

HUMAN GROWTH FOUNDATION

fourth friday



From the President's Desk

SPRING 2003

On March 28th & 29th we held our Annual Conference in Kansas City, MO. Including our Board of Directors, exhibitors, members and guests we had more than 200 participants, making this one of the best attended annual conferences. From the comments I heard at the meeting and read on the list-serve, this was also a meeting that was seen as one of our best by many of the participants. In addition to our business meeting, we heard a number of educational presentations. Dr. Warren Rosen spoke both Friday evening and Saturday morning, discussing issues of brain functioning and learning. In addition he moderated a panel of young people and their parents talking about what it is like to have short stature and take growth hormone injections. One of our board members, Dr. Jack Fucqua of Indianapolis, discussed the relationship of puberty and growth. Dr. Sandra Blethen from Serono (formerly from Genentech) gave her predictions regarding the future uses of growth hormone. Dr. Ray Hintz from Stanford University explained the safety issues relating to growth hormone. Dr. Wayne Moore from Kansas

City discussed issues of transitioning from childhood to adult growth hormone replacement. The conference concluded with a fascinating presentation by board member Dr. Frank Diamond (Vice President of HGF), who related his experiences with a group of people in rural Equador who have growth hormone resistance. The quality of the presentations was reflected by the inquisitive questions from the audience—always an excellent indication that the presentations raised important issues.

A special highlight of the meeting was the presentation of the first Human Growth Foundation Award to Dr. Robert Blizzard. Dr. Blizzard was one of the founders of this organization, and has continued to support our efforts over the years. Upon receiving the award, he introduced several people in the audience who had also been instrumental in the early days of HGF. He related the story of how in the 1960's and 1970's HGF had helped to arrange for collection of human

pituitary glands. These glands were then flown to Maryland, where growth hormone was purified in order to treat children who were growth hormone deficient. It was truly a pleasure to be able to recognize Dr. Blizzard and others who put in so much work to enable treatment with growth hormone before the hormone was commercially available.

All in all, we had a very successful meeting. We continued our tradition of a Silent Auction (thanks this year to the efforts of advisory board member Kelly Betts), which increased contributions to the John Hickey Fund. This fund is now approaching \$50,000, which is half way to our goal of \$100,000. One of the goals of this fund is to help support the training of fellows in pediatric endocrinology.

Stephen Kemp, M.D., Ph.D.
President HGF

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"As a teacher, I sometimes see a very short child who appears to have a disturbed psychological relationship with his parents. Can emotions effect the way a child grows?"

Psychosocial short stature (PSS) is a well recognized medical entity that has also been called emotional deprivation. Three clinical "subtypes" have been reported. In PSS type II children are "rejected" by their parents and are psychologically and occasionally physically or sexually abused. Alcoholism may be present in the parent. In early childhood these children manifest bizarre eating and drinking patterns such as food stealing, eating from garbage cans, and drinking from toilets or puddles. Disturbed sleep patterns result in nocturnal "roaming" and "restlessness" and EED recordings reveal reduced stage IV sleep and "slow wave" sleep. Speech delay may occur and temper tantrums are common. Affected children may manifest a curious absence of response to pain (agnosia). They tend to be very "passive" shy children, and are rarely aggressive. These behaviors often disappear by teen years to be replaced by depression. The PSS type II child grows very slowly and may appear to have an isolated growth hormone deficiency. These subjects are usually adequately nourished and may not be underweight for height. Steatorrhea (foul smell-

ing, "fatty" stools) may be present but true malabsorption does not occur. Encopresis (fecal soiling), enuresis (bedwetting), and urinating in inappropriate places have been described. Boys and girls are equally effected.

Endocrine testing often reveals growth hormone deficiency, and sometimes deficiencies in testing of the child's adrenal and thyroid functions. Gonadotropin deficiency may result in delayed puberty. Treatment of such children with growth hormone, however, results in little improvement in growth rate or increase in IGF-1, the growth hormone "effector" molecule. Remarkably, when these children are removed from their home and placed in a more "loving" environment, their growth hormone response to stimulation testing returns to normal within a few weeks and they experience a dramatic "catch-up" growth (without hormone treatments) of as much as five to six inches in a single year!

