

In This Issue Reviews & Comments

page

- 33** Genetics of Stature
- 35** Gender of Growth Hormone Recipients in the US and Globally
- 36** Height Velocity Targets for First Year Growth Hormone Responses in Short Children
- 38** Adult Height of Treated Congenital Adrenal Hyperplasia Patients
- 40** Combined GH and Aromatase Inhibitor Therapy in GHD Adolescents
- 41** Factors Predicting Ante- and Postnatal Growth
- 42** Height Sparing in Anorexia Nervosa?
- 43** Growth Plate Changes of Catch-up Growth Following Caloric Restriction: Morphologic and Gene Expression Changes, Especially HIF1 α
- 44** High Growth Rate of Girls with Precocious Puberty Exposed to Estrogenic Mycotoxins
- 45** Long-term Follow-up of Idiopathic CPP Treated with GnRHa
- 46** Genetics of Dwarfism
- 49** Genetics Influences Allelic Expression Patterns
- 50** Growth Hormone Therapy Improves Mental and Motor Development in Young Prader-Willi Patients
- 51** Central Adrenal Insufficiency, Pituitary and Neuroradiological Alterations in Prader-Willi
- 52** Genital Function and Sensitivity Following Feminizing Surgery
- 54** Diagnosis of Congenital Central Hypothyroidism in Infants
- 55** Effect of Levo-thyroxine Treatment on Weight and BMI in Children with Acquired Hypothyroidism
- 56** Geographic Distribution of Childhood Diabetes and Obesity: Workforce of Pediatric Endocrinologists

GROWTH HORMONE ADMINISTRATION: IS IT SAFE AND EFFECTIVE FOR BODYBUILDING AND IMPROVED ATHLETIC PERFORMANCE?

ALAN D. ROGOL, MD, PHD

*Departments of Pediatrics
Indiana University School of Medicine
Indianapolis, Indiana
University of Virginia
Charlottesville, Virginia*

INTRODUCTION

Athletes and the media have demonstrated great interest in the subject of administration of growth hormone (GH), popularly referred to as *doping*. Thus, a review of the evidence for safety and efficacy in athletes, especially, adolescents, is warranted. Many other drugs are administered off-label, particularly a majority given to children and adolescents. However, recombinant human GH (rhGH) is unusual because off-label prescribing and

administration is illegal if given for indications not approved by the US Secretary of Health and Human Services (HHS). In this article—following short sections on the physiology of GH and the clinical role of rhGH—the data pertinent to athletic performance and problems with detection of doping are presented. This article ends with the specific legal issues and the activity surrounding further legal action with reference to rhGH and athletes.

The consideration of rhGH as an ergogenic aid and its potential to enhance athletic performance and/or body composition goes back many decades.¹ Due to the banning of rhGH use for officially sanctioned sport, there has been a large effort to detect its

From The Editor's Desk

Dear Colleague:

We have applied for and expect to be granted the opportunity of granting CME credits for reading GGH. Thus, while you enjoy the lead article and each one of the reviews you may also meet your requirements for licensure in the comfort of your home or office. In the near future the CME application and questionnaire will be posted on line. Once you complete it you will attain the necessary credits. Hopefully this feature will add to the value you place to the journal.

The current issue of GGH includes a very timely review of the safety and effectiveness of growth hormone for body building and improved athletic performance. The article by Dr. Alan Rogol brings us up to date and clarifies the issues that were widely discussed during this past summer's Olympic Games in China. However the article should also serve the pediatric endocrinologist to guide their patients and their families who seek this treatment to enhance their children's abilities. It should also serve as a resource to warn them of the illicit use of this product for such purposes, as well as to caution them to avoid falling prey to the multiple ineffective, expensive, and unregulated products available for purchase through the Internet. I also want to bring to your attention the reviews on the genetics of stature and the genetics of dwarfism. These excellent reviews include a synthesis of the state of the art of the most current papers and concepts in the field. Also noteworthy is the review dealing with the limited workforce of pediatric endocrinologists.

The economic situation of GGH continues to worsen with the downturn of the economy, yet we do not qualify for a bailout. Therefore I would appreciate your support in the form of a generous contribution so we may continue fulfilling your educational needs. I am sure you are being swamped with donation requests, please put GGH on top of your list and make your tax-deductible contribution to Pediatric Sunshine Academics, Inc. at www.PedSacademics.org or mail to 1040 Alston Road, Santa Barbara, CA 93108.

Happy Holidays and Best Wishes for 2009
Fima Lifshitz, MD
Editor-in-Chief

presence in athletes.^{2,3} More than ten years and millions of dollars have been spent on devising and implementing tests to detect doping. Despite anecdotal reports of the widespread use of doping no athlete has been sanctioned for the use of rhGH, even with the multiple seizures of rhGH from athletes and teams.

Why should pediatric endocrinologists be concerned about this seemingly esoteric subject? Pediatric endocrinologists have been counseling children, adolescents, and their parents about the height-increasing properties of rhGH for decades. The use of rhGH is legitimate in children who are truly small, such as those with GH deficiency, and other disorders (Table 1). As athletics and sports play an ever increasing and important role in the lives of children and adolescents, parents seek a competitive edge for their children. Families spend thousands of dollars on coaching and equipment in hopes of the possibilities of college scholarships and/or professional contracts. Therefore, pediatricians are now being asked to prescribe rhGH because of parental “beliefs” that it will improve athletic performance in children and adolescents. Although very expensive, parents may consider rhGH as seemingly little different from very expensive coaches, equipment, and training camps.

