



Growth Messenger

The Human Growth Foundation

From the President's Desk

SUMMER/FALL 2009

Important Growth News!

Dr. Akihiro Yasoda et al from Kyoto, Japan, recently reported exciting experiments that hold hope for the cure of Achondroplasia. Achondroplasia is the most common skeletal dysplasia, occurring in approximately one out of every 10,000 births. Children have markedly shortened proximal upper and lower extremities and reach a very short adult height; they also suffer from a variety of other orthopedic problems. The condition is caused by a constitutive gain of function mutation of the FGFR3 gene, meaning that a gene's "on switch" is "stuck" in the "on" position. FGFR3 turns on a bone pathway called MAPK that is important for controlling "endochondral" growth. This refers to growth of chondrocytes, or cartilage cells, within the growth plate at the ends of the bones. The mutation causes disturbed division and differentiation of growth plate chondrocytes that alter the normal architecture and growth of the bone. Currently, there is no medical treatment for this condition.

Yasoda et al studied C-type Natriuretic peptide (CNP) and its receptor guanylyl cyclase-B (GCB). These proteins play an important role in stimulating endochondral bone growth. Through genetic engineering, the scientists were able to produce mice with Achondroplasia that also "over expressed" genes for CNP in the liver. These mice had higher levels of CNP in the blood and grew in a way that was similar to wild type (normal) mice... the impaired bone growth was "rescued" by the presence of the extra CNP! The doctors also showed that giving CNP intravenously to 3 week old Achondroplastic mice corrected their growth problem. The treatment appeared to have no adverse effects. While similar studies have yet to be performed in human beings, the research appears to hold promise for a future treatment of Achondroplasia!

Your HGF continues to provide funding every year to young investigators interested in chondrodysplasias in order to advance scientific progress in this important field!

A Successful Annual Meeting

The foundation met in Philadelphia for our Annual Meeting. On Friday night a presentation by Dr. Adda Grimberg of Children's Hospital of Philadelphia explored the gender differences in referrals for poor growth. Girls are referred significantly less frequently than boys, and are often substantially shorter when they are sent to the pediatric endocrinologist. A major goal of the foundation is to promote early and appropriate referrals by primary care providers of children with short stature to specialists in growth evaluation. With this goal in mind, the HGF continues to provide educational grants to provide speakers on childhood growth to pediatricians who are meeting around the country! On Saturday the Foundation Board awarded our annual HGF Award to a Giant in Growth, Dr. Fima Lifshitz. Dr. Lifshitz has made important contributions to the role of nutrition in human growth. He is the editor of a widely read textbook of Pediatric Endocrinology, and Editor in Chief of an important medical journal, *Growth, Genetics and Hormones*. He has trained 37 young doctors in the field of growth and pediatric endocrinology. Dr. Lifshitz reminded the group that under nutrition remains the major cause of poor growth worldwide, and the Foundation has elected to explore further activities in the field of childhood nutrition. We also had the opportunity on Saturday afternoon to listen to a presentation from Katarzyna Gawron, PhD con-

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cerning her research. Dr. Gawron was awarded HGF's "Small Grant Award" last year. The Board also reviewed a number of new educational materials for parents including information about Insulin Like Growth Factor-1, and Small for Gestational Age babies. These and other HGF educational materials will be posted on our website, that continues to receive hundreds of thousands of hits yearly!

New Board Expertise

We are very pleased to welcome Dr. Andrew Hoffman, an internist-endocrinologist from California, who is an expert on adult growth hormone deficiency, to our Board!

Thanks Patti!!

Special Thanks to our Executive Director, Patti Costa, who completes 10 years with HGF. Patti has been diligently working to help secure grants to fund HGF, talking to parents by phone and in person, attending scientific meetings around the country to spread the message of HGF, and advocating for children with growth disorders. The Board made a special presentation to Patti for her fantastic service to HGF and all the children!!

Frank B. Diamond, Jr., MD

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The Human Growth Foundation has registered with iGive.com and is asking you to do the same. This is an easy way to help raise funds for HGF. Once you have registered at iGive.com, each and every time you shop on line or search the web please sign on to iGive.com or iSearchiGive.com. This online mall features over 700 online stores that will make donations to HGF. Searching the web starting at iSearchiGive.com also helps to raise a penny or more for HGF per each qualified search.

If you make your first purchase within 45 days of registering, HGF will receive a \$5.00 bonus.