PSS type I refers to "non-organic" failure to thrive (FTT) in the first two years of life. In landmark studies from the 1940's, Spitz examined "emotionally neglected" babies in orphanages and found evidence of increased anxiousness, retarded growth and development, and increased death rates despite adequate

food and hygiene. In more recent reports, mothers of infants with non-organic FTT demonstrate less verbal and physical interaction with their babies than normal mothers, and the affected infants are frequently underweight for height and growing slowly in length. Endocrine testing is usually normal. PSS type III differs from type II in that affected children have no evidence of the bizarre behaviors of PSS type II, and their parents are often depressed and self-aware of their dysfunctional interaction with their children. GH testing in these slowly growing children is frequently normal and they respond to growth hormone treatment with a rapid acceleration in linear growth.

These conditions remind us that the love, stimulation, and interaction that characterize a healthy parent-child relationship is a potent "growth factor" not to be forgotten!

Frank Diamond, MD
Vice President, HGF

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FROM THE HGF INTERNET SUPPORT LISTS:

HYPOGONADISM, GHD, AND CONSTITUTIONAL GROWTH DELAY

Sally and John are normal parents in all respects. They have a son named Jeffrey, who at the age of six, was diagnosed with idiopathic growth hormone deficiency, but appeared normal in all other respects. Since then, he has taken an appropriate dosage regimen of recombinant growth hormone (rGH). He is now 13 years old and 5' 5" in height; is growing at approximately 2.5" a year, and has not entered puberty. A recent physical examination, blood chemistries, and bone age study revealed no significant development of the secondary sex characteristics. Follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estrogen, DHEA/DHEAS, and androstenedione, which are tests to determine development stage, indicated prepubertal levels. There was a two year delay in bone age.

The pediatric endocrinologist told Sally and John that Jeffrey had hypogonadotropic hypogonadism (HH). The physician suggested that Jeffrey would continue to grow at his current rate of 2.5" per year, without any change in rGH therapy or other drug intervention, until he

stopped growing. The physician also said after Jeffrey reached his final height, he would prescribe gonadotropin or luteinizing hormone releasing hormone (LHRH) replacement therapy to induce the development of the secondary sex characteristics; and at an appropriate time, he would discontinue the gonadotropin therapy and introduce testosterone replacement therapy to obtain and maintain an adequate androgen level for masculine appearance, strength and endurance. The physician further told the parents that Jeffrey is and would probably remain sterile, but not impotent, as a result of the HH and the suppression of FSH and LH by the testosterone replacement therapy. He said that it might be possible for Jeffrey to discontinue testosterone temporarily and to recommence gonadotropin therapy for the purpose of inducing spermatogenesis to have a child. Having overcome their initial surprise upon being told of Jeffrey's medical conditions, the parents wanted to know more about HH.

Hypogonadism is "a condition resulting from or characterized by abnormally decreased gonadal function, with retardation of growth and sexual development."¹ It is directly caused by non-existent or inadequate levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), collectively known as "gonadotropins."

Hypogonadotropic hypogonadism (sexual infantilism) has been identified as "...a cause of partial or complete failure of puberty, may be familial and may have other associated abnormalities of hyposmia (smell), intellectual retardation, perceptive deafness, color blindness, skeletal deformities, and gynecomastia. Pituitary function is usually normal with the primary defect believed to be hypothalamic...."²

Gonadotropin deficient males may have undescended testes, gynecomastia, moderately delayed adrenarche, or bone age delay. "The rate of linear growth is normal, and final adult height is normal with testosterone therapy, although linear growth can continue longer in these boys than in boys with normal pubertal progression. Obesity can develop upon initiation of testosterone therapy."³

Syndromes that involve hypogonadism caused by gonadal dygenesis include Turner, Klinefelter, Kallman and Noonan syndromes.⁴

"Disorders of the hypothalamus and pituitary can impair secretion of gonadotropins and consequently cause decreased androgen production and defective spermatogenesis, either as an isolated defect or as part of a more complex pituitary insufficiency.... Thus destructive lesions of the pituitary

such as infarction, pituitary macroadenomas, metastatic or suprasellar tumors, infections, or granulomatous process can cause panhypopituitarism and lead to a secondary testicular defect.”⁵

