HUMAN GROWTH FOUNDATION

fourth friday

FALL 2002

From the President's Desk

In past articles I have outlined the process by which the Human Growth Foundation makes every effort to accomplish the goals of our mission statement: "*helping children and adults with disorders related to growth or growth-hormone through education, research, support and advocacy*".

In an effort to maximize the efficiency of the day-to-day running of the National Office, Patti Costa, the Executive Director, strives to utilize as many cost effective measures as possible. As a result, HGF has one of the lowest administrative cost versus income ratios among non-profit organizations. Our overhead operating expenses are less than six percent.

A direct way to help support HGF is to renew your membership annually and, if possible, to upgrade your membership. The next levels would be, Supporting $50, Donor $100, Institutional $200, and Century Club (lifetime) $1,000 for individuals and $1,500 for Corporate.

There are numerous other ways to donate funds:

1.) ***"Gift of Growth"***—a donation in someone's name for various occasions: birthdays, weddings, anniversaries, or remembrances.
2.) ***"Research Fund"***—allows us to award our annual Small Grants. Such grants fund research into various growth issues, which hopefully will one day lead to a breakthrough in treatment and prevention.
3.) ***"Planned Giving"***—provides for a donation in a person's will.
4.) ***"The John Hickey Fund"***—one of the purposes of this fund is to raise money for supporting postdoctoral fellows training in Endocrinology. To date $40,000.00 has been raised, but it needs to reach at least $100,000.00.
5.) **"Matching Funds"**—Many employers have matching grant or matching gift programs. Example: with a match from your employer a gift of $50.00 becomes a gift of $100.00. All memberships constitute a donation, therefore, please check with your employer to see if they participate in this program when paying your membership/donation. (See page 5 for a sampling of companies that participate.)
6.) While HGF is not on the check off list for the **United Way Campaign** donations in the work place, it is still possible to designate HGF. The donor simply writes in "Human Growth Foundation" including the address:

997 Glen Cove Avenue
Glen Head, New York 11545

7.) ***"Combined Federation Campaign"*** —Support to HGF can also be made through CFC. Our CFC Number is 125.

Remember **all** donations to HGF are tax deductible.

Some of the services we are able to provide because the generous donations we receive are:
1.) Pediatric, Teens, and Adult Internet Support Lists—these lists are vital links for individuals to communicate with one another.
2.) Chat Rooms—separately scheduled chat sessions for adults, parents and teens.
3.) Educational brochures—pertaining to various growth disorders available free of charge for families.
4.) Annual Meetings—an informational gathering for members, guests, medical professionals and pharmaceutical firms.

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

IN THIS ISSUE

Ask the Doctor

My 10 year old was treated for a brain tumor with surgery and radiation therapy four years ago and has no signs of residual disease today. He has stopped growing, however, and his testing shows that he is growth hormone deficient. Do we need to worry that treating him with growth hormone will make his tumor come back?

You have asked an excellent question that worries many parents who have been through this medical crisis with their children. Fortunately, more and more children are surviving their cancers: the overall 5 year survival rate is now greater than 70%, and for some illnesses like acute lymphoblastic leukemia and Hodgkins disease survival ranges from 80-90%. With the advent of better supportive care and an aggressive combination of treatment and multidrug protocols, overall mortality of childhood cancer has dropped by 40% in the last 20 years! While this improvement is wonderful news, it also means that many more children now live to develop later complications of their treatment and disease. Hormone disturbances are the most common of these late effects and occur in approximately 40% of cases.

Growth hormone deficiency develops from tumors which form in or near the hypothalamic and pituitary growth centers, and following high dose radiation therapy of the brain. Radiation treatments of tumors of the eye socket, nose, throat, and face also may result in growth hormone deficiency. When patients receive high doses of radiation, growth hormone deficiency may develop within 5 years of treatment. This GH deficiency is sometimes "disguised" by growth due to abnormally early pubertal development (sexual precocity).

