin and IGF1, but subsequently exposed after normalization of nutrient supply in postnatal life to increased levels, insulin resistance often develops. Carrying this thesis forward, they postulate that postnatal “catch-up” growth might, therefore, be associated with a higher risk of developing insulin resistance, especially when other risk factors such as genetic predisposition and/or obesity coexist.

To investigate this possibility, 49 children with IUGR (22 boys) with birth weight <10th percentile for gestational age were studied. Children with malformations and/or genetic disorders were excluded. Stature was corrected for mid-parental height. Children were divided into two groups according to their corrected height; specifically, those with corrected height z-score ≥ 0 and those < 0 . Insulin resistance was evaluated using OGTT, fasting glucose and insulin levels, and a G/I < 6 to interpret insulin resistance. Thirty-nine percent (19/49) of the children with IUGR had a corrected stature > 0 z-score and 61% had not reached their genetic height, as expressed as MPH z-score. Corrected stature at the age evaluated correlated with birth weight, whereas actual height was related to birth length, MPH

and BMI. Twenty-two percent or 11 of 49 IUGR children had a G/I < 6 . The endocrine variables in children as divided on the basis of G/I < 6 and > 6 are provided in Table 1. All the parameters related to insulin resistance correlated with alanine aminotransferase (ALT) and gamma glutamyltransferase (γ -GT) levels. IGF system parameters were in the normal range and correlated neither with growth nor with insulin sensitivity.

The first aim of the study was to assess the prevalence of insulin resistance in children and adolescents with IUGR. The authors considered that insulin resistance was at a high prevalence since 22% of the children were so classified, and these data are consistent with previous studies reporting impairment in insulin sensitivity in children with IUGR. The second objective was to prove the *catch up growth hypothesis* that catch up growth induces insulin sensitivity. The data in this study suggest that catch up growth is not a risk factor. They further comment that the finding of high prevalence of insulin resistance did not show a significant influence over postnatal growth - is consistent with the intrauterine reprogramming previously postulated by the authors and is consistent with a genetic predispositioning determining both low birth weight and