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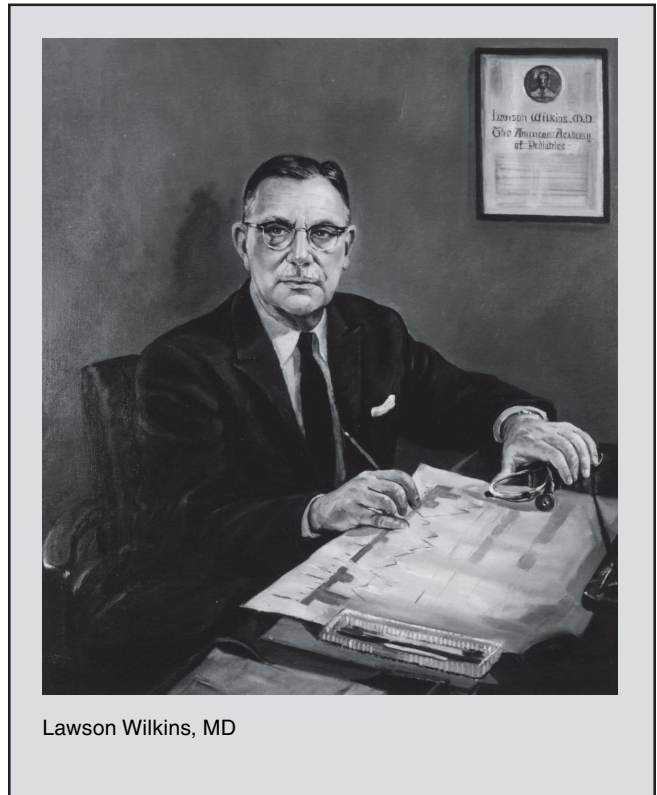
LAWSON WILKINS - PIONEER IN PEDIATRIC ENDOCRINOLOGY AND GROWTH DISORDERS: REVISITED 2003

Robert M. Blizzard, MD

Editor-in-Chief

EDITORIAL INTRODUCTION

In March 1987 in *Growth, Genetics & Hormones*, Vol. 3, No. 1, the lead article with the same title as above was published (the original article is available at the *Archive* section of www.GGHjournal.com). Dr. Wilkins was the founder of pediatric endocrinology. His contributions to pediatrics and pediatric endocrinology were substantial. He was a consummate teacher, practitioner, and investigator, and his personal characteristics were of an exceptional human. He must be known by those who use his name frequently, including members of the Lawson Wilkins Pediatric Endocrine Society and those who utilize his articles in the pediatric literature as references for their own writing. It is for this reason that in this current issue of *Growth, Genetics & Hormones* the article published in *GGH* in 1987 is revisited. In respect to this updating, the two considerations incorporated include an updating of chronological time and the providing of references with highlights concerning Lawson Wilkins as a leader, teacher, pediatrician, and investigator.



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Forty years have passed since 1963, when Dr. Lawson Wilkins died at the age of 69. His demeanor, his accomplishments, and the esteem in which he was held by his peers and his extended family of pediatric endocrine fellows whom he trained are not known to the third and fourth generations of pediatric endocrinologists who are members of the Lawson Wilkins Pediatric Endocrine Society. Since volumes could be written about each aspect of Dr. Wilkins' life, an abbreviated biography is inadequate. Nevertheless, a brief history of Dr. Wilkins' life presents the opportunity to update the image of a man who should be known by pediatric endocrinologists, pediatricians, and geneticists.

Lawson Wilkins was born in 1894 in Baltimore. His father, Dr. George Wilkins, was probably the most highly respected family practitioner in the city. Historical accounts indicate that George Wilkins was intellectually

curious, dedicated to his patients, and attentive to detail. His son exhibited the same characteristics. Mrs. Wilkins' death, when Lawson was five years of age, significantly strengthened the already close bond between father and son.

After receiving a baccalaureate degree from Johns Hopkins University in 1914, Lawson Wilkins began medical school there. In 1917, along with many other medical students, he volunteered to go to Europe and served as an orderly in a medical unit during World War I. After the war, he was accepted as an intern in internal medicine at Yale for a year. He then returned to Baltimore to serve a pediatric internship at Johns Hopkins Hospital where the influence of Drs. Blackfan, Park, Kramer, and the other giants of pediatric medicine of the period further whetted his keen intellectual appetite.

It was most likely his desire to follow in his father's footsteps as a practitioner that prompted him to enter pediatric practice in Baltimore in the early 1920s. Until the time he accepted a full-time academic position in 1946, Dr. Wilkins had practiced pediatrics for 25 years with intense intellectual curiosity and great compassion for his patients. This author has on several occasions in the past met adults in Baltimore who remembered Dr. Wilkins fondly as their pediatrician. These individuals had no idea that Dr. Wilkins had made major contributions to medicine as an endocrinologist and a geneticist.

In 1935, Dr. Edwards Park, who was instrumental in the development of various subspecialties in pediatrics, invited Lawson Wilkins to establish an endocrine clinic in the Harriet Lane Home of the Johns Hopkins Hospital. Dr. Wilkins was reluctant since endocrinology at that time was the trade of quacks and charlatans. He accepted the position, however, and with Drs. Fuller Albright, John Eager Howard, George Thorn, Robert Williams, and a few others, he transformed endocrinology into a respectable subspecialty.

Wilkins focused on the problems in pediatric endocrinology - particularly problems of growth and genetics - while his confreres tended to the accumulation of knowledge about endocrinology in adults. Although he was intensely interested in the metabolism and control of carbohydrate and fat metabolism, he assiduously avoided a clinical interest in diabetes. Possibly this was because Dr. Harriet Guild of the Harriet Lane staff had established a diabetes clinic and, characteristically, Dr. Wilkins would not intrude on the work of others unless invited. Interestingly, he never considered diabetes a disease of the endocrine system, although he believed hypoglycemia was.

Lawson Wilkins was more than a scientific giant. He was a man of great magnetism and personality. Few who knew him could forget his bass voice which he put to good use singing ballads and bawdy songs long into the night. He loved to sail his boat on the Chesapeake Bay and tell jokes, which he masterfully embellished. He also adored - and was adored by - Lucile Mahool, his first wife, and Teence Anderson, to whom he was married after Lucile died in 1959.