Shopping at iGive.com or searching the web using iSearchiGive.com will help HGF continue to provide services to the many families and individuals who reach out to us.

Ask the Doctor, con't.



I have been asked to discuss the question about whether growth hormone (GH) therapy can cause diabetes (hyperglycemia). First, I would like to point out that I am a pediatric endocrinologist with over 24 years of experience treating children, adolescents and young adults with growth hormone, most of whom had GH deficiency, and I have never had a patient who developed an elevated blood sugar level. However, in the last 5-10 years, more children and adults are being treated with GH who may have an increased risk of diabetes, due to their increased weight (obesity) or to a strong family history of Type 2 diabetes mellitus. In order to answer the question about GH therapy and possible diabetes, I would like to discuss some basic physiology.

A critical concept in understanding growth hormone activity is that it has two distinct types of effects:

- **Direct effects** are the result of growth hormone binding its receptor on target cells. Fat cells (adipocytes), for example break down triglyceride, and suppresses their ability to take up and accumulate circulating lipids.
- **Indirect effects** are mediated primarily by an insulin-like-growth factor-I (IGF-I), a hormone that is secreted from the liver and other tissues in response to growth hormone. A majority of the growth promoting effects of GH is actually due to IGF-I acting on its target cells.

Growth hormone has important effects on protein, lipid and carbohydrate metabolism. In some cases, a direct effect of growth hormone has been clearly demonstrated, in others, IGF-I is thought to be the critical mediator, and in some cases it appears that both direct and indirect effects are at play. GH is one of a battery of hormones that serves to maintain blood glucose within a normal range (glucoregulatory hormones). These include insulin, glucagon, and cortisol, in addition to GH. GH is often said to have anti-insulin activity, because it suppresses the abilities of insulin to stimulate uptake of glucose in peripheral tissues and enhance glucose synthesis in the liver. Somewhat paradoxically, administration of GH stimulates insulin secretion leading to hyperinsulinism (elevated insulin

levels). Chronic elevation of GH has been shown to produce insulin resistance, in some people, which is similar to what is seen in people who develop type 2 diabetes mellitus. If a person, with a strong family history of type 2 diabetes mellitus (non-insulin dependent diabetes mellitus), and who already has insulin resistance due to obesity, were to be treated with GH therapy for a long period of time, it is reasonable to assume that hyperglycemia, and eventually, diabetes mellitus, will develop.

Diabetes mellitus is most commonly a slowly progressive disease, starting with insulin resistance (hyperinsulinism), often associated with obesity, and progressing to an elevated fasting blood glucose level (above 100, but less than 126 mg/dl). This is called Impaired Fasting Glucose (IFG), and is usually treated with diet and exercise. The next phase in the progression to diabetes mellitus is Impaired Glucose Tolerance (IGT), which is associated with an elevated 2 hour post-meal blood sugar level above 180 mg/dl. If a person has both IFG and IGT, then treatment may include oral medication in addition to diet and exercise. Then, if the fasting blood sugar is above 126 mg/dl, on multiple occasions, the diagnosis of diabetes mellitus is usually made.

Children with GH deficiency are usually not significantly obese and not at risk for diabetes. However, the indications for GH therapy may include children and adolescents who receive higher doses of GH, and may be at greater risks for hyperglycemia. These include the diagnosis of Idiopathic Short Stature (ISS), Prader-Willi Syndrome, Noonan Syndrome and Turner Syndrome. Unfortunately, the epidemic of obesity that has occurred in adults all over the world, has affected far too many children, and some of these people may be candidates for GH therapy. In adult growth hormone deficiency (AGHD), and in some children at risk for diabetes mellitus, it may be beneficial to consider avoiding daily GH dosing. Less frequent dosing not only minimizes the risk of insulin resistance, but has been shown to be just as effective in treating AGHD. GH replacement therapy given 3 times weekly, in doses resulting in serum IGF-I concentrations in the mid-normal range of adults, ranging in age from 25-35, has been shown to be just as effective as daily dosing in improving lipid profile, body composition, bone mass and turnover, and



Ask the Doctor, con't.

to reverse cardiovascular abnormalities.

In conclusion, we pediatric endocrinologists probably haven't been looking for the occasional patient who has an elevated blood sugar (IFG or IGT), but we should consider obtaining a simple fasting blood sugar level in patients who may be at risk. For those physicians who prescribe GH to adults, as a chronic therapy, it may be a good idea to screen, at least annually, for hyperglycemia.