Table 1. FDA-approved indications for rhGH therapy in children

Growth hormone deficiency
Chronic kidney disease
Turner syndrome
Small-for-gestational age infants who fail to catch-up to the normal growth percentiles
Prader-Willi syndrome
Idiopathic short stature
SHOX gene haploinsufficiency
Noonan syndrome

PHYSIOLOGICAL ROLE OF GH

The physiological role of GH is to increase linear growth in children, to promote anabolic (tissue building) metabolism, and to alter body composition as part of this anabolic role. Growth hormone actions include the hepatic and local synthesis and release of its main mediator-protein, insulin-like growth factor (IGF)-I. The growth-promoting effects of GH include longitudinal bone growth by actions at the epiphysis and the differentiation of the prechondrocytes. GH shares some of these roles with IGF-I, meaning that the direct effect of GH and/or local production of IGF-I are both necessary for optimal growth.⁴

Stimuli to GH release include deep sleep, exercise, stress—including heat stress—hypoglycemia, and some amino acids. Some pharmacological agents are also stimuli to

the release of GH, for example, beta-2 adrenergic agonists, clonidine, L-DOPA, and estrogens and androgens (through an estrogen dependent mechanism). Inhibitory influences include obesity or ingesting a carbohydrate-rich diet. The direct effects of GH lead to increased glucose availability, increased free fatty acid levels and an increase in amino acid uptake by muscle. Longer term effects are mediated via IGF-I and include endocrine and paracrine effects in muscle and bone.⁴

Alterations in GH-deficient subjects include: the reduction of lean body mass, an increase in body fat, and a reduction in bone mineral density. From this the major metabolic effects of GH can be deduced. Administering rhGH reverses many of these alterations. However, it is not quite so simple, because GH has different effects depending upon the time following natural secretion (GH) or exogenous administration (rhGH). It is insulin-like in the first few minutes, but after several hours GH becomes diabetogenic and is anti-insulin at the liver and at peripheral sites, glucose utilization is decreased, lipolysis is increased, and the tissues are refractory to the acute insulin-like effects for several hours. The direct actions of GH include amino acid transport in muscle permitting protein synthesis and an increase in nitrogen balance, increased fat mobilization through lipolysis (increased triglyceride hydrolysis to free fatty acids and glycerol and reduction in fatty acid re-esterification) and an augmentation of lipid oxidation (Figure 1). These effects may be detected not only by decreases in body fat and in adipocyte size, but also by a decrease in lipid content per adipocyte.⁴

CLINICAL ROLE OF rhGH

Short children are prescribed rhGH to promote linear growth⁵ (Table 1) and that is the most visible result of rhGH treatment in infants, children, and adolescents. Additionally, rhGH prevents hypoglycemia in some infants with congenital hypopituitarism. In adults, rhGH is administered⁶ to promote physiologic and psychological well-being (Table 2).

Table 2. FDA-approved indications for rhGH therapy in adults

Growth hormone deficiency
Muscle wasting due to HIV/AIDS
Short bowel syndrome

The outcome of rhGH replacement therapy in a GH-deficient child or adolescent may be an increase in fat-free mass, both body cell mass (muscle) and total body water (especially the extra-cellular compartment), and a decrease in body fat with a redistribution from central to peripheral.⁷ Controlled experiments in hypopituitary adults have shown that the baseline decrease in functional capacity of approximately 20% reverts to