At a meeting in Baltimore of the Lawson Wilkins Pediatric Endocrine Society in the mid-1960s, Dr. John Eager Howard* related the following about Dr. Wilkins: "When I first met Wilkins, which was at a time I had heard about his studies that Dr. Park exalted, I was even more impressed by the vitality of the man than by his scientific studies. In response to my knock on the door, the rafters fairly reverberated to the booming voice that urged us to come in. His whispers in a conference could cause consternation, for his 'That fellow is putting out pure hogwash' might have been heard all over the room. But I should hasten to say that his comments were rarely uncomplimentary, for an immense generosity toward others was one of his most endearing qualities." In accord with Dr. Howard's observations, this author found Dr. Wilkins to be a paradox in that he was gruff but gentle. And while he always dominated the situation, he never exhibited dominating behavior toward individuals.

Another mark of the quality of Dr. Wilkins' personality was the grace with which he relinquished his pediatric endocrine clinic and training program to Dr. Claude Migeon and this author in 1960. During the next three years, before he died in 1963, he was present much of the time, he remained intellectually curious, and he continued to contribute in all respects.

SCIENTIFIC CONTRIBUTIONS

Lawson Wilkins greatly expanded our knowledge of endocrine physiology and pathophysiology. Some of us have been fortunate enough to have shared in his experiences in establishing pediatric endocrinology as a subspecialty. Drs. Albert Bongiovanni,* Claude Migeon, and Walter Eberlein shared his interest in adrenal steroid metabolism and the pathophysiology produced by deficiencies of various enzymes for cortisol synthesis, including defects in 21 hydroxylation and 11 hydroxylation that produce congenital virilizing adrenal hyperplasia. In 1950, Drs. John Crigler, Robert Klein, Lytt Gardner,* Claude Migeon, and Eugenia Rosemberg joined Dr. Wilkins in successfully treating the first patients with congenital virilizing adrenal hyperplasia with cortisone. As always, Dr. Wilkins applied the knowledge he gained from his physiologic studies to therapy.

(*Deceased)

Drs. Melvin Grumbach and Judson Van Wyk worked with Dr. Wilkins in his studies of sexual differentiation. In this area, Dr. Wilkins applied what had been learned from the animal experiments of Alfred Jost to postulate and prove that the anatomy in gonadal agenesis and pseudohermaphroditism in human beings could be explained by the presence or absence of androgens and Mullerian inhibiting factor.

It was with Dr. Wilkins that Lytt Gardner* developed his interest in genetics and cytogenetics. It was Dr. Wilkins and his students who were among the first to apply the cytological techniques of Dr. Murray Barr to identify the inactivated X chromosomes (Barr bodies) in the nuclei of patients with Klinefelter's syndrome and in female pseudohermaphrodites. These diagnostic aids facilitated the diagnosis and therapy of patients with abnormalities of sexual development.

With Dr. Wilkins, Dr. George Clayton demonstrated that enzyme defects in the synthesis of thyroid hormone metabolism produce pathologic changes in the thyroid that simulate thyroid carcinoma. Dr. Wilkins had previously demonstrated during his years in practice the effect of thyroid hormone on cholesterol and creatinine metabolism.

Dr. David Smith* and this author benefitted from Dr. Wilkins' astute record keeping; he was a master in maintaining growth charts and other documents. With him, we published the effect of thyroxin treatment on the mental development of cretins.

These were classic physiologic studies in which the effects of a hormone were investigated clinically. He had demonstrated during this same period that the epiphyses in patients with thyroid deficiency were misshapen as they calcified (epiphyseal dysgenesis) and delayed in appearance, and that epiphyseal dysgenesis was a frequent finding in the untreated cretin. With treatment, the epiphyses that had not appeared because of thyroid hormone deficiency were often dysgenetic when they did appear, but the epiphyses that were expected to appear following the chronologic age that treatment was begun were always intact in their development.

THE SECOND GENERATION AND BEYOND

Other pediatric endocrinologists from the United States who trained with Dr. Wilkins between 1946 and 1960 were Drs. Thomas Shepard, Gerald Holman, José Cara,* David Mosier, William Cleveland, Ralph David, Orville Green, Malcolm Martin, Samuel Silverman, and Robert Stempfel. Many students from abroad who are now professors also trained with Dr. Wilkins. These include Drs. Jean Bertrand, John Eckert, John Gerrard, Casaer

Bergada, Theodoros Papadatos,* and Andrea Prader* who followed in Lawson's image as a major founder of pediatric endocrinology in Europe, and Henning Anderson.* These endocrinologists and professors have trained the third generation of pediatric endocrinologists who in turn have trained the fourth generation.

Dr. Wilkins wanted to be called "Lawson" by "his boys" as he called those who trained under him, but esteem for him was so great that he remained "Dr. Wilkins" to most for many years.

It is not by chance, however, that there was only one female fellow, Dr. Eugenia Rosemberg, prior to 1960. It was simply Dr. Wilkins' policy not to accept women as fellows. He respected the intellect of female physicians, but he was reluctant to let them examine the male teenagers who came to him for consultation. With the acceptance of Drs. JoAnne Brasel, Virginia Weldon, and Irene Solomon as pediatric endocrine fellows at Johns Hopkins in the early 1960s (when he was professor emeritus but still active), he relented and realized that he had been unduly restrictive.

We in pediatric endocrinology, pediatrics, and genetics are indeed blessed to have had such a man to lead us. The history of Lawson Wilkins is well worth passing along to the third and fourth generations of pediatric endocrinologists, and it is to be hoped that they will pass it along to the fellows who train with them.

(*Deceased)

REFERENCES AND THEIR HIGHLIGHTS

1. Wilkins L. Presidential Address to American Pediatric Society. *Am J Dis Child* 1962;104:449-456.

Dr. Wilkins wished to chastise pharmaceutical firms for their focus on the commerce of manufacturing and marketing drugs and to warn physicians to avoid the pitfalls of over prescribing medications and/or prescribing the newest medicine in the pipeline when its efficacy and the potential long-term toxicity are obscure. This masterful presentation was both educating and chastising. The following capsulizes Wilkins' closure: (1) Remember the Oath of Hippocrates, (2) Give no drug if it is not needed. Placebos rarely have a place in pediatrics, (3) Remember that practically every effective drug has potentials for toxic side-effects, (4) Neither discuss nor prescribe drugs by brand name, (5) Never use a drug or mixture without full knowledge of its chemical nature and pharmacological action, (6) Do not attempt to learn your new therapeutics from the trade brochures or even the PDR, (7) Do not hasten to use the 400+ new drugs coming on the market each year -

particularly if they are variants of drugs with which you already have had experience, (8) Wait, wait, wait - and then wait. Let the other fellow poison his patients.