Frank B. Diamond, Jr. MD



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ON THE HGF DISCUSSION FORUMS

THE GROWTH PLATE: PART I

In this column, we introduce the first of several articles that provide an overview of the growth plate of the skeletal long bones: its anatomy; morphology; physiology; and more.

Anatomy

Anatomically, longitudinal skeletal bones consist of four major areas in the following order, moving from the ends of the bone to the middle of the bone: the epiphysis, growth plate, metaphysis, and diaphysis. The epiphyses of the bones join with ligaments, tendons, and muscle to form joints. The growth plate is a narrow disk that is positioned horizontally between the epiphysis and metaphysis. The metaphysis is that part of the bone where the end of the bone starts to narrow and meet the diaphysis. The diaphysis is the shank of the bone, which contains bone marrow.

Morphology

Morphologically, the growth plate is the ossification center for the production of chondrocytes (mature cartilage cells) that enter the epiphysis and the metaphysis, and ultimately mature into bone tissue. The longitudinal bone growth results from the duplication of chondrocytes by division (proliferation) and differentiation of composition and function.¹

The bone growth occurs at the growth plate by a process called "endochondral ossification" in which cartilage is first formed and then remodeled into bone tissue. The growth plate consists of three principal layers that are positioned horizontally across the bone: resting zone, proliferative zone, and hypertrophic zone. The resting zone is located close to the epiphysis; the proliferative zone is in the middle of the resting zone and the hypertrophic zone. The hypertrophic zone is located next to the metaphysis. Chondrocyte proliferation (reproduction of mature cartilage cells), hypertrophy (increase in the proliferation of mature cartilage cells), and extracellular matrix secretion of osteocytes result in chondrogenesis (formation of cartilage). The newly formed cartilage is invaded by blood vessels and bone cell precursors, which remodel the hypertrophic bone cartilage into bone. The net effect is that new bone tissue is progressively created at the bottom of the growth plate, next to the metaphysis, resulting in bone elongation.¹

"The growth plate contains one cell type, the chondrocyte, at different stages of differentiation. *Resting zone chondrocytes* replicate at a slow rate, and act as the stem-like cells that replenish the pool of proliferative chondrocytes. *Proliferative zone chondrocytes* replicate at a high rate, and the resulting daughter cells line up along the long axis of the bone. As a result, clones of chondrocytes are arranged in columns parallel to this axis, a process

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critical to the formation of bones with elongated shape."²

The resting zone cartilage makes important contributions to endochondral bone formation at the growth plate: (1) it contains stem-like cells that give rise to clones of proliferative chondrocytes; (2) it produces a growth plate-orienting factor, a morphogen, that directs the alignment of the proliferative clones into columns parallel to the long axis of the bone; and (3) it may also produce a morphogen that inhibits terminal differentiation of nearby proliferative zone chondrocytes; and thus, may be partially responsible for the organization of the growth plate into distinct zones of proliferation and hypertrophy.³

Skeletal bone forms in the embryo from a network of embryonic connective tissues (mesenchyme), which results in the formation of cartilage. Longitudinal growth takes place in the growth plate, which can be likened to a "manufacturing center" for chondrocytes (mature cartilage cells) and osteocytes which are connective tissue cells that are a part of the cartilagenous matrix that constitute the epiphyseal ossification center. In the ossification center needle-like bodies (spicules) are produced that connect to form a meshwork of interconnecting spaces that are filled with chondrocytes. "Within the growth plate, chondrocyte proliferation, hypertrophy, and cartilage matrix secretion result in chondrogenesis [formation of cartilage]. The newly formed cartilage is invaded by blood vessels and bone cells that remodel the newly formed cartilage into bone tissue."²

Physiology

"This process of longitudinal bone growth is governed by a complex network of endocrine signals, including growth hormone, insulin-like growth factor I, glucocorticoids, thyroid hormone, estrogen, androgens, vitamin D, and leptin. Many of these signals regulate growth plate function, both by acting locally on growth plate chondrocytes and also indirectly by modulating other endocrine signals in the network. Some of the local effects of hormones are mediated by changes in certain hormone factors that control chondrocyte proliferation and differentiation."²

"Receptors for many hormones such as estrogen, GH, and glucocorticoids are present in or on growth plate chondrocytes. These hormones may

influence processes in the growth plate directly. Many growth factors, i.e., IGF-I, Indian hedgehog, PTHrP, fibroblast growth factors, bone morphogenetic proteins, and vascular endothelial growth factor are considered essential regulators of chondrocyte proliferation and differentiation."¹ These aspects of the physiology of bone growth will be discussed in future parts of this article on the growth plate.

