

in which the key is selective overexpression of IGF-I in  $\beta$ -cells.

Transgenic mice were developed in which mouse IGF-I was linked to the rat insulin promoter and thus targeted to the  $\beta$ -cell, where IGF-I expression was many fold greater than in control animals. In these mice, at 6 months of age there was a 1.5 fold increase in  $\beta$ -cell mass but normal pancreatic insulin content. Circulating concentrations of IGF-I were comparable in control and transgenic animals. The latter did not develop hypoglycemia, hyperinsulinemia, or neoplasms and had normal life span and reproduction.

At two months of age, administration of streptozotocin (STZ) led to the development of insulinitis, hyperglycemia, hypoinsulinemia, and death at four months of age in the control groups from two strains of mice (C57BL and CD-1) utilized. In the C57BL mice which overexpressed IGF-I only in the  $\beta$ -cell, STZ led to transient modest hyperglycemia, impaired insulin secretion, mild but reversible insulinitis, and subsequent normal life span. In the CD-1 transgenic mice, hyperglycemia and hypoinsulinemia following STZ were extreme, but again transient with long term survival (Figure). After recovery from hyperglycemia, the growth was normal in the  $\beta$ -cell-targeted IGF-I transgenic animals.

Histological examination in C57BL mice revealed a mild decrease in islet  $\beta$ -cells and budding of insulin containing cells from pancreatic ductal epithelium. Thus, IGF-I appeared to at least partially protect  $\beta$ -cells from destruction while also increasing generation of new  $\beta$ -cell precursors. Since the  $\beta$ -cell IGF-I receptor is found on the  $\beta$ -cell membrane, the high levels of IGF-I synthesized by the  $\beta$ -cell specific IGF-I transgenic mice must be acting in a paracrine or autocrine manner to protect  $\beta$ -cells insulted by STZ.

Histological examination in the CD-1 mice revealed much less severe insulinitis in the transgenic STZ treated mice than in the control STZ treated animals. There was slow recovery from insulinitis, but with  $\beta$ -cell proliferation and neogenesis, blood sugar and insulin serum levels were restored to normal.

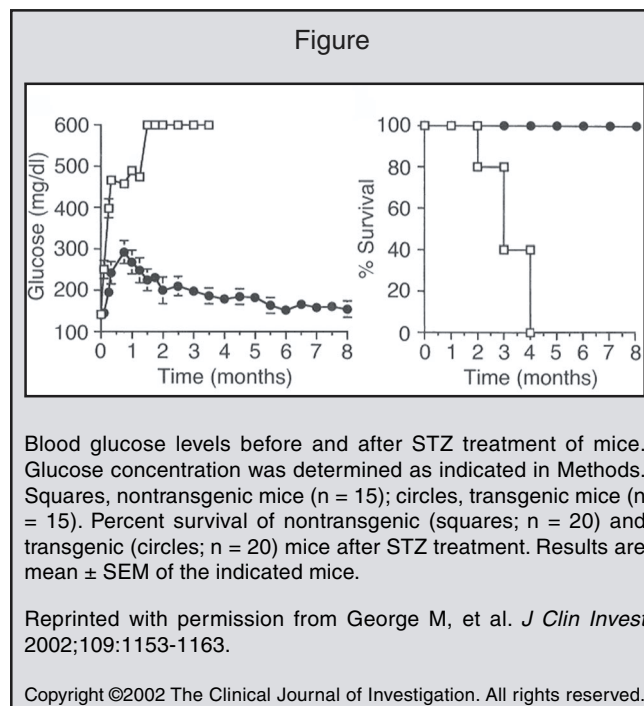
The authors concluded that co-expression of IGF-I and insulin in  $\beta$ -cells protected these cells from permanent destruction by STZ by increasing resistance to the inflammatory insult itself, augmenting  $\beta$ -cell division, and encouraging differentiation of new  $\beta$ -cells. They suggest that IGF-I may be a candidate gene for

transfer to pancreatic  $\beta$ -cells in the gene therapy of patients developing type 1 diabetes mellitus.