2. Bongiovanni AM. Presentation of the John Howland Medal and Award of the American Pediatric Society to Dr. Lawson Wilkins. *J Pediatr* 1963;63:803-807.

Dr. Bongiovanni pays tribute to Lawson Wilkins for all of his accomplishments with the help of Wilkins only sibling and records: "He had a child like curiosity and spirit of inquiry that kept him young. He was never struck with the prejudices of a prior era. His advantages were scholarly acquaintance with earlier discoveries, an intimate knowledge of clinical aspects, and a firm hold on the basic sciences. His multiple interests are reflected in the diversity of titles to his innumerable publications, which include studies on serum potassium, ulcers of the tongue, rickets, immunization against dysentery, meningitis, pyuria, epilepsy and many diverse aspects of endocrinology." The presentation in this reference was a remarkably successful rendering of insight about the personality and personal characteristics of Lawson Wilkins.

3. Wilkins L. Acceptance of the Howland Award. *J Pediatr* 1963;63:809-811.

Dr. Wilkins paid extensive gratitude to his mentors and colleagues, including fellows, which reflected his true sincerity for his colleagues' contributions and collaborations, and to educate his listeners. As he stated, "I wish to take the privileged opportunity to emphasize the importance of the clinician and clinical investigator in contributing to basic and fundamental knowledge." His views about clinical investigation in abbreviated wording was as follows: It is the clinician who must seek out and bring to attention the human experiments of nature . . . no one can reproduce in the laboratory most of the inborn enzymatic defects

. . . I always permitted my assistants to delve into any type of problem which interested them . . . The scientist must have an insatiable curiosity to seek knowledge along any lines

. . . The clinical investigator must have curiosity and, if he has such curiosity, nearly every patient he sees will call forth many questions of real importance which have never been answered. The clinical investigator will be impelled to attempt to answer these questions by studies upon the patient.

4. Wilkins L. The Evolution of Endocrine Diagnosis and Treatment: The Addison Lecture. *Guys Hospital Gazette* 1954;March 19th, pages 1-9.

Dr. Wilkins gave a masterful presentation of the history of clinical endocrinology beginning with Graves' classical description of thyrotoxicosis in 1834 and a current (1954) discussion of the interrelationships of the endocrine glands and their hormones including diagnostic methodology available, differentiation of CAH in males from other types of sexual precocity, diagnosis of sexual infantilism, etc. The result was a very erudite lecture revealing how successful Dr. Wilkins was in sorting out the diagnoses and treatment of various pediatric endocrinopathies. The content of this lecture was incorporated into the 2nd Edition of his textbook, *The Diagnosis and Treatment of Endocrine Disorders in Adolescence and Childhood* (1957).

5. Blizzard RM. Pediatric Profiles: Lawson Wilkins (1894-1963). *J Pediatr* 1998;133:577-580.

Dr. Blizzard was invited to write such a profile as the *Journal of Pediatrics* was composing a series on the profiles of those who had pioneered in the specialty of pediatrics. His initial goal was to introduce an unusual story to the readers of his first encounter with Lawson Wilkins. This unusual encounter characterized Wilkins' personality - honesty, directness, a no nonsense approach, leadership, preciseness, and the expectation that one hearing a private conversation would keep the confidence of the discussants. The paper also describes in subsections The Wilkins personality, Wilkins as a physician, Wilkins as an investigator, and Wilkins as a teacher. The article ends with brief descriptions of his last years and conclusions.

6. Bongiovanni AM, et al. To Honor Lawson Wilkins, MD in His 65th Year. *J Pediatr* 1960;57:317-325.

Dr. Bongiovanni provides a personal accounting given by Dr. Edwards A. Park (pages 317-322) of his professional relationships with Lawson Wilkins and accountings of personal relationships with Lawson Wilkins by some of his colleagues of the early historic days, including Douglas Hubble of Scotland. The accountings of Hubble and Park are particularly insightful and should be read by those wishing to more completely understand Dr. Wilkins as a clinical investigator and as a unique personality.

7. Money J. Foreword to the 3rd Edition of *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. By Lawson Wilkins with the editorial assistance of Robert M. Blizzard and Claude J. Migeon; 1965;pages vii-xi.

Dr. Money wrote this foreword after Lawson Wilkins' death with the primary objective of recording Dr. Wilkins' professional and personal characteristics by one who had worked closely with him for more than a decade.

Dr. Money delivered a very thorough and appropriately lengthy personal and professional history of Dr. Wilkins. Dr. Money's closing paragraph is particularly pertinent as it is conceptually flattering and truthfully accurate: "Lawson Wilkins achieved fame, but as a by-product of accomplishment. His life's goal had been to achieve, not to become famous."

8. Fisher DA. A Short History of Pediatric Endocrinology in North America. *J Pediatr* 2003 (In preparation).

The purpose of this article is to record for posterity a historical perspective of the founding and development of pediatric endocrinology as a subspecialty, of the Lawson Wilkins Pediatric Endocrine Society, of pediatric

endocrine training programs, of pediatric diabetes as a discipline, and of advances in understanding, diagnosing, and treating pediatric endocrinopathies since 1950. A very excellent and complete presentation of the topic has been written by Dr. Fisher. As part of this, Lawson Wilkins' major roles as pediatrician, founder of the subspecialty, clinical investigator, and academician are evident.

9. Migeon CJ. *The Origins and Establishment of the LWPEES*. <http://www.lpwes.org/history.html>. The concept and history created by Lawson Wilkins invitation in 1963 of a scientific gathering to the formal creation in 1972 of a Society is interestingly detailed.

Abstracts from the Literature

Body Mass Index and Segmental Proportion in Children with Different Subtypes of Psychosocial Short Stature

Psychosocial short stature (PSS) has been classified by the authors into 3 categories: (1) Type IIA are hyperphagic children, in whom there is reversible growth hormone (GH) insufficiency with rapid catch-up growth with a change in their living environment but with minimal response to exogenous GH; (2) Type IIB is a heterogeneous sub group of non-hyperphagic children who have normal GH secretory dynamics and minimal or absent increase in growth rate with change in their environment and variable response to GH; and (3) Type III are children with anorexic eating habits, with an onset as early as infancy, with failure to thrive, depression, normal GH secretory dynamics, and significant growth response to exogenous growth hormone. Gohlke et al

report anthropometric evaluations of 46 children with PSS, before and after change in their environment (Table 1).

