

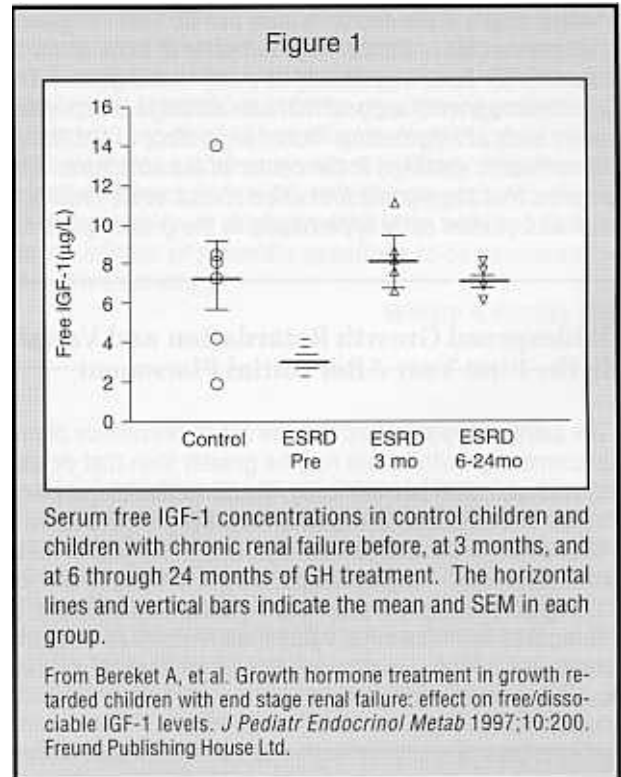
Growth Hormone Treatment in Growth-Retarded Children With End-Stage Renal Failure: Effect on Free/Dissociable IGF-1 Levels

One of the causes for growth retardation in children with end-stage renal disease (ESRD) is thought to be an abnormality in the biologic effects of GH. Despite high serum levels of hGH in ESRD and usually normal values of insulin-like growth factor 1 (IGF-1), somatomedin biologic activity is low. This has been attributed to binding of IGF-1 by an excess of IGF-binding proteins (IGFBPs), leading to decreased free IGF-1 concentrations.

Bereket et al tested this hypothesis by measuring free IGF-1 by direct immunoradiometric assay (IRMA) in 5 children with ESRD. In 2, free IGF-1 also was measured after centrifugal ultrafiltration of serum. Free IGF-1 concentrations were one third to one half those measured by direct IRMA, suggesting that the IRMA measured both free IGF-1 and that fraction that was easily dissociable from IGFBPs. In basal specimens, the mean free/dissociable IGF-1 levels were lower in ESRD patients than in body mass index-, age-, and pubertal status-matched control subjects ($3.0 \pm 0.3 \mu\text{g/L}$ vs $7.3 \pm 2.1 \mu\text{g/L}$; $1.24 \pm 0.05\%$ vs $2.12 \pm 0.7\%$, respectively). The mean free/dissociable IGF-1 peaked at $8.5 \pm 1.0 \mu\text{g/L}$ after 3 months of treatment with rhGH, declining to $6.9 \pm 1.4 \mu\text{g/L}$ between 6 to 24 months of therapy (Figure 1). Growth rate and total IGF-1 values also rose during rhGH administration. Thus, the increase in growth rate during rhGH administration was associated with a rise in free/dissociable IGF-1 levels.

Bereket A, et al. *J Pediatr Endocrinol Metab* 1997;10:197-202.

Editor's comment: These data support the concept that the growth-promoting effects of rhGH in children with ESRD is related to an increase in free IGF-1 concentrations. In this paper, the authors did not report a relationship between the



basal or incremental growth rate and the concentration or incremental increase in free/dissociable IGF-1 values. Additional studies will be helpful in clarifying fully the mechanisms by which rhGH increases growth in ESRD.

Allen W. Root, MD

Pancreatic Agenesis Attributable to a Single Nucleotide Deletion in the Human *IPF1* Gene Coding Sequence

IPF1 is a homeodomain protein critical for development of the pancreas in mice and is a key factor for the regulation of the insulin gene in the beta cells. Disruption of this gene in transgenic mice produces failure of pancreatic development. In this report, a single nucleotide deletion within codon 63 in a patient with pancreatic agenesis apparently does the same. The patient was homozygous for the point deletion and both parents were heterozygous, in contrast to the normal allele structure in 184 individuals. The cytosine deletion was in codon 63. A frameshift beginning at the C-terminal border of the transactivation domain of *IPF1* was consistent in all cells. The data indicated that a truncated protein lacking the homeodomain (and nuclear localization signal) is produced from the mutation. If the parallel between humans and affected mice holds, the pancreatic buds do form, but they undergo only limited ductal outgrowth and branching, with a blockage of both pancreatic endocrine

and exocrine differentiation. Although there was no clear history of consanguinity, the studies strongly suggest that the abnormal alleles are likely to have been derived from a single common ancestor.