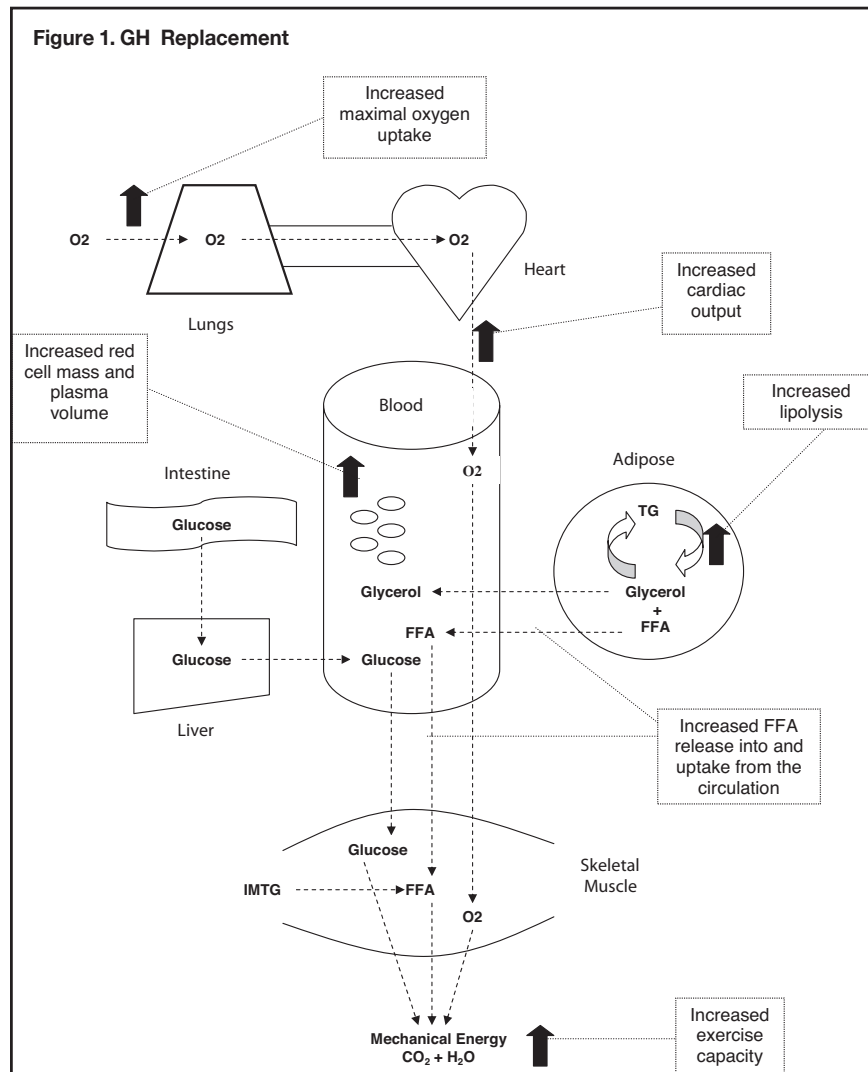
normal when measured as maximal oxygen uptake (VO_{2max}), aerobic capacity, maximal power output, or ventilation threshold with rhGH treatment.^{8,9} The increase in VO_2 was proportionate to the increase in lean body mass (the respiring tissue). A decrease in fatigue was also reported; this is likely due to the decrease in the ventilatory threshold or lactate threshold as a percentage of maximal oxygen uptake. This was perceived as being able to *work* within a comfortable range.

How might this happen? One should note that the requirements for the increase in work require metabolic fuels, oxidation (intermediary metabolism), and useable energy. The immediate burst comes from the oxidation of glucose and the more prolonged capacity from the oxidation of free-fatty acids. By increasing ventilation and oxygen transport by hemoglobin GH directly leads to an enhanced delivery of substrate and oxygen to respiring muscle. Increased cardiac output (stroke volume and left ventricular ejection fraction) permits the distribution of the oxygen to the capillary network and

to the extraction of the oxygen by muscle fibers, either to be used directly or stored in myoglobin. Other effects that enhance the delivery of oxygen include diminished systemic vascular resistance. In all of these physiologic responses GH and exercise are likely additive and, perhaps, synergistic. Indirect effects of GH (likely mediated by IGF-I) are related to the alteration in lean body mass and in more efficient thermoregulation.

GH AND ATHLETIC PERFORMANCE

In the 1940s the first GH was extracted from human cadaver pituitary glands.¹⁰ The GH that was derived was in such limited quantities that there was none available for the purposes of testing it for athletic performance.¹¹ Only human and monkey pituitary GH has efficacy in man.^{12,13} In 1985 synthesized rhGH received FDA approval. Thus a virtually unlimited supply became available and clinical studies were undertaken in children and adolescents with subnormal growth and in adults with GH deficiency, aging, as well as for performance or aesthetic purposes. The evidence is neither clear nor robust that rhGH produces salutary ergogenic and performance benefits among athletes.¹⁴



Reprinted with permission Gibney J, et al. *Endocr Rev.* 2007;28:603-24. Copyright © Endocrine Society. 2007. All rights reserved.

Definition of Doping

The International Olympic Committee (IOC) defines doping as the “*use of an expedient (substance or method) which is potentially harmful to athletes’ health and/or capable of enhancing their performance, or the presence in the athletes’ body of a prohibited substance or evidence of the use thereof or evidence of the use of a prohibited method*”. There is no mention of intent or of how the substance entered the body. If the substance is in the athlete’s body then the athlete is responsible. That is the basis for sanctions for testing positive for a prohibited substance. Sir Arthur Porritt, first chairman of the IOC Medical Commission, noted, “*To define doping is, if not impossible, at best extremely difficult, and yet everyone who takes part in competitive sport or who administers it knows exactly what it means. The definition lies not in words but in integrity of character.*”

In fact, there are huge pressures to excel. Athletes are driven to perform their best and along with the pressure to win there is often an attitude that doping is necessary to achieve success. Expectations about success include potentially lucrative financial rewards with winning, such

as collegiate scholarships and salary as a professional athlete. The rationale for taking ergogenic effectors such as rhGH is that by becoming bigger and stronger the athlete will perform better. It should be noted that performance is much more than just strength or endurance; for the athlete must produce, control, and efficiently use the energy in a fashion that maximizes athletic performance.

There is a system in place for therapeutic use exemptions to doping for those athletes who require the *substance* for health; for example, insulin is permissible for those with diabetes mellitus. This is a formal process overseen by the US Anti-Doping Agency (USADA) as the local agent for the world anti-doping effort as directed by the World Anti-Doping Agency (WADA).