Significant improvement in height velocity SDS after intervention was observed in all groups. ANOVA failed to show any significant differences in growth velocity between groups. There was no significant change with treatment in body proportion in type IIA (hyperphagic) or in type IIB (heterogenous) children. In type III (anorexic) children, the body proportions decreased significantly after intervention indicating relatively shorter upper segments after treatment. In those who received GH treatment (n = 21), there was no significant change in body proportion after GH therapy. Body Mass Index

Table 1

Clinical Data of 46 Children with PSS

Classification	Type IIA (n = 20)	Type IIB (n = 16)	Type III (n = 10)
Mean age at presentation (years)	8.6	7.6	10.2
Age range (years)	4.9-15	3.8-14.9	5.4-14.9
Sex	9F. 11M	4F. 12M	6F. 4M
IUGR	2F. 2M	0F. 5M	2F. 2M
Mean bone age delay at presentation (years) (SD)	1.69 (1.0)	1.69 (1.3)	2.0 (1.5)
Prepubertal at presentation	18	15	9
Type of intervention			
Social services only	17	5	3
Social services and GH therapy	3	11	7

Adapted from: Gohlke BC, et al. *Eur J Pediatr* (220) 161: 250-254.

(BMI) did not increase in any of the groups after intervention and there were no significant changes in bone age. Multiple regression analysis showed that the type of PSS was a predictor for height velocity after intervention. The greatest effect in removal from adverse home events were in the type IIA (hyperphagic) subjects. The authors state that their findings should be helpful to clinicians managing children with PSS because of the emphasis on appetite disturbance and the variable treatment responses.

Gohlke BC, et al. *Eur J Pediatr* 2002;161:250-254.

First Editor's Comment: PSS, first described in 1947 by Talbot et al,¹ is often difficult to diagnose. Variable GH secretory dynamics, and responses to exogenous GH therapy make it important to attempt to better understand the etiologies involved and their potential response to psychosocial changes. The current manuscript report data on a large number of subjects with PSS and suggested that BMI is not useful in predicting response to treatment, but that categorization based on appetite may be of use in predicting growth changes. It is unfortunate that their data were not analyzed separately for those with intrauterine growth retardation (IUGR) and for those with and without GH insufficiency. However, the heterogeneous composition and variable treatment of these children strengthen the conclusions based on categorization of subjects by their eating behavior.

Reference

1. Talbot NB, et al. *N Engl J Med* 1947;236:783-789.

William L. Clarke, MD

Second Editor's Comment: PSS should be considered by pediatric endocrinologists or pediatricians in the differential diagnosis of short stature when a short child is seen in the clinic. If the possibility of this diagnosis is not considered and explored in the history, the diagnosis will be missed. PSS occurs much more frequently than is realized. Many parents of children with PSS (particularly Type II A of the English classification) are not concerned about their child's stature because the parents are psychologically rejecting the child.

PSS is a spectrum of entities as Gohlke, Frazer, and Stanhope state. The classification is muddy for this reason. In the patients reported by Gohlke et al there was no child less than 3.8 years of age. In the classification listed in Lifshitz's *Pediatric Endocrine Text*¹ (3rd Edition, 1996), infants with PSS comprise a broad clinical spectrum. This should be kept in mind so that the diagnosis of PSS is made and treatment properly

instituted, which in my opinion is not GH, but removal of the child from the adverse environment, particularly for type II.

Types of PSS as Described in the 3rd Edition of *Pediatric Endocrinology*¹

At least three subtypes of psychosocial short stature have been recognized (Table 2). The first (type I) occurs in infants and children 2 years of age or younger. These infants usually have failure to thrive (nutritional deficiency), as well as short stature, and have been very adequately described by Krieger, Whitten, and colleagues.²⁻⁶ There is no evidence that these children have a hormonal disturbance, such as growth hormone deficiency, and they usually recover when sufficient calories are ingested. Their parents do not usually blatantly reject the child. The mothers characteristically have multiple children or responsibilities. They are usually disorganized, and the children do not receive the food or the attention they need, but the attention they receive is usually adequate for infants to again grow, if they are given adequate nourishment. Nevertheless, growth in some may be inadequate without further psychosocial interventions, as reported by Bithoney et al.⁷⁻⁹

Type II PSS has been called transient hypopituitarism, reversible hyposomatotropism, emotional deprivation, maternal deprivation, psychosomatic dwarfism, abuse dwarfism, and the "garbage can" syndrome. The term PSS is preferable to definitions that include the presence or absence of GH, the presence or absence of overt psychologic abuse, or emotional deprivation. This type occurs characteristically in children 3 years of age and older.

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Table 2

Characteristics of Various PSS Syndromes¹

Type	Age of Onset	Failure to Thrive	Bizarre Behavior	Depression	GH Secretion	Parental Rejection	GH Responsiveness
I	Infancy	Usually	No	Often	Normal	No (see text)	?
II	≥3 years	Some & some overweight	Usual	Very often	Decreased or absent often	Usual	Minimal at doses used
III	Infancy or later	Not usual	Not usual	Yes	Normal	Concern, not rejection	Significant at dose used

Adapted from: Blizzard RM, Bulatovic A. In: Lifshitz F, ed. *Pediatric Endocrinology 3rd Edition*. New York: Marcel Dekker, 1996:83-93.

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 adrenocorticotrophic 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.

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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^{+/-} 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 *in 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.

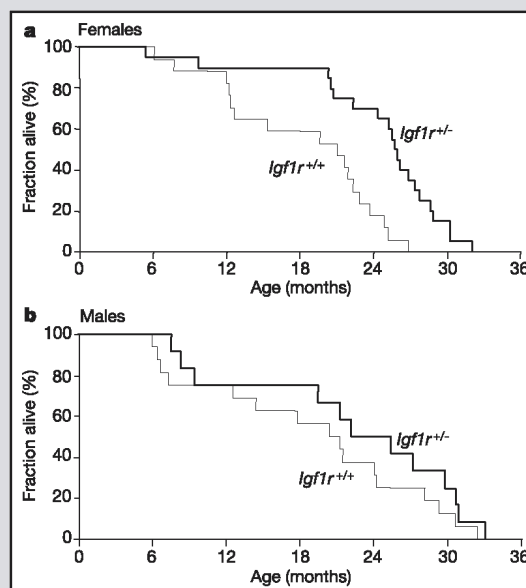
Bluher et al demonstrated that in mice in which there has been localized “knock out” of fat specific insulin-receptors (FIRKO) (in contrast to generalized loss of IRS which leads to insulin resistance, diabetes mellitus, and obesity), there was extension of life span despite normal caloric intake and 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.

