

HUMAN GROWTH FOUNDATION

fourth friday



From the President's Desk

SUMMER/FALL 2006

It's a pleasure for me to write to you as the newly elected President of the Human Growth Foundation. I am thrilled by the opportunity to serve our members and to carry on the many activities and traditions of HGF! Special thanks go to my predecessor, Dr. Stephen Kemp, for the many years he guided our Foundation on a path of progress and growth. It's a sign of his significant commitment to HGF that he will continue to serve as a board member after retiring as president! I am also looking forward to working with our new officers, two distinguished pediatric endocrinologists: Dr. Emily L. Germain-Lee from Johns Hopkins University, as Vice-President, and Dr. John Fuqua from the University of Indiana, as Secretary. We are also fortunate to have the continued service of our dedicated Treasurer, Ms. Teresa O'Leary, a well-known New York attorney.

Where are we going at HGF? Our most important goals are to continue to provide reliable and "cutting edge" educational information to our members and to support the needs of children and adults with growth or growth hormone disorders. Our

busy website and list serves are undergoing a "make over". We are planning new educational pamphlets to address several recent endocrinologic advances including the role of insulin-like growth factors in human growth disorders. We will continue to vigorously advocate for access to funding for growth related research and therapy for children and adults in need. In addition, HGF's own yearly growth-related research grants, which now total more than 1 million dollars in aggregate, will continue to offer opportunities and incentives to young physician-scientists pursuing careers in growth related research. At our recent Annual Conference in Dallas, we presented a number of excellent topics related to psychosocial and medical aspects of growth. A new HGF emphasis will be aimed at better informing primary care providers about the urgent need for early diagnosis of growth disorders such as Turner Syndrome

and Intrauterine Growth Retardation.

While HGF's future is bright, we need your help! Please tell your friends about HGF and encourage them to become members and to view our website, www.hgfound.org. Mention HGF to your physician as an excellent "reference" source on growth related information. Please think of HGF as you plan your charitable giving, as your contributions help us to continue to achieve our mission! We have an exciting year ahead and look forward to getting started together!

Sincerely,

Frank B. Diamond, Jr., M.D.
President
HGF

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Ask the Doctor

We took our son to see the endocrinologist because he was short and was not growing well. The endocrinologist did a work up, which showed that he was not growth hormone deficient, and he said our son had Idiopathic Short Stature. He said that we had several options—one was to treat with growth hormone and the other was to try IGF-I treatment. What is the difference between these two treatments? Are they equally safe?

Growth hormone has been used to treat growth hormone deficiency since the late 1950's. In 2003, the FDA approved use of growth hormone to treat Idiopathic Short Stature (ISS). Growth hormone has a long record of safety. There are a few things that occasionally happen with growth hormone treatment. One is a build up of pressure in the central nervous system called "Idiopathic Intracranial Hypertension," also called "pseudotumor cerebri." This condition is usually discovered because it causes severe headaches. It is a rare occurrence. Out of the 20,000 children taking growth hormone when it was found to be related to GHT, only 15 children were affected. Stopping growth hormone almost always eliminates the problem, and it usually does not reoccur if the growth hormone is restarted slowly. There were concerns about leukemia occurring with growth hormone therapy, but the large data bases do not support an association; there are no more cases of leukemia in the growth hormone data bases than would be expected in the general population. Overall, growth hormone appears to be a very safe medicine to use. There is a lot of

information in the data bases collected since 1985 to validate its use.

It is thought that growth hormone works by stimulating other tissues (especially the liver) to make insulin-like growth factor I (IGF-I formally called "somatomedin"), and that it is the IGF-I that acts on the growing bone to promote growth. IGF-I is one part of a very large complex that circulates in the blood. The other parts of the complex are a binding protein (IGFBP-3) and an acid-labile subunit (ALS). By being in the complex, the IGF-I stays in the blood for a longer time, and is not as likely to have unpleasant effects on other tissues (such as causing a low blood sugar, since it is "insulin-like"). It is known that there are some people who do not grow because—even though they make enough growth hormone—the growth hormone they make does not cause the body to produce more IGF-I. The most common reason for this is that some people do not have a normal growth hormone receptor. The name for this condition is Growth Hormone Insensitivity Syndrome or GHIS. Last year the FDA approved treating people with GHIS with IGF-I. These children do grow when they are given IGF-I, but there have been some side effects. The most common side effects are low blood sugar (which rarely happens if the injection is taken at the same time as a meal), an increase in lymphoid tissue (tonsils and adenoids), and idiopathic intracranial hypertension.