Death of the Chondrocyte and the "Birth" of Bone Growth

"At a certain point, the chondrocyte cells in the resting zone stop dividing and terminally differentiate into hypertrophic chondrocytes. During the hypertrophic process, chondrocytes [align in columns parallel to the length of the bone], increase their height about 6- to 10-fold, and thus hypertrophic differentiation makes an important contribution to longitudinal growth. The hypertrophic chondrocytes calcify the surrounding extracellular matrix and produce factors that attract the invading bone cells and blood vessels, including vascular endothelial growth factor. Hypertrophic chondrocytes undergo apoptosis [cell death] shortly before the blood vessels invade the . . . [cell matrix that contains the chondrocytes]."²

"The rate of growth plate chondrocyte proliferation, and hence the rate of longitudinal bone growth, falls progressively with age. That decrease in growth plate function appears to be due to a mechanism intrinsic to the growth plate rather than a hormonal or other systemic mechanism. . . . The term 'growth plate senescence' has been used to describe this intrinsic process that involves both a decline in the function and cellularity of the growth plate." This decline occurs because stem-like cells in the resting zone have a finite proliferative capacity that is gradually exhausted. In humans, the growth plate cartilage is completely replaced by bone at the time of sexual maturation. This event, termed epiphyseal fusion, appears to be triggered when the proliferative capacity of the growth plate chondrocytes is finally exhausted.¹— to be continued.

Earl Gershenow
Web Master



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Endnotes

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Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892-1862, USA. ola.nilsson@nih.gov

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“THE GIFT THAT KEEPS ON GROWING”

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.

Teenscape



Hi Elizabeth,
My name is Cynthia and I am 14 years old. I have Turner Syndrome and I have been taking shots for about a year. My doctor gave me the name of another girl in his office who also has Turner Syndrome. We have become very close. Our mothers met each other at the office and didn't even know that their daughters had Turners! I am glad to know her.

Do you know of any sites where I can look and find other girls my age with Turner Syndrome? You can e-mail me your answer. Thanks for your time.

I hope to hear from you soon!
Cynthia

Hi Cynthia,
I researched for you about locating other girls your age with Turner Syndrome. You may want to try contacting the Turner Syndrome Society of the United States at www.turner-syndrome-us.org.

If you need additional information please feel free to call the Human Growth Foundation at 1-800-451-6434 and ask for the Turner Syndrome Booklet. Have you asked your doctor to connect you with any other girls from his practice that you may be able to speak with.

Please let me know if you need any other information and keep me posted as to how you are doing.
Elizabeth

Hi Elizabeth,
My name is Alicia and I am 14 years old. I weigh 60 lbs. and I am 4' 9" tall. I am not very happy about any of this. I wish I could grow taller. My mom is going to take me to the doctor soon. I want to know if you felt it was worth it.

Did you actually take the pills for 5 1/2 years?
Please e-mail me back.

Thank you,
Alicia

Hi Alicia,
Thank you for your e-mail about growth hormone. You said that you will be seeing a doctor soon. Is this the first time that you will be speaking to someone about growth hormone?

If so, he will probably send you to a pediatric endocrinologist. This doctor will have additional questions for you and may take a bone age x-ray of your left hand and wrist (to see if your bones have fused). The next step would be to test you to see if you are growth hormone deficient.

I was glad that I took growth hormone. You do not take pills. Growth hormone is given by injection for however long the doctor suggests.

I had to give the shots in either my arms, legs or stomach once a day. Please keep me up to date.
Elizabeth

Hi Elizabeth,
I have been seeing an endocrinologist for about a year. I have had three bone age pictures in the past year. I do not know what to do because I do not like shots/needles. I wish I could take a pill. I am tired of them taking blood. I think that is what is bothering me. Please e-mail me back.

Chelsea

Hi Chelsea,
The needles are very small and there are devices that you can use that make it much easier to do. You can also put a numbing cream on your arm or leg. What did your endocrinologist have to say about growth hormone? Talk to you soon.

Bye,
Elizabeth



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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 2010, and in the future.