Holznerberger M, et al. *Nature* 2003;421:182-186.

Bluher M, et al. *Science* 2003;299:572-574.

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

Figure
Lifespan extension in *Igf1*^{+/-} mice with respect to *Igf1*^{+/+} (WT) mice



a - *Igf1*^{+/-} females (thick line) live a mean of 33% longer than their wild-type littermates (756 ± 46 compared with 568 ± 49 days; *P* < 0.01, *t*-test). Kaplan-Meier analysis of survival revealed a later decline in *Igf1*^{+/-} mice compared with wild type (*P* < 0.001, Cox's test). **b** - *Igf1*^{+/-} males live 15.9% longer than wild-type littermates (679 ± 80 compared with 585 ± 69 days; NS).

Reprint with permission from: Holznerberger M, et al. *Nature* 2003;421:182-186.

(GHD) such as Ames (*Prop^{dl/dl}*) and Snell (*Pit1^{dw/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

Hypothalamic Insulin Signaling is Required for Inhibition of Glucose Production

Insulin has many energy modulating actions that take place in the hypothalamus, such as inhibition of feeding. The investigators studied the effects of infusing insulin, an insulin mimetic, and inhibitors of insulin action. Infusion was done in the intra-third cerebral ventricle (ICV). Hepatic glucose production and peripheral glucose consumption were determined. Steady state of serum insulin concentrations were achieved by using systemic pancreatic-insulin clamps.

ICV infusion of insulin/insulin mimetic at basal insulin concentrations led to a 7-fold increase in glucose infusion rate to maintain euglycemia. Thus, ICV glucose enhanced peripheral insulin action. Employing radiolabeled glucose and kinetic glucose studies, the investigators demonstrated that ICV insulin decreased the rate of hepatic glucose production by 40+% while not altering peripheral glucose consumption. Inhibition of insulin action in the hypothalamus by co-infusion of insulin antibodies or an antisense disrupter of insulin receptor synthesis antagonized the effect of insulin on glucose production. Further studies demonstrated that the intracellular mechanism(s) through which hypothalamic insulin exerted its effect on glucose production involved the phosphoinositide-3-kinase signal transduction pathway and ATP sensitive potassium channels. However, the manner in which

hypothalamic insulin impaired hepatic glucose production was not identified by these studies. The authors suggest that hypothalamic insulin (as well as other factors such as leptin and melanocortins) may monitor and modulate exogenous energy intake relative to endogenous energy consumption. Failure of hypothalamic insulin function may lead to peripheral insulin resistance and may be a factor in the pathogenesis of the dysmetabolic syndrome and type 2 diabetes mellitus.

Obici S, et al. *Nature Med* 2002;8:1376-1382.

Editor's Comment: *The physiological importance of insulin action within the central nervous system is well described in the content of this manuscript. The demonstrations reported open yet another site at which a metabolic error may lead to clinical illness. It is crucial to determine the specific mechanisms by which the hypothalamic action of insulin is recognized at the hepatic level and to develop a method(s) by which one may assess hypothalamic insulin function in the intact human.*

Allen W. Root, MD

Hyperzincemia and Hypercalprotectinaemia: A New Disorder of Zinc Metabolism

The authors describe five patients (including a mother and her son) who had a multidimensional illness comprised of recurrent infections, rash, arthritis/vasculitis, hepatosplenomegaly, and growth retardation in infancy and childhood. Although these findings were consistent with zinc deficiency, the patients had marked hyperzincemia due to its binding to greatly elevated amounts of a zinc-binding protein called calprotectin. Calprotectin is a calcium and zinc binding protein complex of two S100 plasma proteins termed S100A8 and S100A9 (also termed proteins MRP8 and MRP14, respectively). It is present in the cytosol of phagocytes and is released into plasma as phagocytic neutrophils are destroyed. In these patients, plasma zinc concentrations were 5-10 times higher than the upper normal range (18 $\mu\text{mol/L}$), while calprotectin concentrations were 1000 fold greater than the upper normal value (850 $\mu\text{g/L}$), suggesting that free plasma zinc concentrations were likely to be low. Individual patients were anemic, thrombocytopenic, and had low numbers of monocytes and B lymphocytes.

Chromatographic analysis of S100A8 and S100A9 proteins was normal, suggesting no major mutations or post-translational modifications of calprotectin. Since there was no evidence of increased neutrophil turnover rate, the investigators hypothesized: (1) that the increased plasma concentrations of calprotectin reflected its decreased rate of degradation; (2) that the patients were zinc deficient because of the high affinity of calprotectin for zinc; and (3) that calprotectin itself may have been cytotoxic to neutrophils and other tissues.

Sampson B, et al. *Lancet* 2002;360:1742-1745.

First Editor's Comment: *The new syndrome comprises patients with an apparent "functional zinc deficiency" despite high plasma concentrations of this element. Although "free zinc" concentrations were not measured, they were thought to be low. In addition, the authors did not report the effects of a trial of therapy with supplemental zinc in these subjects. Thus, the*

Table

Clinical and laboratory data of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	18	9	14	35	21
Sex	M	F	M	F	M
Growth failure	<3rd percentile	<3rd percentile	<3rd percentile	Normal	Normal
Hepatosplenomegaly	Yes	Yes	Yes	Yes	Yes
Dermatological symptoms	Vasculitis	None	None	Vasculitis, eczema	Vasculitis, furuncles ulcers
Rheumatic symptoms	Arthritis	Arthritis	Arthritis	Arthritis, uveitis	Arthritis
Plasma C-reactive protein (mg/L)†	41-143	100-200	22	17	45-146
Haemoglobin (g/L)	80	90	109	125	80
Total white-cell counts (10 ⁹ cells/mL)	2-0	3.7-5.0	1.5	5.0	3.8
Monocytes	0		1.9%	1.9%	4.3%
Plasma zinc (mol/L)‡	180-200	82-96	160-200	175	77
Plasma calprotectin (g/L)§	6.5	1.4, 2.55	9	6.1	1.5

†Reference <10 mg/L. ‡Reference 10-18 mol/L. §Reference <1 mg/L

Adapted from Sampson B, et al. *Lancet* 2002;360:1742-1745.

hypothesis regarding "functional zinc deficiency" remains unproven. Since calprotectin is a calcium binding protein, it would have been of interest to report total and ionized calcium values in these patients.