Abuse of rhGH

The illegal indications for rhGH are listed in Table 3. Growth hormone is listed under class S2 of hormones and related substances in terms of the 2006 WADA and IOC prohibited list of doping agents. Other peptides in this category include erythropoietin (EPO), corticotrophin (ACTH), IGF-I, and insulin. It is likely that rhGH is being abused at an increasingly prevalent rate. However, it should be noted that much of what is purported to be rhGH—especially products promoted on the Internet—is not. Of course, any drug taken orally cannot be rhGH. Many of the products advertised online and in magazines are GH releasers, mainly amino acids and rarely, analogues of GH releasing hormone (GHRH).¹⁵ It is also worth noting that these are considered “dietary supplements” and not subject to FDA oversight. The notion that amino acids release GH is on solid scientific ground given that tests for GH sufficiency may include arginine, or the closely related amino acid, ornithine. What isn’t stated is that very concentrated solutions of these amino acids are administered intravenously before GH is released. Also not prominent is the physiologic concept of the absolute and then relative refractory period following GH release, irrespective of the cause.

Table 3. Off-label/illegal use of rhGH

Anti-aging

Athletic performance enhancement

Body building

A casual Internet search (in June, 2008) using the key words “hGH AND sport performance” yielded approximately 158,000 web links, mainly to sites that had multiple supplements to sell. Many of the listed products require administration for many months. A few examples included:

- Chromium, l-ornithine, l-arginine, l-lysine, l-glutamine, l-glycine, “pituitary” powder, colostrums, placental

extract and choline. 60-day supply \$49.95

- hGH energizer containing: vitamin B-6, tribulus, l-arginine, l-leucine, l-glutamine, l-lysine, gamma-aminobutyric acid (GABA), l-isoleucine, l-valine, colostrums, l-ornithine and l-glycine. It is touted as an “all natural hGH supplement.” 90-day supply \$29.95
- A nasal spray. It contains: alpha GPL, GABA, multiple amino acids, many as noted above, l-DOPA, bean extract, momiyo extract and alpha-ketoglutarate—I suspect that many other substances are included! 90 day supply \$59.95

Finally, something that might be rhGH for injection, but one must complete a form for a free (medical) consultation and thus presumably for a physician to write a prescription. It is important to note that if a prescription is written for anti-aging, body building, or athletic performance, a felony has been committed by the prescriber, the recipient, and (presumably) the dispenser (Table 3). Cost is not noted, but likely ranges in the \$5,000 to \$50,000-range depending on the size of the recipient and the dose per kg.

There are many reports that have noted an increasing prevalence of rhGH abuse. These primarily come from anecdotal “information” on the benefits of GH posted on the Internet, as well as a dated, but very favorable write-up in *The Underground Steroid Handbook*,¹⁶ The press has reported an increasing number of seizures from elite athletes including cyclists and swimmers. What is it that athletes expect to obtain from taking rhGH? The athletes want improved performance, but such studies are difficult to do, either as alleged “clinical trials” or observational studies in athletes, for they rarely take agents singularly, but often a “cocktail” of multiple dietary supplements and one or more doping agents.

Although rhGH has not been shown to unequivocally increase muscle strength or to improve performance,¹⁴ it is considered one of the drugs of choice, because it is extremely difficult to prove that one is receiving it. The structure of rhGH is identical to the main isoform of naturally secreted GH. The pulsatile secretion of native GH means that its levels fluctuate widely, from undetectable to clearly within the doping range. Both GH and rhGH have a short half-life in the circulation. Exercise is potent stimulus to GH release and release may be modified by variations in nutrition and legitimate nutritional supplements.

Studies of rhGH in Athletes

Liu and colleagues¹⁴ have systematically reviewed the effects of rhGH on athletic performance. Using stringent criteria for a meta-analysis, they scanned 7599 titles from the largest databases, reviewed 252 abstracts in detail, and retrieved 56 articles for full-text evaluation. Following their review, 44 articles representing only 27

unique studies met the strict inclusion criteria. A total of 303 participants received rhGH for an average of 20 days but a significant number received rhGH only once. The subjects were mainly young men (average age 27 years) and were recreational and not elite athletes. The average dose was 36 µg/kg/day which is approximately 5- to 10-fold the therapeutic dose for adults with GH deficiency. Lean body mass increased in the rhGH-treated groups compared to those not treated (2.1 kg [95% CI, 1.3 to 2.9 kg]) with a small, not statistically significant, decrease in fat mass (-0.9 kg [CI, -1.8 to -0.0 kg]). Body weight did not change significantly. Only 2 studies appropriately evaluated change in strength;^{17,18} these were the longest trials of 42 and 84 days duration. On 1-repetition maximum voluntary strength (1-RM) testing, those who received rhGH showed no change in biceps strength (-0.2 kg [CI, -1.5 to 1.1 kg]) or quadriceps strength (-0.1 kg [CI -1.8 to 1.5 kg]). In the second study none of the 7 other muscle groups evaluated showed a positive change in strength.