There are two IGF-I preparations available. One is just IGF-I, and it is being sold under the brand name Increlex. It must be given to people with GHIS as a twice daily injection. However, if

the patient produces enough IGFBP-3, it appears to be possible to give it as a single daily injection. A second option is Iplex, containing both IGF-I and IGFBP-3. The combination allows it to remain longer in the blood and may keep it from having as many problems with side effects, especially low blood sugar. Currently both of these preparations have been FDA approved for use in treating severe GHIS, but not ISS or even partial GHIS (it may be that some cases of ISS may be caused by partial ISS). The efficacy and safety of the IGF compounds have not been tested in anything but severe GHIS. However there are presently some studies underway which are designed to test the effectiveness and safety of IGF-I in these other groups of patients.

At this time the most prudent course of action for treating ISS is to try growth hormone first, and if it doesn't work, it may be possible to treat with one of the IGF-I preparations.

Stephen F. Kemp, M.D., Ph.D.

Pediatric Endocrinologist
Arkansas Children's Hospital
University of Arkansas
for
Medical Sciences



The Use of Drugs to Enhance Linear Growth Near or During Puberty

Many parents find out near or when their child is in puberty, that their child has growth hormone deficiency (GHD), or has Idiopathic Short Stature (ISS).¹ Their pediatric endocrinologist has introduced to them the concept of "bone age,"² as contrasted with chronological age; and, told them that delayed bone age is advantageous for short stature persons who are still growing because it provides additional time for linear growth. The parents usually want to know how much growing time their children have left to grow taller and how much taller their children will grow.

Normally, a girl's linear growth peaks after a pubertal growth spurt at 12 years and puberty and linear growth end at 15.5 years; and, a boy's linear growth peaks after a pubertal growth spurt at 14.5 years and puberty and linear growth end at 17.5 (all figures are approximate).³ The GHD child may not have a pubertal growth spurt; or it may be impeded because of a lack of adequate IGF-I, which is caused by insufficient GH, and possibly by insufficient testosterone in boys. When the GHD child does produce sufficient sex steroids (testosterone and estradiol), bone age increases; and, the growth plates fuse, which stops further linear growth of the skeletal long bones. Without rhGH therapy, the growth rate continues to remain low, puberty ensues without a significant growth spurt, leaving the child with short stature.

When the GHD or ISS child is near or in puberty, and there is not a

significant amount of bone age delay, or bone age is accelerating (i.e., advancing at too great a rate) to allow for significant linear growth, there are drugs that can enhance the child's growing period. The drugs work by suppressing estradiol and other hormones that are involved in its production. Although GH, testosterone, and estradiol are involved in the normal progression of bone growth and bone age, in both boys and girls, it is estradiol (E2) (one of three estrogens, the others being estrone (E1) and estriol (E3)), that causes the acceleration of bone age and the fusion of the growth plates of the skeletal long bones, which brings an end to linear growth.

In females the greatest amount of estradiol comes from the ovaries. Estradiol from the ovaries is the result of follicle stimulating hormone (FSH) of pituitary origin. Much of the remaining estradiol is the result of the conversion of the adrenal androgens (androstenedione and DHEAS) to testosterone, which then metabolize in part, to estradiol. In males, testosterone is primarily the result of luteinizing hormone (LH) triggering the Leydig cells of testes to produce testosterone; and secondarily, from the adrenal androgens (androstenedione and DHEAS).

There are two principal classes of drugs that are currently being administered to prevent the acceleration of bone age and epiphyseal fusion of the skeletal long bones. One class of drugs results in stopping the production of LH and FSH (the gonadotropins), the latter of which is responsible for the production of estradiol and testosterone produced by the ovaries. Currently, the principal drug is leuprolide acetate (Lupron), which is a

luteinizing hormone releasing hormone agonist (LHRHa). Although Lupron acts to suppress estradiol originating from the pituitary, it does not suppress the estradiol metabolized from the androstenedione or DHEA produced in the adrenal cortex.⁴ It is usually administered by monthly intramuscular injections in the thighs or buttocks; costs in excess of \$1,000 per injection; are not comfortable; and if not properly injected, can be painful or cause abscesses.

The other class of drugs prevents testosterone from metabolizing or converting to estradiol. The substance is an *aromatase* inhibitor (AI). Currently, the principal AI drugs used for this purpose are anastrozole (Arimidex)⁵ and letrozole (Famera). AIs prevent the conversion of testosterone produced in the testes into estradiol; but, do not prevent the production of testosterone, as do the LHRHAs. Thus, in boys, the secondary sex characteristics associated with growth and development during puberty are not suppressed as they are with Lupron;⁶ and the boys may continue to develop sex characteristics while they continue to grow taller. AIs are administered by daily oral medication, significantly less expensive than Lupron, and not painful.