Zinc deficiency may be congenital or acquired. Acrodermatitis enteropathica (OMIM 201100) is an autosomal recessively transmitted disease characterized by bullous lesions of the skin, alopecia, diarrhea, and growth failure with hypozincemia. Administration of supplemental zinc ameliorates these abnormalities. Approximately 50% of patients with acrodermatitis enteropathica have a loss-of-function nonsense or missense mutation in SLC39A4 (Solute Carrier Family 39 [Zinc Transporter], Member 4) encoding a renal- and intestine-specific transmembrane zinc transporter protein (OMIM 607059, chromosome 8q24.3). Zinc deficiency may be acquired due to dietary

deficiency, decreased absorption due to co-ingestion of zinc-binding materials such as clay or phytates, malabsorption as in patients with chronic inflammatory bowel disease, or excessive excretion as in patients with sickle cell disease and hyperzincuria.

Allen W. Root, MD

Second Editor's Comment: *I am puzzled by the possibility of copper deficiency in these patients. The clinical picture and the anemia and leucopenia are typical of it. A deficit of this mineral would likely result in a deficiency of Ca/Zn SOD (super oxidase desmutase) though I do not know of studies of its effects on calprotectin.*

Fima Lifshitz, MD

Initial Treatment Dose of L-Thyroxine in Congenital Hypothyroidism

The American Academy of Pediatrics (AAP) recommends an initial L-thyroxine dose of 10 to 15 mcg/kg/d for the treatment of congenital hypothyroidism (CH).

Several studies have shown that early high dose therapy which quickly produces serum T-4 levels within the "normal" neonatal range may be associated with the

development of near normal IQ scores; whereas therapy with lower dosages are associated with a delay in achieving normal T-4 concentrations by as little as 1 week may result in lower IQ scores. Thus, pediatricians and pediatric endocrinologists need to be familiar with treatment regimens that achieve the T-4 goal with as little delay as possible, yet do not produce untoward side effects such as craniosynostosis.

Selva and colleagues present data obtained in 47 congenitally hypothyroid neonates (BW 3-4kg) using a prospective randomized study of 3 different L-thyroxine dosing regimens (Group 1 – 37.5mcg/d; Group 2-loading dose 62.5mcg/d x 3d, then 37.5mcg/d; Group 3 – 50mcg/d). Serum T-4, free T-4, T-3, free T-3, and TSH were measured at baseline, 3 days, and 1, 2, 4, 8, and 12 weeks after starting treatment. No changes in treatment dose were made for 2 weeks. At that time, dosages were altered using the following important algorithm to maintain serum T-4 concentrations between 10 – 15 mcg/dL; a) T-4 < 8.5mcg/dL, increase dose by 12.5mcg/d, b) T-4 between 8.5 and 9.9mcg/dL, increase dose by 6.25mcg/d, c) T-4 between 15.1 and 16.5mcg/dL, decrease dose by 6.25mcg/d, d) T-4 greater than 16.5mcg/dL, decrease dose by 12.5mcg/d.

Pre-treatment thyroid levels were similar in all three groups. Infants in Groups 2 and 3 achieved target T-4 levels by 3 days, while infants in Group 1 did so by 1 week of age. Subjects in Group 3 had T-4 levels above 16mcg/dL by 1 week, while the others were in the target range at both 1 and 2 weeks. TSH remained elevated in Groups 1 and 2 for the first 2 weeks. After 2 weeks, serum T-4 remained within the target range in all three groups, but doses were adjusted as outlined above. At 12 weeks, mean L-thyroxine dose was 36.7 mcg/d (approximately 6mcg/kg/d) in all groups, which was associated with ideal target levels of T4, T3, and TSH. Free T-4 levels rose above normal by 1 week and remained above normal at 12 weeks in all age groups. There were no significant differences in TSH concentrations at 12 weeks among the groups.

When patients were divided into severe and moderate CH categories based on serum T-4 above or below the median value, the differences in initial T-4 levels were abolished by 3 days for Group 3 infants and by 1 week for the others.

The authors state that their data shows that a loading dose of 62.5mcg/d x3 days followed by a dose of 37.5mcg/d raises serum T-4 levels quickly but does not normalize TSH levels. However, the sustained dose of L-thyroxine (50mcg/d – Group 3) normalized TSH levels within 2 weeks and abolished any difference in serum T-4 levels between severe and moderate CH infants by 3 days. Consequently, they recommend the use of a higher target range of 10 to 18mcg/dL for T-4 for the first

2 weeks of therapy to insure that the benefits of therapy are maximized.

Selva K, et al. *J Pediatr* 2002;141:786-792.

Editor's Comment: *It may seem surprising to read a paper dealing with the "correct" L-thyroxine dose for treating infants with CH, when most neonatal screening programs have been in place for approximately 20 years and have been highly successful in identifying these infants and seeing that they receive what has been considered "appropriate" treatment. However, the medical community, despite well-delineated guidelines from the AAP, has yet to define "appropriate" treatment. The article by Selva et al helps clarify three different treatment regimens. They are to be commended for the prospective randomized protocol followed. It is interesting that they refrain from "recommending" a single or favorite regimen. Indeed all three regimens work well if the goal is to normalize serum T-4 within 1 week. Quicker attainment of the target range requires a loading dose for three days. The accompanying algorithm for adjusting L-thyroxine doses is helpful and all of these data and recommendations need to be disseminated to those caring for neonates.*

William L. Clarke, MD

Second Editor's Comment: *This detailed analytical study is accompanied by a detailed analytical report pointing out that several groups have demonstrated as much as a 20 point IQ deficit in severely affected CH infants who did not have rapid and complete conversion of serum hormonal levels of T4, T3, free T4 and T3, and TSH to normal. The article convinced me that a treatment protocol as used for group 3 is currently the best available.*

In an accompanying editorial by Dr. Nancy Hopwood¹ of the University of Michigan, emphasis is given to the importance of using only tablets of T4 because liquid preparations may be unreliable. She also points out that persistent TSH elevation can result from faulty absorption of T4 in patients with milk allergy, malabsorption of various causes, with soy formulas, iron therapy, and with acidic juices in children of all ages. The article by Selva et al and the editorial by Dr. Hopwood fit together splendidly.