Minor effects of rhGH have been noted on basal metabolism with a slight decrease in respiratory exchange rate reflecting the preferential burning of fat rather than carbohydrate, at rest. Additionally, very little effect on exercise capacity has been reported. The results may be summarized by noting that lactate levels trended higher, plasma free fatty acid concentrations and glycerol concentrations were significantly increased—reflecting the lipolytic metabolic effect of rhGH—but the respiratory exchange ratio did not change. These studies showed very little ergogenic effects of rhGH in recreational athletes. The studies were of short duration and most likely did not represent how elite athletes administer rhGH, either with reference to dose, duration of doping, or addition of other supplements—both legal and illegal. Based on countless reports in the media, it is clear that many athletes abuse steroids in addition to the *noted* amounts of rhGH. None of the studies would have been able to detect differences of 0.5 to 1.0 % in “performance”. These small differences are those that are relevant to the time (track) events, distance or height (field) events that separate the champion from any other finishing position. Similar issues relate to a host of sports other than track and field, but may be even more difficult to quantitate.

Recently, rhGH (19 µg/kg/day) administered for one week was noted to increase strength, peak power output, and IGF-I levels in a group of abstinent dependent users of anabolic androgenic steroids.¹⁹ Great care was taken to be certain that no anabolic steroids were detected in appropriately obtained urine samples. Body weight increased—this was likely water retention—as did peak power output. Although this is a very special group of athletes and is a single study, it was quite carefully performed.

Adverse events were common in the larger group of studies in the Liu et al meta analysis.¹⁴ These mirrored those of adult subjects who administered rhGH in what were at that time, child and adolescent doses. Adverse events included soft tissue edema, joint pain, carpal tunnel syndrome, and excessive sweating. Most were related to fluid retention and considered to be secondary to the rhGH effects on salt and water balance by the kidney.

In a clinical trial designed to determine the pharmacodynamics of rhGH abuse, Nelson and co-workers²⁰ administered rhGH or placebo and testosterone (in men only) or placebo, or both in a double-blind study to young recreational athletes for 8 weeks. The final doses of rhGH were approximately 4-fold (women) and 6-fold (men) the normally prescribed dose for GH deficient young adults. Although there were no “efficacy” data with reference to body composition or athletic performance, the data are important with reference to adverse events. Although no subject discontinued the study due to adverse events related to rhGH, minor adverse events were reported in all groups, including the placebo groups. Swelling was reported in a greater number of rhGH subjects than placebo subjects (men: 67% versus 2.5%, $P=0.02$; women: 65% versus 31%, $P=0.06$). Subjects receiving rhGH reported more joint pain and *pins and needles* sensations; however, statistical significance was reached only in the men ($P=0.02$ and $P=0.03$). These data show the relatively small “therapeutic” index for rhGH and likely have implications for those athletes purportedly administering much higher doses.

In a clever sub-analysis of the placebo group, only reported in abstract form,²¹ this group of investigators queried the placebo group about whether they were receiving active drug. The male athletes who believed that they were administered rhGH, even though they received the placebo, had both *perceived* improvement in performance measures and improvement in one of several *measured* indicators of physical performance. Although the study design²⁰ was not powered for this endpoint, it certainly does complicate the outcomes of trials with rhGH for performance endpoints.

Virtually all studies reviewed by Liu and colleagues¹⁴ had significant limitations. The major ones included:

- Very few studies evaluated strength and exercise capacity
- Small effects would not have been found
- Short duration of the studies, many for only one dose
- Doses of rhGH and other supplements are very likely different in the real world.

Liu and colleagues concluded, “*Claims regarding the performance-enhancing properties of growth hormone are premature and are not supported by our review of the literature. The limited published data evaluating the*

effects of growth hormone on athletic performance suggest that although growth hormone increases lean body mass in the short term, it does not appear to improve strength and may worsen exercise capacity. In addition, growth hormone in the healthy young is frequently associated with adverse events.”¹⁴

CURRENT DETECTION OF rhGH DOPING

The ability to detect rhGH has been quite a difficult task for analytical chemists, because the amino acid sequence of rhGH is identical to that of the main GH isoform secreted by the pituitary; unlike other peptide hormones it has no N-linked glycosylation sites; its secretion is pulsatile with a short half-life (16 to 20 minutes); there are circulating GH-binding proteins; potential cross reactivity with other peptide hormones (eg, prolactin); and it is stimulated by exercise and stress. Blood sampling is required for all detection methods, because less than 0.1% may be found in the urine. Its renal secretion is poorly understood and greatly variable within and between subjects.²²

The analytical approaches rely on immunoassays as opposed to the more established doping tests for anabolic steroids, which depend on GC/MS technology (Figure 2). There are 2 general approaches to detection of doping with rhGH. The first, (direct) approach measures the GH isoform composition by the differential immunoassay method.²³ For this approach one constructs pairs of antibodies whose primary focus is all of the isoforms of GH and a second set which is virtually restricted to the 22kD isoform—the one that is 100% of the rhGH. The first assay is called *permissive* (pituitary) and the second *specific* (recombinant). The rationale is that the more one takes of the rhGH (22kD), the less pituitary GH (especially, 20kD)