In addition to pancreatic agenesis, 3 cases of severe pancreatic hypoplasia and 1 case of complete absence of the islets have been reported. The authors are tempted to speculate that the phenotypes of pancreatic hypoplasia and selected agenesis of the islets might represent a spectrum of less severe mutations that may impair but not abolish *IPF1* functions. Alternatively, these disorders may be a consequence of mutations and other factors that are essential for full development of the pancreas. Most intriguingly, the authors postulate that abnormal *IPF1* function also may be a candidate factor in the development of insulin-dependent diabetes mellitus.

Stoffers DA, et al. *Nat Genet* 1997;15:1-50. Letter.

Editor's comment: An intriguingly rare condition is probably explained by these investigators. Recently, a white female infant was diagnosed with pancreatic agenesis shortly after birth, and with pancreatic exocrine insufficiency at 18 days of age. Neonatal diabetes mellitus was the working diagnosis initially. Ultrasound examination demonstrated pancreatic agenesis. Normal development has continued until 5 years of age with replacement of insulin and pancreatic enzymes. A strong family history of noninsulin-dependent diabetes mellitus existed and supports the possibility of partial affectation.

Pancreatic agenesis needs to be considered in the differential diagnosis of neonatal diabetes and also with

the observation of malabsorption in the newborn period. A similar study of the IPF1 gene coding sequence might be revealing in the Johanson-Blizzard syndrome, which is characterized by pancreatic insufficiency in addition to other anomalies such as congenital deafness, poor formation of teeth, corneal atresia, and urogenital anomalies.

With time it becomes more and more apparent that one mis-substitution of an amino acid at a critical place on a gene can totally change the life of the host far beyond what we ever could have believed 10 years ago.

Robert M. Blizzard, MD

Gonadal Function After Bone Marrow Transplantation for Acute Leukemia During Childhood

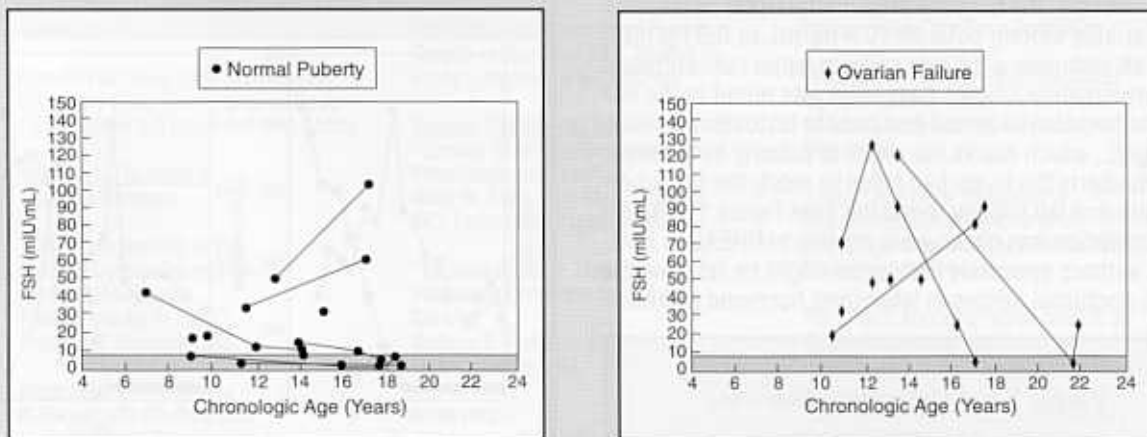
Bone marrow transplantation (BMT) is a major advancement in the treatment of childhood leukemia and in other disorders, as many children are surviving for long periods. Consequently, Sarafoglou et al examined the impact of BMT on gonadal function following high-dose chemotherapy and hyperfractionated total body irradiation (radiation given 3 times daily for several days) in 33 surviving children treated for acute leukemia. All patients were prepubertal and less than 12 years at the time of BMT. The median age at last examination for boys was 14 years (10.4 to 17.1 years) and 16.9 years (9.5 to 21.9 years) for girls.

Of the 17 boys, 14 (82%) had spontaneous puberty, 13 (76%) had age-appropriate plasma concentrations of

testosterone; 2 (11%) remained clinically and hormonally prepubertal; and 1 (6%) had overt Leydig cell failure requiring androgen replacement therapy, although this individual also received testicular irradiation. Thirty-six percent of pubertal boys had increased levels of luteinizing hormone (LH), reflecting evidence of Leydig cell damage; and 64% had increased levels of follicle-stimulating hormone (FSH), reflecting germ cell damage. Pubertal boys with increased LH were significantly younger at BMT (5.4 ± 0.8 years vs 7.8 ± 0.8 years).

Of 16 girls, 9 (56%) had spontaneous puberty with onset of menarche at a median age of 13 years (9.5 to 15.8 years). Six of these 9 girls (67%) had increased LH and in-

Figure 1



Plasma concentrations of FSH in girls after BMT with normal puberty/menarche (left panel) and in girls with ovarian failure (right panel). Solid lines connect serial determinations in the same patient. Shaded area represents the range for the normal population (follicular phase of the menstrual cycle). BMT, bone marrow transplantation; FSH, follicle-stimulating hormone.

From Sarafoglou K, et al. Gonadal function after bone marrow transplantation for acute leukemia during childhood. *J Pediatr* 1997;130:214.