LHRHAs and AIs are labeled and approved by the FDA for use in the treatment of advanced metastatic breast cancer. Having been so approved, they may be used for other medically appropriate uses without applying for approval by the FDA. Although those drugs are efficacious in suppressing the accelerated bone age and epiphyseal fusion, the long-term safety for the use of those drugs either has not been demonstrated or has

not been demonstrated or has not been generally accepted by the medical profession.⁷ On the other hand, those drugs have not been shown to be unsafe for such use in the long term.

Given the demand for achieving a minimally acceptable height in today's society, parents and physicians continue to explore the LHRHAs, AIs, and other promising modalities for linear growth. What may be lost in the focus on linear growth are other medically necessary reasons for the administration of growth hormone, which include, but are not limited to, prevention and remediation of atherosclerosis, lipid imbalance, osteoporosis, obesity, metabolic syndrome, physical weakness, lack of muscle tone and coordination, diminished lung volume and respiratory muscle strength, depression, lethargy, lack of motivation, and psychosocial issues that can adversely affect nearly every aspect of the quality of life for the child and family, into and throughout adulthood.

End

⁷GHD is classified as "pituitary" or "classic" when the pituitary does have the capacity to produce adequate GH; or as "functional" when the pituitary has the capacity to produce, but does not produce, adequate GH. ISS is not a diagnosis; but rather, is a designation given to children who are -2.25 standard deviations from the norm in height-to-age or low growth velocity, low levels of insulin-like growth factor-I (IGF-I); not likely to reach the final height of 5'3" for boys or 4'11" for girls; and, "pass" the growth hormone stimulation

test (GHST) See the FDA Talk Paper, T03-56, July 25, 2003 at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANSO1242.html>. When given rhGH, the classic ISS child may grow cumulatively several additional inches. Children who are designated as having ISS, but who grow significantly more than a few inches cumulatively while taking rhGH, most likely have an underlying etiology for their short stature that has not been identified. For example, there is "the potential for IGF-I gene polymorphisms or binding protein abnormalities influencing the development of ISS-related growth failure." **The molecular basis of Idiopathic Short Stature.** Rosenfeld RG. *Growth Horm IGF Res.* 2005 Jul; 15 Suppl A:S3-5. Lucile Packard Foundation for Children's Health, 770 Welch Road, Suite 350, Palo Alto, CA 94022, USA. ron.rosenfeld@lpfch.org. Another kind of underlying etiology is functional GHD, such as growth hormone neurosecretory dysfunction, in which a properly working pituitary doesn't receive the neuroendocrine message to produce GH.

²Ossification centers of the skeleton appear and progress in a predictable sequence in normal children, and skeletal maturation can be compared with normal age-related standards. This forms the basis of *bone age* or *skeletal age*, the only readily available quantitative determination of net somatic maturation and thus a mirror of the tempo of growth and maturation [in normal children]." Williams Textbook of Endocrinology, 10th Ed., Saunders (Philadelphia: 2003) at p. 1007.

³Williams Textbook of Endocrinology, 10th Ed., Saunders (Philadelphia: 2003) at p.1128.

⁴The use of Lupron is not appropriate in LHRH independent cases of central precocious puberty, which involve sources of testosterone outside of the hypothalamic-pituitary axis that metabolize to estradiol. Rather the use medroxyprogesterone acetate or an aromatase inhibitor e.g., letrozole

(Famera) or anastrozole (Arimidex) is considered appropriate in such cases. See Williams Textbook of Endocrinology, 10th Ed., Endnote 3, at p 1222, Table 24-45.

⁵Arimidex is also used to remedy imbalances (1) between estrogen and androgen concentrations thought to be responsible for gynecomastia in pubertal boys; and (2) in male fertility.

Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial.

Plourde PV, Reiter EO, Jou HC, Desrochers PE, Rubin SD, Bercu BB, Diamond FB Jr, Backeljauw PF. *J Clin Endocrinol Metab.* 2004 Sep;89(9):4428-33. AstraZeneca Pharmaceuticals LP, Chesapeake 2B-126, 1800 Concord Pike, P.O. Box 15437, Wilmington, Delaware 19850-5437, USA. paul.plourde@astrazeneca.com.