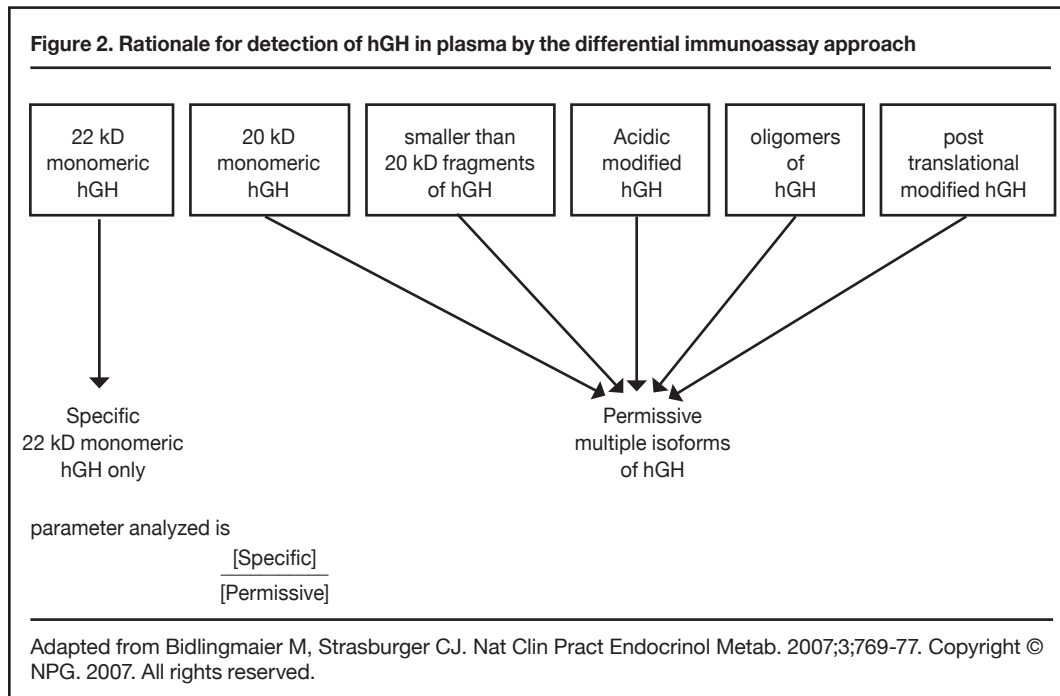
will be secreted; implying that the ratio of the assay of the *specific* to the *permissive* will rise. As an example, the ratio rises from 0.6 to 1.5 in subjects administered rhGH, but this assay would only be valid within a few days of the last injection of rhGH. The validation of this technique requires knowledge (ie, testing) of the effects of exercise on the recombinant/pituitary ratio, an independent confirmatory test, knowledge of the *window of opportunity*, and data from athletes—both recreational and elite. This method is unable to detect doping²² with pituitary derived GH or the abuse of the GH secretagogues, IGF-I itself or in combination with its major circulating binding protein, IGFBP-3 (IGF-I/IGFBP-3).

The second is the indirect approach in which specific analytes dependent on GH (or IGF-I) are measured. Variables from the IGF system and collagen/bone have been chosen because they change markedly during rhGH administration and it appears that combinations of variables using discriminant functions are the most promising. Detection of rhGH supplementation is possible at least until 2 weeks following the last administration, although there is progressively decreasing sensitivity after the first week. Normative data in athletes have been established.²⁴ The physiological changes in GH-dependent markers in adolescent athletes are far more dramatic than in older athletes, thus making it quite difficult to detect doping in this age range without constructing a complex algorithm that would depend more on maturational age than it would on the chronological age—another complication for doping control.^{25,26} Data using this approach have noted only minor effects due to trauma or micro-injury or ethnic background.^{3,27} As with any assay, rigorous standardization is required

and interference by concomitant drug abuse, especially anabolic steroids, is a likely complication. For the moment the most informative combination of analytes is IGF-I and procollagen III peptide levels and individual discriminant functions for men and women.

FUTURE RESEARCH IN DOPING

The doping-detection field in the future will require the determination of combinations of rhGH-dependent



analytes that remain detectable for a longer period of time than the ones currently available, and perhaps other methods for the direct determination of the IGFs and GH-secretagogues. It would seem that abuse of rhGH (or other peptide hormones) manufactured by the major global pharmaceutical companies could be markedly diminished by adding, for example, an inert fluorescent marker that would be excreted in the urine. Detection of that unnatural marker might then be considered a doping offence. Most likely this would markedly diminish, but not stop, doping offences with these hormones. One can only speculate what is stopping the pharmaceutical manufactures from doing so.

The era of gene doping, for example adding GH or IGF-I genes to specific muscles, is upon us. Experiments have been done in animals.²⁸ No detection methods presently available could detect this type of doping.

LEGAL ISSUES

As is true for most drugs, physicians may prescribe off-label, meaning that trials for that particular condition have not been performed but that it is logical to use an already approved drug for a specific patient. However, rhGH is quite different; it is illegal to prescribe rhGH off-label for age-related conditions (anti-aging) or for performance enhancement (Table 3). Unlike most FDA-approved medications, rhGH can only be prescribed for indications specifically authorized by the Secretary of HHS (for indications, see Table 1). Because it is not administered orally and it was formerly classified as a drug, rhGH is not considered a dietary supplement and is not subject to the Dietary Supplement and Health Education Act (DSHEA).

The precise language of the Federal Drug and Cosmetic Act²⁹ (FDCA) under section 303 is:

1. *Except as provided in paragraph (2), whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 505 and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines authorized by title 18, or both.*
2. *Whoever commits any offense set forth in paragraph (1) and such offense involves an individual under 18 years of age is punishable by not more than 10 years imprisonment, such fines as are authorized by title 18 or both.*
3. *Any conviction for a violation of paragraphs (1) and (2) of this subsection shall be considered a felony violation of the Controlled Substances Act for the purposes of forfeiture under section 413 of such Act.*
4. *As used in this subsection the term "human growth*

hormone" means somatrem, somatropin, or an analogue of either of them.