As growth hormone and its "effector" molecule, insulin like growth factor-1 (IGF-1), are powerful stimulants of cell division and proliferation, it is reasonable to be concerned about the effect of these compounds on tumor regrowth. Several small scientific studies seemed reassuring, but they did not report long term follow-up, allow for confounding variables, or compare outcomes of GH treated children with untreated "control" children. A large multicenter trial in Great Britain compared 180 children with brain tumors who received growth hormone treatment between 1965-1996 and 891 non-growth treated childhood brain tumor survivors (Swerdlow AJ et al J Clin Endocrinol Metab 85:4444-4449). The children were followed for an average of 6 1/2 years on GH therapy. Thirty-five cases of first recurrences occurred in the GH-treated children and 434 in the untreated children. Remarkably, the relative risk of first recurrence in the GH-treated population, adjusted for possible confounding prognostic variables, was decreased, as well as was the relative risk of death!

The study authors tried to reduce the "selection bias" for GH treatment of children with a better initial prognosis, but did not take into account other important prognostic factors such as the presence of metastatic disease, quantity of residual tumor, and tumor histology (some cell types being more "aggressive"). The issue of development of other new malignancies and a higher risk in cancer survivors, was not addressed. Also noteworthy was that the GH doses used by the European doctors were lower than those usually prescribed in the United States.

An American study of 13,539 survivors enrolled in the Childhood Cancer Survivor Study was recently reported by Dr. Charles Sklar and others (J.Clin Endocrinol Metab 87:3136-3141, 2002). This multicenter study included 361 GH treated 5 year survivors and 172 GH treated children who survived brain tumors. Like the British study, the Childhood Cancer Survivor Study reported a lower relative risk of recurrence of the original tumor for GH-treated survivors for all the major cancer diagnoses. However, growth hormone treated children were diagnosed with 15 new neoplasms which were different from their original cancer.

All of these "second neoplasms", (SN) were solid tumors. This finding was primarily related to an increased risk of

Ask the Doctor, con't.

"second neoplasms" in growth hormone treated survivors of acute leukemia. There was also minimal evidence for growth hormone treated survivors of CNS tumors developing an increased number of SN, primarily non-malignant meningiomas. Overall, the risk of development of solid second tumors in association with growth hormone treatment was reported to be 3-4/1000 persons at 15 years from diagnosis. The authors cautioned that this retrospective study may have been affected by unrecognized biases in patient selection or other important factors, and that the number of events was extremely small to draw definitive conclusions.
In conclusion, GH therapy does not appear to increase the risk that your child's original brain tumor will return. There is "marginal evidence" based on a small number of events that GH treatment might pose a very small risk of development of a second neoplasm. This risk must be weighed against the importance of ensuring healthy growth and development in your youngster.

Frank Diamond, MD
Vice-President HGF

From the HGF Internet Support Lists

Continuing to Grow in Height Without Delaying Puberty

Recently discussed on the HGF-*PEDS List* was the question of delaying puberty in males who are at the early or mid-puberty stages. Your 4 ft. 8 in. son, age 15, who has grown approximately 2 in. a year in the past few years, is in the early or mid stages of puberty, but is not having the growth spurt that would put him at or over 5 ft. in height. You ask, "Can anything be done now to increase his height before his growth plates close? The answer, is a qualified, " yes."

LHRH (luteinizing hormone releasing hormone) in the hypothalamus causes the production of LH (luteinizing hormone). LH results in the production of estrogen (estradiol). Lupron suppresses LH, thus suppressing estrogen to prepubertal levels. In both boys and girls, estradiol contributes to acceleration of bone age and causes epiphyseal fusion (closure of the growth plates) of the skeletal long bones. In males, estradiol is a metabolite of testosterone made in the testes and from precursor adrenal androgens; in females, estradiol is secreted by the ovaries.

Until recently, a drug called "Lupron" (luprolide) has been used in girls and boys, to delay the epiphyseal fusion of the skeletal long bones to allow for additional linear height, to the extent there is "room" in the growth plates for the growth.

Lupron is a luteinizing hormone releasing hormone agonist (LHRHa), a substance that mediates or regulates LHRH. By reducing LH to prepubertal levels, Lupron causes the regression and suppression of the secondary sex characteristics; and thus, is generally used only in the early stages of puberty for psychosocial reasons. The administration of Lupron is not without some pain. It is administered monthly by intramuscular injection (IM) with a 23 gauge, 1" in length needle given in the thigh. Lupron is also very expensive.