Reference

1. Hopwood NJ. *J Pediatr* 2002;141:752-4.

Robert M. Blizzard, MD

Survival Profile for Down Syndrome

Down syndrome is the most common form of inherited intellectual disability. In addition, it is associated with growth deficiency, hypotonia, characteristic craniofacial appearance and developmental anomalies involving the heart and other organ systems. Survival of these patients has changed dramatically over the last several decades primarily because of surgical intervention for cardiac defects. For example, life expectancy increased from 12 years in England in 1949 to recent estimates of over 50 years in western countries. These estimates are based on cross-sectional data because there is little longitudinal information available. Moreover, it is known that adults with Down syndrome are predisposed to a number of disorders including obesity, hypothyroidism, epilepsy, dementia, and Alzheimer's disease; however the impact of these disorders on survival is unknown.

To define the survival profile for those with Down syndrome, Glasson and colleagues assessed survival in 1,332 patients (45% female) born between 1902 and 2000, mostly in Australia. Most patients had had standardized intelligence testing. Death had occurred in 20%. Kaplan-Meier survival probabilities were calculated separately for sex, level of intellectual disability and decade of birth.

The analysis showed that the overall life expectancy for patients with Down syndrome approaches that of the general population in Australia. Seventy-five percent of cases had survived to 50.0 years, 50% to 58.6 years

and 25% to 62.9 years of age. The mean life expectancy for males was greater than females by 3.3 years with the median survival probabilities of 61.1 for males and 57.8 for females. The difference was attributed to a higher incidence of heart defects in females. When examined by decade born, each successive birth group showed increased survival consistent with progressive improvement in medical care. No association was found between level of intellectual disability and survival, which was surprising to the authors because an association had apparently been found in an earlier study.

Approximately 25% of all Down syndrome deaths occurred between the ages of 58 and 63 years. No clear explanation for this was found nor is there any certainty that the trend will continue in patients born more recently. The authors raise the possibility that it could reflect mortality associated with the above mentioned chronic diseases to which adults with Down syndrome are predisposed.

Glasson EJ et al. *Clin Genet* 2002;62:390-393.

Editor's comment: *The information contained in this paper should be very useful to physicians, genetic counselors and others who deal with families concerned about long term survival in Down syndrome.*

William Horton, MD

Mutagenesis Does Not Explain Paternal Age Effect in Achondroplasia

Achondroplasia is the prototype of chondrodysplasia in humans. Its major features include short limb dwarfism and a large head with mid-facial hypoplasia. Achondroplasia arises most often as a sporadic event to normal parents and there is a pronounced paternal age effect. It results from activating mutations of Fibroblast Growth Factor Receptor 3 (*FGFR3*), which encodes the transmembrane receptor. *FGFR3* mutations have several unique features including that they arise *de novo* almost exclusively during spermatogenesis and that almost all involve the same G-to-A transition at base pair 1138 (G1138A) of the gene resulting in a glycine to arginine substitution in the transmembrane domain of the receptor. Taken together, these observations have led to the commonly accepted views that *FGFR3* is exceptionally mutagenic and that the paternal age effect reflects replication errors that occur during spermatogenesis. Spermatogenesis continues throughout life and presents many more opportunities for erroneous copying of DNA than does oogenesis in which replication ceases before birth.

Although this explanation makes good sense, there is now evidence that *it is incorrect*.

To test if increased mutagenesis accounted for the paternal age effect in achondroplasia, Tiemann-Boege et al determined the frequency of the common G1138A *FGFR3* mutation in sperm from 118 healthy men ranging in age from 18 to 80 years. They expected to detect a progressive increase in sperm mutation frequency comparable to the increase in number of achondroplasia births to older fathers. However, to their surprise, using a carefully controlled polymerase chain reaction assay, they found only a small increase in the G1138A mutation which by itself could not account for the paternal age effect.

More specifically, they observed that the mutation rate for G1138A averaged about 1 per 11,000 haploid genomes over all ages. Broken down by age, the mutation frequency changed little between the ages of 18 - 40 and 55 - 80 years. It increased about 2-fold between the two age groups, but this was nowhere near

the increased frequency of achondroplasia births in older fathers.

The authors addressed in considerable depth various possible explanations for their findings. Several involve experimental biases or artifacts. For example, fathers of children with sporadic achondroplasia may constitute a subgroup of men with distinct mutation properties that differ from the sperm donor population. There may be unappreciated ascertainment biases with regard to the makeup of donor population or in previous studies. Despite extensive controls, there could have been underreporting of mutations in the PCR assay. These studies may have led to overestimating the magnitude of the paternal age effect.

Two of the possibilities deserve special attention. The first is that there may be an age-dependent increase in germ-line permutations at the G1138A site that are neither converted to a full mutation or repaired before fertilization. One candidate lesion would be an unrepaired G/T mismatch resulting from deamination of 5-methyl cytosine. The cytosine at position 1138 is known to be highly methylated in sperm and therefore a candidate for such a pre-mutation, which might go undetected under conditions of PCR.

Another possibility is that the G1138A mutation gives a selective advantage to sperm that carry it. The authors acknowledge the highly speculative nature of this possibility, but point out that FGFR3 is expressed and presumably active in mature sperm cells. They also caution that invoking this possibility must include an explanation of how a potential selective advantage would increase with age.

Tiemann-Boege et al. *PNAS* 99 2002;14952-57.

Hurst LD, Ellegren H. *Nature* 2002;420:365-66.

Editor's comment: *Many observations over the last several years have led to the dogma that FGFR3, especially the site where achondroplasia mutations arise, is extraordinarily mutable during spermatogenesis and that this mutability increases dramatically with age. The idea that DNA is prone to replication or mitotic errors, that there are many more opportunities for such errors to occur during spermatogenesis compared to oogenesis, and these can somehow accumulate with age has been conceptually appealing and is easy to explain during counseling. However, the results reported here cast serious doubt on its validity. Assuming they hold up, which seems highly likely given the considerable lengths to which the authors went to control their experiments and validate their results, the dogma will need to change.*

The notion of genetic pre-mutation in achondroplasia is not new. It was proposed by John Opitz and others long before mutations of FGFR3 were discovered. It never gained much momentum, probably because it lacked experimental data with regard to a specific locus or mutation; however, the paper by Tiemann-Boege et al may add new life to this concept.