5. *The Drug Enforcement Administration (DEA) is authorized to investigate offenses punishable by this subsection.*

SUMMARY AND CONCLUSIONS

There are a number of legitimate uses of rhGH in infants, children, adolescents, and adults. It is different from most drugs in that its off-label use is illegal for those unapproved indications related to athletic performance, body building and anti-aging. Although difficult to show any ergogenic advantage in clinical trials, none of the trials have been large enough or have narrow enough end points to have a valid outcome given the changes in performance that are relevant to world-class athletes. Some progress is being made in the ability to detect doping with rhGH, but to date no national or international athlete has been sanctioned for abusing rhGH. This does not mean that rhGH is not being used by athletes, just that the testing is not yet robust enough to capture those abusing rhGH. Further research is clearly needed to improve the detection techniques, and also to determine if rhGH as administered to athletes is actually ergogenic or enhances one's image in body building.

As difficult as it is to note either changes in performance or body composition in adults, it is much more difficult to detect these alterations in adolescent athletes, whose natural pubertal progression involves a marked ramping-up of the GH/IGF-I system, as well as the analytes that are being considered for the detection of doping.

References

1. Sonksen PH, Holt RI. Commentary on physical effects of short-term rhGH administration in abstinent steroid dependency. *Horm Res.* 2008;69:355-6.
2. Powrie JK, Bassett EE, Tosen T, et al, on behalf of the GH-2000 Project Study Group. Detection of growth hormone abuse in sport. *Growth Horm IGF Res.* 2007;17:220-6.
3. Gibney J, Healy ML, Sonksen PH. The growth hormone/insulin-like growth factor-I axis in exercise and sport. *Endocr Rev.* 2007;28:603-24.
4. Melmed S, Kleinberg D. Anterior pituitary. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. *Williams Textbook of Endocrinology*, edition 11. New York, NY: Saunders; 2007:155-261.
5. Quigley CA. Growth hormone therapy of non-growth hormone deficient growth disorders. *Endocrinol Metab Clin North Am.* 2007;36:131-86.
6. Ho KK. GH deficiency Consensus Workshop Guidelines: Consensus guidelines for the diagnosis and treatment of adult with GH deficiency II: a statement of the GH research Society in association with the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, Japan Endocrine Society, and the Endocrine Society of Australia. *Eur J Endocrinol.* 2007;157:695-700.
7. Roemmich JN, Huerta MG, Sundaresan SM, Rogol AD. Alterations in body composition and fat distribution in growth hormone deficient prepubertal children during growth hormone therapy. *Metabolism.* 2001;50:537-47.
8. Clayton P, Gleeson H, Monson J, Popovic V, Shalet SM, Christiansen JS. Growth hormone replacement throughout life: insights

- into age-related response to therapy. *Growth Horm IGF Res.* 2007;17:369-82.
9. Sherlock M, Toogood AA. Aging and the GH/insulin like growth factor-I axis. *Pituitary.* 2007;10:189-203.
 10. Blizzard RJ. Growth hormone as a therapeutic agent. *Growth Genet Horm.* 2005;21:49-54.
 11. Li CH, Papkoff H. Preparation and properties of growth hormone from human and monkey pituitary glands. *Science.* 1956;124:1293-4.
 12. Knobil E, Hotchkiss J. Growth hormone. *Ann Rev Physiology.* 1964;26:47-74.
 13. Knobil E, Greep RO. The physiology of growth hormone with particular reference to its action in the rhesus monkey and the "species specificity" problem. *Rec Progr Horm Res.* 1959;15:1-69.
 14. Liu H, Bravata DM, Okin I, et al. Systematic review: the effects of growth hormone on athletic performance. *Ann Int Med.* 2008;144:747-58.
 15. Saugy M, Robinson N, Saudan C, Baume N, Avois L, Mangin. Human growth hormone doping in sport. *Br J Sports Med.* 2006;40:35-9.
 16. Duchaine D. *The Original Underground Steroid Handbook*, 1981.
 17. Deysig R, Frisch H, Blum WF, Waldhör T. Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. *Acta Endocrinol (Copenh).* 1993;128:313-8.
 18. Yarasheski KE, Campbell JA, Smith K, Rennie ML, Holloszy JO, Bier DM. Effect of growth hormone and resistance exercise on muscle growth in young men. *Am J Physiol.* 1992;262:E261-7.
 19. Graham MR, Baker JS, Evans P, et al. Physical effect of short-term recombinant human growth hormone administration in abstinent steroid dependency. *Horm Res.* 2008;69:343-54.
 20. Nelson AE, Meinhardt U, Hansen JL, et al. Pharmacodynamics of growth hormone abuse biomarkers and the influence of gender and testosterone: a randomized double-blind placebo-controlled study in young recreational athletes. *J Clin Endocrinol Metab.* 2008;93:2213-22.
 21. Hansen JL, Nelson AE, Meinhardt U, Walker IH, Ho KK. The power of the mind: an evaluation of the placebo effect in a study of growth hormone on physical performance. Annual Meeting of The Endocrine Society, June 2008, San Francisco [Abstract].
 22. Holt RI, Sönksen PH. Growth hormone, IGF-I and insulin and their abuse in sport. *Brit J Pharmacol.* 2008;1-15.
 23. Bidlingmaier M, Strasburger CJ. Technology insight: detecting growth hormone abuse in athletes. *Nat Clin Pract Endocrinol Metab.* 2007;3:769-77.
 24. Healy ML, Dall R, Gibney J, et al. Toward the development of a test for growth hormone (GH) abuse: a study of extreme physiological ranges of GH-dependent markers in 813 elite athletes in the post-competition setting. *J Clin Endocrinol Metab.* 2005;90:641-9.
 25. Mora S, Pitukcheewanont P, Kaufman FR, Nelson JC, Gilsanz V. Biochemical markers of bone turnover and the volume and the density of bone in children at different stages of sexual development. *J Bone Miner Res.* 1999;14:1664-71.
 26. Rauchenzauner M, Schmid A, Heinz-Erian P, et al. Sex- and age-specific reference curves for serum markers of bone turnover in healthy children from 2 months to 18 years. *J Clin Endocrinol Metab.* 2007;92:443-9.
 27. Erotokritou-Mulligan I, Bassett EE, Kniess A, Sönksen PH, Holt RI. Validation of the growth hormone (GH)-dependent marker method of detecting GH abuse in sport through the use of independent data sets. *Growth Horm IGF Res.* 2007;17:416-23.
 28. Barton-Davis ER, Shoturma DI, Musaro A, Rosenthal N, Sweeney HL. Viral mediated expression of insulin-like growth factor I blocks the aging-related loss of skeletal muscle function. *Proc Natl Acad Sci USA.* 1998;95:15603-7.
 29. US Food and Drug Administration. Federal Food, Drug and Cosmetics Act, Section 303. Penalties. Subsection (e) <http://www.fda.gov/opacom/laws/fdcact/fdcact3.htm>

