There is a greater psychologic component, and GH response may be inadequate after stimulation with pharmacologic agents, such as arginine or insulin. Other abnormalities indicating adrenocorticotropic hormone (ACTH), thyroid stimulating hormone, and gonadotropin deficiency may be noted; however, GH deficiency is the most common endocrine aberrancy. The parents in this group usually reject their children and abuse them psychologically. The fathers and/or mothers are frequently chronic alcoholics. Occasionally type I patients are observed to advance into type II, which is not surprising.

Type III of PSS was described by Boulton et al,10 who studied seven children aged 3.6 – 11.6 years who did not have the bizarre signs and symptoms of type II patients. They were significantly depressed and/or had a disorder of attachment often dating from infancy. In contrast to previously reported patients they secreted GH when tested and had a significant increase in growth when given growth hormone treatment. A lesser response was obtained with a placebo. The authors emphasized that type III PSS patients did not show lack of discrimination in relationships, nor did they display the self-destructive behavior, pain agnosia, or bizarre eating and sleeping disorders seen in many type II patients. In addition, the parents were not indifferent and rejecting, as are those with PSS type II. The parents also had insight into the problem, which was not characteristic of the parents of other patients with PSS and several felt guilty and/or had depression.

The classifications discussed here by the English group and that presented in Lifshitz’s Endocrine Text are compatible. Type I, as described above, should remain as type I and be applied to infants and very young children. Type II pertains to children with severe PSS of the hyperphagia type. In my opinion, type II should be limited to this group. Type III is where further subclassifications should be placed. For example, type IIIA could (should) be the group described by Boulton10 and type IIIB of the type referred to by Gohlke et al. With this classification type IIIA & B can be subdivided or a type IV added as further subgroups are recognized. I wonder if Drs. Gohlke et al or others agree with my thinking? A letter to the Editors of GGH will be most welcome.

References

Robert M. Blizzard, MD

Leanness, Extended Lifespan & IGF-1 Receptor Mutations in Mice: Fascinating Observations

In flies and worms, loss-of-function mutations in insulin and insulin-related cell signaling pathways have led to increase in life span of the species studied. In order to evaluate these pathways in a mammalian specie, the present investigators developed mice with hemizygous loss of one insulin-like growth factor-1 receptor (IGF-1R) allele and studied their longevity. The hemizygous IGF-1<sup>−/−</sup> mice were generated by deletion of exon 3 of
the gene encoding IGF-1R; these mice had 50% of the IGF-1R levels that intact animals had. Homozygous inactivation of the gene encoding the IGF-1R (IGF-1R−−) was lethal. During nursing, IGF-1R+− and intact (IGF-1R++) mice grew identically; after weaning there was a slight decrease in growth (-6% to -8%) in hemizygous mice relative to intact animals through 11 weeks of age. IGF-1R+− female mice lived 33% longer and males 16% longer than did IGF-1R−− mice, and female hemizygous mice outlived their male counterparts. (Figure) As anticipated, serum IGF-1 concentrations were higher in IGF-1R+− mice than with control animals, while insulin levels were normal. Glucose tolerance was impaired in IGF-1R+− male but not female mice. Energy balance in mutant and control animals was similar in food intake, body temperature, physical activity, metabolic rate and fertility. The ability to withstand an oxidative stress was greater in mutant than control animals both in vivo and vitro. In cultured fibroblasts, the amounts of several signal transduction molecules downstream of the IGF-1R were decreased relative to the activity of control fibroblasts. In particular, levels of phosphorylated p66 shc, an activator of mitogen activated protein (MAP) kinase, were reduced by one-half, suggesting that perhaps a decrease in the rate of cell division might be an important factor in increasing longevity. The investigators conclude that in mice the partial inhibition of IGF-1 signaling leads to increase in life span.

Bluher et al demonstrated that in mice in which there has been localized “knock out” of fat specific insulin-receptors (FIRKO) (in contrast to generalized loss of IRS which leads to insulin resistance, diabetes mellitus, and obesity), there was extension of life span despite normal caloric intake and without clinical or biochemical abnormalities. FIRKO mice were approximately 20% lighter and their body fat content approximately 60% lower than control animals, despite eating similar quantities of food. Control animals lived an average of 753 days, while FIRKO mice lived 887 days (+134 days, +18%); median life span in FIRKO was increased by +3.5 months and maximum life span by +5 months. Fertility of the FIRKO mice was not reported. The investigators concluded that low body fat content (leanness) rather than decreased food intake was the primary factor contributing to increase in life span of the FIRKO mice.


Editor’s Comment: There is increasing evidence that insulin, growth hormone (GH), and IGF-1 are intimately involved with the duration of life. Experimentally, partial caloric deprivation increases life span while decreasing serum concentrations of IGF-1. Mice with GH deficiency (GHD) such as Ames (Propdf/df) and Snell (Pit1dw/dw) mice are extremely long-lived albeit dwarfed and infertile, as are mice in which the GH receptor has been “knocked-out.”

The manuscripts present several interesting observations in addition to those on longevity. Thus, partial inactivation of the IGF-1R gene led to slightly subnormal growth in mice, suggesting that variants of this gene might play a role in the diversity of height in man. Also of interest were the gender specific effects of partial loss of IGF-1R which was more pronounced in females than males which indicated that sex-specific factors may modulate the effects of IGF-1R.

While it is not possible to transpose these data to man, they make one wonder whether we may be adversely affecting life span by treating our GHD adult patients with rhGH. Perhaps it might be less risky to treat the cardiovascular and skeletal abnormalities of the adult with GHD with agents other than rhGH.

Allen W. Root, MD