The possibility that sperm which harbor activating mutations of FGFR3 have a selective advantage for motility, fertilization or the like, is intriguing. Of note is that activating FGFR3 mutations found in the achondroplasia family of disorders have been detected in several types of cancer, including multiple myeloma and bladder, breast and colon carcinoma. The mechanisms through which the mutations contribute to neoplasia are not well understood. However, they may well give the cancer cells a competitive advantage over the normal cells.

William Horton, MD

Is Insulin-Like Growth Factor-1 Monitoring Useful in Assessing the Response to Growth Hormone of Growth Hormone-Deficient Children?

In order to assess the relationship between insulin-like growth factor-1 (IGF-1) and the growth hormone (GH) dose utilized to treat GH-deficient children, the IGF-1 response was compared with the changes noticed in height-standard deviation scores (H-SDS) and height velocity during treatment.

The study was carried out in 24 prepubertal GH-deficient patients with a mean age of 10.5 ± 1.8 years and a mean bone age of 8.4 ± 2.1 years. H-SDS for chronological age and bone age before therapy were -2.6 ± 0.8 and -1.2 ± 0.8 , whereas height velocity was -1.1 ± 1.5 cm. Serum IGF-1 and insulin-like-growth factor binding protein-3 (IGFBP-3) levels were measured before, after 6 months and 12 months of GH treatment,

and correlated with the GH dose. IGF-1 increased significantly during the first six months of therapy, but did not increase any further at twelve months, despite the use of higher GH dosages (0.14 vs. 0.1 IU/kg/day), whereas IGFBP-3 increased at both 6 and 12 months. There was no correlation between GH dose and IGF-1 and IGFBP-3 levels. Height velocity as well as height for chronological age and bone age were significantly greater after one year of treatment with GH. The authors concluded that the increment in IGF-1 during therapy did not correlate with the interval height increase and was found to be less useful than height increments in adjusting the GH dose needed to treat prepubertal GH-deficient children.

Lanes R, Jakubowicz S. *J Pediatr* 2002;141:606-610.

Editor's Comment: *The monitoring approach that individualizes therapy and includes both biochemical and auxological determinations to titrate the GH dose utilized to treat GH deficiency is considered standard practice in treatment with GH. A common practice is to monitor height increments and serum IGF-1 and IGFBP-3 concentrations to guide with the treatment of GH-deficient patients. However, in this study IGF-1 and IGFBP-3 levels were not found useful in assessing the response to GH treatment. There are wide variations in IGF-1 levels during the day, as well as different stages throughout time, and even in the same individual. Of great importance is the nutritional status and intake of the patients in relation to the IGF levels. Any one or several of these factors might have played a role in the*

lack of a clinically relevant, as well as statistically significant, difference in IGF levels found in this small group of patients studied. The reader is advised to read the editorial on this paper published in the same journal by Dr. Barry Bercu¹ entitled "Titration of growth hormone dose using insulin-like growth factor-1 measurements: Is it feasible in children?" This study once again demonstrates that careful measurements of height and the monitoring of growth progression is the most important marker in the assessment of short children with or without GH deficiency, as well as during treatment with GH.

Reference

1. Bercu B. *J Pediatr* 2002;141:601-5.

Fima Lifshitz, MD

Leptin Measurement in Urine and its Relationship to Other Growth Peptides in Serum and Urine

Leptin is a 167 amino acid product of adipocytes that has multiple physiologic effects including appetite suppression, alteration in energy balance, acceleration of pubertal onset, and both stimulatory and inhibitory effects on bone mineralization. Its role in human physiology other than for appetite suppressive effects and possible hypogonadotropism, is uncertain. The authors have adapted a two-site immunoradiometric assay (IRMA) for measurement of leptin in serum to its determination in urine. In this assay, two mL of urine (unmodified by acidification or dialysis) are incubated initially in a plastic tube coated with antibody (#1) to leptin, followed by incubation with a second, radiolabeled antibody (#2) to leptin with specificity to a different epitope. Free labeled antibody (#2) is removed and radiolabeled bound antibody (#2) quantitated. Leptin in urine (lep/u) is calculated by comparison to standards of leptin similarly prepared. Lep/u was quantitated in timed overnight urine collections in 188 (100 females) children and adolescents 5-19 years of age. Serum and/or urinary levels of growth hormone (GH), insulin-like growth factors (IGF-I and IGF-II), and IGF binding proteins (IGFBP3 and IGFBP-1) were also determined. The IRMA for lep/u was validated by dilution and recovery experiments. In the cross-sectional survey, total lep/u was similar in prepubertal boys and girls (0.2 ng/night). Lep/u values increased to a peak in boys at Tanner genital stage III (0.8 ng) and then declined; in girls, lep/u continued to increase through breast stage V (1.1 ng) and values were significantly higher in adult females than in males. The maturational patterns of lep/u were similar to those described for serum leptin (lep/s) changes. Log transformed values of lep/u and

random lep/s were highly correlated. Lep/u levels were variable related to age, stage of sexual maturation, BMI, IGF-I, and IGF-II. In two adults in whom overnight urines were collected consecutively for more than 30 nights, nocturnal lep/u values varied night-to-night by 42-75%. In a substantial number of specimens (20+%) obtained from both the children and adults, lep/u was not measurable. The authors conclude that measurement of timed overnight lep/u is a feasible method for longitudinal assessment of leptin production in children, adolescents, and adults.

Zaman N, et al. *Clin Endocrinol* 2002;58:78-85.

Editor's Comment: *The majority of secreted leptin is catabolized in the kidney to smaller peptides. The investigators relied, in part, upon the specificity of two antibodies directed to different epitopes of leptin to validate the IRMA for lep/u. However, it would have been of interest to examine the physicochemical properties of urinary leptin by size exclusion chromatography and/or mass spectroscopy to determine more accurately the nature of the peptide measured by the IRMA. It would also have been of interest to have measured urinary/serum levels of gonadotropins and sex hormones and to assess their relationships to lep/u and stages of sexual development (perhaps a manuscript already in preparation). Nevertheless, the data are of interest and the described method may be helpful in furthering our understanding of the relationship between growth, sexual maturation, and leptin.*

Allen Root, MD

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

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/m²/d) and fludrocortisone (100 – 150 mcg/m²/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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