In males, rGH therapy contributes to both the development and maturation of the Leydig cells that produce sperm. In the female, rGH contributes to the development of ovarian follicles that produce ova.⁶

Newborn males with micropenis, cryptorchidism, and subnormal levels of gonadotropins can be diagnosed and treated with gonadotropin replacement therapy during the prenatal period.⁷ Elevated levels of DHEA/DHEAS and androstenedione are associated with HH, whereas low levels of androgens are associated with GHD, thus providing a diagnostic method to prevent unnecessary delay in treatment for HH.⁸ (As an aside that is relevant to male fertility, newborn males with Leydig cell failure are hypergonadotropic upon testing with gonadotropin releasing hormone (GnRH), but can be treated with gonadotropin replacement therapy.)⁹

There can also be an issue of whether absence of sexual development is caused by HH or is the result of constitutional growth and

maturity delay (CGMD). No single test is a definitive method for a differential diagnosis. Severe constitutional growth and maturational delay (CGMD) can be differentiated upon priming with pulsatile GnRH. There is a significantly lower pituitary LH reserve in permanent HH than in CGMD.¹⁰ However, the metoclopramide test is significantly more sensitive than the GnRH test in differentiating HH and CGMD.¹¹ Leuprolide acetate (Lupron) stimulation can also differentiate between hypogonadotropic hypogonadism (HH) and CGMD.¹² There are mixed study results with respect to whether gonadotropin or mixed gonadotropin therapy can result in normal testosterone levels and in spermatogenesis.¹³

Where there are irregularities in, or underdevelopment of, or the absence of sex organs early on, the question of whether that child will produce gonadotropins presents itself early in life. But in prepubertal GHD males and females, the question will remain open until puberty is supposed to commence unless the question arises earlier based on the surfacing of developmental issues. It is important to know of the possibility of hypogonadism because it occurs frequently enough in conjunction with GHD to warrant knowing

about it. No parent should be lulled into thinking that “My child has idiopathic (isolated GHD); the rGH will solve the problem; and that will be the end of it.”

¹ Dorland's Illustrated Medical Dictionary, 28th Ed. (W.B. Saunders, Philadelphia: 1994)

² Hypothalamic and pituitary function in hypogonadotropic hypogonadism. Paulson DF, Wiebe HR, Hammond CB. *Urology*. 1975 Sep;6(3):333-6.

³ Gonadotropin deficiency in boys: clinical characteristics and growth. Van Dop C, Burstein S, Conte FA, Grumbach MM. *J Pediatr*. 1987 Nov;111(5):684-92. Department of Pediatrics, University of California, San Francisco 94143.

⁴ Williams Textbook of Endocrinology, 9th Ed. (W.B. Saunders, Philadelphia: 1998) at pp. 1331-1356, 1555-1557.

⁵ Williams Textbook of Endocrinology, 9th Ed. (W.B. Saunders, Philadelphia: 1998) at pp. 841-842.

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⁷ Early postnatal treatment of hypogonadotropic hypogonadism with recombinant human FSH and LH. Main KM, Schmidt IM, Toppari J, Skakkebaek NE. *Eur J Endocrinol*. 2002 Jan;146(1):75-9. University Department of Growth and Reproduction, Section 5064, National University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

⁸ Clinical value of adrenal androgen measurement in the diagnosis of delayed puberty. Cohen HN, Wallace AM, Beastall GH, Fogelman I, Thomson JA. *Lancet*. 1981 Mar 28;1(8222):689-92

⁹ Hypergonadotropic hypogonadism in newborn males with primary testicular failure.

Dunkel L, Perheentupa J, Tapanainen J, Vihko R. *Acta Paediatr Scand.* 1984 Nov;73(6):740-4.

¹⁰ Differentiation of male hypogonadotropic hypogonadism and constitutional delay of puberty by pulsatile

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¹² Leuteinizing hormone responses to leuprolide acetate discriminate between hypogonadotropic hypogonadism and constitutional delay of puberty. Street ME, Bandello MA, Terzi C, Ibanez L, Ghizzoni L, Volta C, Tripodi C, Viridis R. *Fertil Steril.* 2002 Mar;77(3):555-60. Department of Paediatrics, University of Parma, Parma, Italy.