Aromatase inhibitors for male infertility. Raman JD, Schlegel PN. *J Urol.* 2002 Feb;167(2 Pt 1):624-9. Comment in: *J Urol.* 2002 Oct;168(4 Pt 1). Department of Urology, James Buchanan Brady Urology Foundation, Center for Male Reproductive Medicine and Microsurgery, New York Presbyterian Hospital, Weill Medical College of Male Reproductive Medicine and Microsurgery, New York Presbyterian Hospital, Weill Medical College of Cornell University, New York, New York, USA.

⁶**Use of aromatase inhibitors to increase final height.** Dunkel L. *Mol Cell Endocrinol.* 2006 Jun 9; [Epub ahead of print] Kuopio University Hospital, Kuopio, Finland. **Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty.** Hero M, Wickman S, Dunkel L. *Clin Endocrinol (Oxf).* 2006 May;64(5):510-3. Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki, Finland. **Inhibition of Estrogen Biosynthesis with a Potent Aromatase Inhibitor Increases Predicted Adult Height in Boys with Idiopathic Short Stature: A Randomized Controlled Trial.** Matti Hero et

al., *J Clin Endocrinol Metab* 2005, Vol 90, No. 12, 6396-6402. **Estrogen al., *J Clin Endocrinol Metab* 2005, Vol 90, No. 12, 6396-6402. **Estrogen Suppression in Males: Metabolic Effects.** Nelly Mauras, et. al., *J Clin Endocrinol Metab* 2000, Vol 85, No. 7, 2370-2377. Nemours Research Programs at the Nemours Children's Clinic (site of primary investigator). **Aromatase Inhibitors in Pubertal Boys: Clinical Implications,** *J Clin Endocrinol Metab.* 2001 Apr;86 (4):1836-8, a letter to the editor (peer review) from Vincenzo Rochira, Department of Internal Medicine, University of Modena and Reggio Emilia, Modena, Italy; and the response of the principal author of the study, Nelly Mauras, Division of Endocrinology, Nemours Children's Clinic, Jacksonville, Florida.**

nmauras@nemours.org, the investigators found that in adolescents previously treated with anastrozole had descriptively similar sperm parameters as other GHD and GH-sufficient adolescent controls.



Earl Gershenow
Web Master
Human Growth
Foundation

⁷There are concerns with fertility issues in boys and girls with LHRHs and AI. However, some of those concerns may be lessened by relatively recent studies. In **Results of long-term follow-up after treatment of central precocious puberty with leuporelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function.** The TAP-144-SR Japanese Study Group on Central Precocious Puberty. Tanaka T, Niimi H, Matsuo N, Fujieda K, Tachibana K, Ohyama K, Satoh M, Kugu K. *J Clin Endocrinol Metab.* 2005 Mar;90 (3):1371-6. Department of Endocrinology and Metabolism, National Center for Child Health and Development, 2-10-1, Okura, Setagaya, Tokyo, 157-8535, Japan. tanaka-t@ncchd.go.jp, the investigators concluded that Lupron is safe as well as efficacious in the long term. Also, in **Sperm analysis in growth hormone-deficient adolescents previously treated with an aromatase inhibitor: comparison with normal controls.** Mauras N, Bell J, Snow BG, Winslow KL. *Fertil Steril.* 2005 Jul;84(1):239-42. Nemours Children's Clinic and Research Programs, Jacksonville, Florida 32207, USA.

"THE GIFT THAT KEEPS ON GROWING"

As the holidays and the New Year approach, consider how meaningful a donation to our **Gift of Growth** program would be for a friend or loved one. This program allows us to expand our assistance to the children and their families, as well as adults. This gesture can guarantee that any occasion will result in a gift that affects others for the better and that never stops giving. Please remember all donations to HGF are tax deductible.



NEWS UPDATES

The foundation is sponsoring the Florida Endocrine Nurses Annual Meeting for the fifth consecutive year. The meeting takes place October 5th—October 9th on Carnival's ship the Inspiration embarking out of Tampa, Florida. Eight educational seminars will be conducted enabling the 75 nurses in attendance the opportunity to earn a total of eight CEU credits. These nurses become very familiar with our goals and our available resources that pertain to the various growth issues of their patients. Awareness of HGF's presence enables us to reach a far broader public base and to further educate them on growth issues.

Our Research Committee is currently evaluating seven investigative research projects involving aspects of growth for the 2006 Small Grants Program. A final decision will be made and the applicants notified in November of this year. It is our hope that such scientific projects will lead to innovative ideas in the future treatment of growth and growth hormone related conditions.