Recently, letrozole ("Famera"), approved by the Federal Food and Drug Administration (FDA) for use in the treatment of advanced breast cancer in females, is being prescribed by some physicians and clinical researchers for use in boys, in lieu of Lupron. Letrozole works by inhibiting the enzyme *aromatase,* which causes the conversion of testosterone to estradiol. The advantages of letrozole in suppressing estrogen in males for additional linear growth are that it is administered orally and it is inexpensive. Most significantly, in males, letrozole does not cause the regression or suppression of the onset and development of the secondary sex characteristics because it blocks estradiol synthesis, but does not suppress testosterone. Thus, it can be administered to males during early and mid-puberty stages.

From the HGF Internet Support Lists

Letrozole is labeled for use as a "first line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown (for) locally advanced or metastatic breast cancer." http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=238. The entire FDA regulatory history of letrozole for use in the treatment of breast cancer is at: http://63.75.126.224/Google/fda_search.pl? client=fdagov&site=fdagov&restrict=&searchselector=O&q=letrozole.

Having been approved by the FDA for use in advanced or metastatic breast cancer, it is lawful for the physician to use it for the treatment of other conditions ("off-label" use) within medically accepted limits. The safety and efficacy for this use of Letrozole have not been established by the FDA. Below are abstracts of studies reported in mainstream medical journals that demonstrate the efficacy of the off-label use of letrozole for delaying puberty for additional growth, which can be used with or without GH or testosterone replacement therapies or supplementation in boys.

"A review of a twelve month clinical trial using a new, effective aromatase inhibitor treatment in boys with delayed puberty shows that the pubertal increase in estrogen levels can be blocked, with concomitant preserved pubertal growth rate. Circulating testosterone levels are greatly enhanced during treatment due to increased gonadotrophin secretion. Despite this, bone age maturation is slow, leading to an increased final height prognosis (mean 5.1 cm) for the boys treated with aromatase inhibitor." Growth rate can be manipulated. Estrogen production in pubertal boys can be blocked by an aromatase inhibitor. Hagenas L. *Lakartidningen*, 2002 Jan 17;99 (3):165-8. [Article in Swedish].

Other noteworthy studies include: [1] Treatment of delayed male puberty: efficacy of aromatase inhibition. Dunkel L, Wickman S.J *Pediatr Endocrinol Metab.* 2001;14 Suppl 6:1541-6. University of Helsinki, Hospital for Children and Adolescents, Finland; [2] Inhibition of P450 aromatase enhances gonadotropin secretion in early and mid-pubertal boys: evidence for a pituitary site of action of endogenous E. Wickman S, Dunkel L. *J Clin Endocrinol Metab.* 2001 Oct;86(10):4887-94.University of Helsinki, Hospital for Children and Adolescents, FIN-00029 Helsinki, Finland. *[Online, full text reprint is available. Request File No. 86.4887 at hgf3@hgfound.org]* ; [3] Use of a specific aromatase inhibitor in delayed puberty. Stanhope R. *Lancet.* 2001 Jun 2;357 (9270):1723-4. Comment in: *Lancet.* 2001 Oct 27;358 (9291):1459-60 PMID: 11705526 *Lancet.* 2001 Oct 27;358 (9291):1459; discussion 1460 PMID: 11705528 Comment on: *Lancet.* 2001 Jun 2;357 (9270):1743-8 PMID: 11403810 Department of Endocrinology, Great Ormond Street Hospital for Children and Middlesex Hospital (UCLH), WCIN IEH, London, UK. *[No Narrative; but online, full text reprint is available for subscribers of The Lancet at hgf3@hgfound.org]*; Drug and hormone interactions of aromatase inhibitors. Dowsett M. *Endocr Relat Cancer.* 1999 Jun;6 (2):181-5. Academic Department of Biochemistry, The Royal Marsden NHS Trust, London, UK.

The question arises as to the use of letrozole by females for delaying epiphyseal fusion. While it appears that the suppression of estrogen would also cause the regression and impede the development of secondary sex characteristics in girls, there are still the advantages of ease of administration and significantly lower cost. NIH has an on going clinical study for females with Precocious Puberty and McCune-Albright syndrome (MAS), the results of which could apply to other conditions that require delaying puberty (off-label use). See Clinical Study: 00-D-0183, Effects of the Aromatase Inhibitor Letrozole on Pubertal Progression and Indices of Bone Turnover in Girls with Precocious Puberty and McCune-Albright Syndrome (MAS), http://clinical studies.info.nih.gov/detail/A_2000-D-0183.html.

Earl A. Gershenow
HGF Internet Support Lists Administrator