George M, et al. *J Clin Invest* 2002;109:1153-1163.

**Editor's Comment:** *This exciting paper raises the possibility that IGF-I might be capable of halting the progression of  $\beta$ -cell loss in patients developing type 1 diabetes mellitus if a method can be found to target this growth factor to the insulted  $\beta$ -cell in the intact patient. Perhaps equally feasible, and possibly even more beneficial, might be the insertion of IGF-I into the  $\beta$ -cells of patients at risk for development of type 1 diabetes mellitus to "protect" or to help them recover from the anticipated insults in the future that will lead to insulinitis. The latter objective may be more useful because the present experiments, which were successful, were conducted in animals that had high IGF-I pancreatic islet contact before the STZ insult. Such an approach would, hopefully, simulate the successful experiment recorded in this article.*

Allen Root, MD



## Growth and Maturation in Marfan Syndrome

The Marfanoid habitus is well known to pediatric clinicians; it is characterized by tall, asthenic habitus. In Marfan Syndrome (MFS), there is multi-organ involvement including eye, heart and muscular/skeletal abnormalities. Erkula et al, largely from Johns Hopkins

data, have retrospectively compiled growth pattern data on 180 clinically diagnosed MFS patients. They have generated growth charts and growth velocity charts for infant, children and adolescent males and females. Not unexpectedly, males and females with MFS are larger

at birth, grow at a greater velocity, and end up taller than average. Interestingly, skeletal maturation is also advanced and puberty is earlier when compared to the general population.

These data are extremely important and very helpful for those caring for children with MFS to determine whether a child is outside the expected range for MFS. This and further accumulated data will be very important in respect to the management of the spinal deformities common in MFS, as well as considering either surgical or hormonal therapies to decrease ultimate height.

The study was done using retrospective measurements, primarily from familial cases where the diagnosis had been made on a clinical basis. The authors express some concern about precision of height and weight measurements since they were collected by non-auxologists and because longitudinal data early in life were very limited. Nevertheless, the data are extremely useful in defining the overall natural history of growth in MFS. The authors point out that the excessive linear growth seen in MFS begins prenatally. The growth velocity is consistently higher than that observed in the general population, although body mass does not exceed that in the general population. This combination leads to the slender habitus in MFS.

An important consideration in MFS is the development of idiopathic scoliosis. On average, it develops earlier in children with MFS than in children in the general population. Since it is a common occurrence in MFS, it needs to be screened early and treated aggressively.

The study also documented that skeletal maturation occurs earlier in MFS than in the average population. This is an important consideration when thinking about various therapeutic modalities such as the timing for

surgical epiphysiodesis or hormonal therapy to produce cessation of growth and for considering utilizing braces to treat scoliosis.

Erkula G, et al. *Am J Med Genet* 2002;109: 100-115.

**Editor's Comment:** *This manuscript should be prime reading for those taking care of MFS patients. Space limits the presentation of the multiple figures presented in the manuscript. These growth charts are available in the original manuscript. These types of growth data are extremely important for relatively rare genetic syndromes and can only be accumulated in centers with enormous experience. Not only is the natural history important to elucidate, but understanding how and when to apply various therapies is extremely important.*

*Interestingly, the authors point out that some individuals with MFS are taller than others and, surprisingly, that some MFS patients are obese. Secondary genes or other mutations that affect height and weight are being sought. Such studies may be revealing in better understanding the variations of normal stature as well. It is the careful study of rare genetic disorders that helps to provide better therapy of diseased states and better understanding of normal development. We should be very grateful to this group, which has collected these data over many years. I cannot help but note and be dismayed that it is very difficult to find funding for this type of research and, yet, it is so extremely important. Therefore, we should be even more grateful to the authors and hope that they will be reporting similar data obtained in the studies of other rare genetic growth disorders.*

Judith G. Hall, OC, MD

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