¹³ Absence of effect of recombinant growth hormone to classic gonadotropin treatment on spermatogenesis of patients with severe hypogonadotropic hypogonadism. Giagulli VA. *Arch Androl.* 1999 Jul-Aug;43(1):47-53. Endocrine Section, Ospedale Santa Maria degli Angeli, Putignano, Bari, Italy.



LEE KITCHENS

HGF wishes to express our sorrow on the passing away of a very dear friend – Lee Kitchens, on May 12th, 2003 at 73 years of age. We extend all of our love and our condolences to his family for their loss.

We were privileged to have known Lee for over 25 years. He enhanced our organization through his support and the expenditure of his time and efforts on behalf of the goals of HGF.

Lee served as a Board member from 1985 – 1986 and was the vice-president from 1986 – 1987. Lee assumed the role of our president from 1988 through 1991. Good friends are always treasured and their loss leaves an emptiness which cannot be filled.

Earl Gershenow
Web Master-HGF



Human Growth Foundation gratefully acknowledges the following corporations for their generous support of the Annual Conference:



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Dear Elizabeth:

My name is Justin and I'm 12 years old. My twin brother Josh and I have growth hormone deficiency. I was wondering if you could answer some of my questions. Did you use the puberty stopper and the growth hormone. I really only want to use the growth hormone. What do you think? I've already gone through all 3 tests. Two out of three show growth hormone deficiency. My potential height without growth hormone is 4'6"

Thank you,
Justin & Josh

Dear Justin & Josh:

Thank you for your e-mail about growth hormone. I did not take Lupron, the medicine to stop puberty. I do know that plenty of people do take it. It is prescribed to stop puberty so that you have more time to grow before your bones fuse. If you do not take it, the window of opportunity to grow will be shorter. Please let me know how you are doing and when you will start your shots. I can help you with that, too. I took growth hormone shots from the age of 10 to 15. I was 4'8" at 10 and grew to 5'5" by 15. I am now 21 years old and in college.

I think it is great that you are going to start taking growth hormone and maybe Lupron. I hope to hear from you soon.

Take Care,
Elizabeth

Dear Elizabeth:

My name is Sue and I wanted to thank you so much for taking the time to e-mail my boys Justin and Josh. They were grateful for your response. The boys just completed their Stim tests and 2 out of 3 show that they are not producing enough growth hormone. The doctor suggested Lupron as well as growth hormone. The boys are 12, have bone ages between 13 and 14 and both started puberty. The clock is ticking for them.

I regret not making the decision earlier to have them go on growth hormone, but I thought they were just perfect the way they were.

One day, while they were leaving school, I spotted them standing next to their friends and saw there was a marked difference in their heights as compared to their classmates. I now knew that I had to do something.

They have not started the shots yet. The medication has arrived. We have an appointment in a few days so

the doctor can get us started. I spoke with the school nurse to make her aware of the boys going on growth hormone.

They are very excited to begin. I hope everything is going well for you and thanks again.

I'll let you know how everything goes.

Sue



E-mail Elizabeth at:
Cp4babies@aol.com

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Type of Membership/Amount Enclosed: New Renew (all contributions are tax deductible)

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The membership year runs from January 1 through December 31. Anyone who joins for the first time after September 1, will have membership through the following year.

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(Call 1-800-451-6434 to find out if there is a chapter near you.)

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50% to local chapters 100% National Office of HGF

How did you learn of HGF?

Type of growth disorder which interests you _____

Doctor's name/address/hospital _____

(Optional) Child's Name _____ DOB _____

Diagnosis _____ Secondary Condition (s) _____

Please contact me. I would like to assist in any way I can to benefit HGF

Please Mail Your Membership to:

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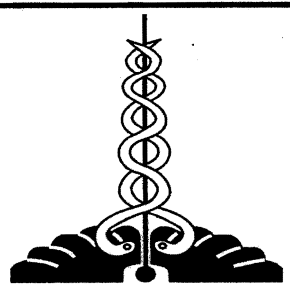
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JOHN HICKEY FUND
Your tax deductible donations have begun the establishment of The John Hickey Fund . However, the fund is an ongoing project. We ask you to keep the JHF in mind when deciding what charitable contribution you are going to make during 2003, and in the future.