HGF's website is in the process of being updated in the coming months. Presentation, design and various areas of the website (with links to other sites), as well as other modifications, are being considered with a view towards making the web page (the public's first impression of HGF) more informative and helpful to the thousands of visitors who log onto it each year.

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Teenscape

Hi Elizabeth,

My son has been taking growth hormones for 8 months now. Although he is only 3, it looks like he will be needing the shots through puberty. I just wondered how it worked for you and if you have any advice as to the best way to handle things as he gets older (regarding friends)...keep it a secret or not.

Thanks so much,
Monica

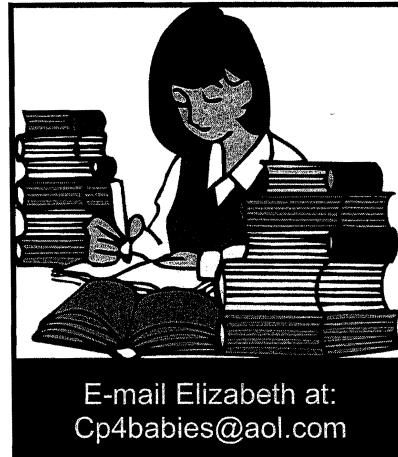
Hi Monica,

You sent me an e-mail asking questions about growth hormone. I am sorry I took so long to answer. You asked how long I took the shots and how it worked for me. I started the shots when I was 10 years old and finished when I was 15. I grew from 4'9" to 5'5". I am now 25 and am very happy that I took growth hormone.

I never kept it a secret from my friends. In fact, they loved to hear about how I was growing and why I took the shots. I used to talk to various groups about growth hormone and still talk about it today. My mom told the school when I was in sixth grade, because some people spoke about how small I was.

The day after my mom spoke with someone at my school, all the teachers told the classes that everyone is different and we should all get along.

That stopped the teasing. I think that it is wonderful that you started your son so early on growth hormone. He will have a long window of time to take the shots before his



E-mail Elizabeth at:
Cp4babies@aol.com

bones fuse.

You might want to call the Human Growth Foundation at 1-800-451-6434 and ask for Patti Costa. She can send you information about growth hormone deficiency. There is also a web site www.hgfound.org you might want to visit.

Please keep me informed about how your son is progressing.

Take care,
Elizabeth

Hi Elizabeth!

First, we would like to thank you for your courage and generosity by sharing your story and by offering to answer questions.

My husband and I are both physicians and parents of Daniel, a healthy smart 2 year old boy recently diagnosed with GH deficiency. Our insurance recently approved the treatment, so I guess we will start treatment shortly. How painful is it? My husband and I will try the shots on ourselves before giving them to Daniel. How bad was it for you? How can we make the daily injections easier? We have tons of questions and we feel so devastated to have our son

go through daily injections. But I guess it is encouraging to see how many great, successful stories are out there, and there are great people like you who turned out to be smart, generous and healthy.

Bless you. Please e-mail us soon, we are looking forward to hearing from you.

Sincerely,
Nora

Hi Nora,

You e-mailed with growth hormone questions.

You asked about how painful the shots were. They never hurt me, in fact I started growth hormone when I was 10 and gave the shots to myself. Sometimes, I would put an ice cube on my arm prior to the shot and that would numb it. There is also a numbing cream you can use. Now, the pharmaceutical companies use a very small gauge syringe that is in a pen device which also helps.

You might want to do what my parents did. We had a calendar and every time I had a shot, I would get a sticker for that day.

You should also go to the Human Growth Foundation web site and join the pediatric internet support list serve for parents. The foundation also has literature you might find interesting. Please call 1-800-451-6434 and one of our representatives will help you.

Please keep in touch regarding your son's progress.

Take care,
Elizabeth

**DON'T FORGET!
HGF COUNTS ON YOUR SUPPORT!**

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2007 MEMBERSHIP APPLICATION

Last Name (s) _____ First Name (s) _____

Primary Occupations _____

Home Address _____

City/State/Zip (Country/Postal Code) _____

Bus. Phone () _____ Home Phone () _____

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

Method of Payment: Check Money Order (membership dues must be paid in US currency)

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.

Individual/Family (\$35) Supporting (\$50) Donor (\$100) Institutional (\$200)

Century Club (\$1000 individuals/\$1500 Corporate)

If this is a gift membership, name and address of donor _____

Chapter Affiliation (if Known) _____

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

Designation Of Dues:

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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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 2007, and in the future.