Editor's Comment:

The lead article in this issue of GGH entitled "Growth Hormone Administration: Is it safe and effective for bodybuilding and improved athletic performance?" by Dr. Alan Rogol reviews the current state of the misguided use of human growth hormone. This topic has been of high interest as prominent professional athletes have been the subject of investigation and hearings by the US Congress. These high profile governmental activities may only be reflecting the tip of the iceberg of a prevalent practice in our society that may be permeating our youth. It is not possible to track the number of individuals receiving illegally distributed growth hormone, but it may account for a \$2 billion per year business in the US.¹ This is primarily a cash only business as the vast majority of users pay out of pocket for the drug. The New York State Bureau of Narcotic Enforcement uncovered highly profitable, illegal distribution of growth hormone; an investigated compounding pharmacy purchased 25 grams of imported growth hormone for \$75,000 and converted each gram into 3000 IUs of growth hormone, then sold the drug for \$6 to \$18 per IU—yielding \$450,000 to \$1,350,000.² In 2007, in this case alone, the company entered into a deferred prosecution agreement with the Massachusetts US Attorney's Office and was fined \$10.5 million over the illegal distribution of growth hormone for non medical uses. Additionally,

there are many other sales through the Internet of multiple products purportedly marketed as growth hormone. These practices preclude the detection and monitoring of adverse events and the potential health consequences of the illegal use of growth hormone.

Pediatric endocrinologists are well acquainted with the wish of children and their parents to administer growth hormone for growth augmentation purposes and are often consulted for its use as an agent for enhancement of their athletic capability and bodybuilding. Beware that the administration of growth hormone for the later purpose is illegal and its efficacy and safety for bodybuilding and athletic performance has not been demonstrated, as discussed in the lead article by Rogol. However, as long as our culture seeks perceived physical enhancements with products like growth hormone, we will have to be aware of the extensive distribution and promotion to our youth and actively participate in curtailing its use. This is quite a challenge, as this and other medications are easily found and sold online. According to The New York Times³ there are over 365 Internet sites that advertise and/or sell controlled medications by mail and offering to supply the drugs without a proper prescription. The US Drug Enforcement Administration found that 85% of all Internet prescription sales involved controlled drugs, compared with 11% of those filled through traditional pharmacies, suggesting that online

sales are destined for misuse. Mr. Califano, a former secretary of Health and Human Services, said: "Abuse of prescription drugs has exploded among college students, and we think that one way they get these drugs is over the Internet."

Fima Lifshitz, MD
Editor-in-Chief

References

- 110th US Congress Committee on Oversight and Government Reform. Hearing on myths and facts about growth hormone, B12 and other substances. February 12, 2008.
- Quinn TJ. Specialty distribution systems helps feds after steroid bust. *New York Daily News*. September 1, 2007.
- Eckholm E. Abuses are found in online sales of medication. *The New York Times*. July 9, 2008. A16.

REVIEWS & COMMENTS FROM THE LITERATURE

Genetics of Stature

Adult height is primarily (approximately 80% to 90%) determined by hereditary factors. Socioeconomic status, nutrition, and disease influence only a relatively small proportion of attained stature. It has long been suspected that there are a multitude of genes that impact upon this polygenic trait, with each gene exerting an additive but only very limited effect. From genome-wide association studies employing single nucleotide polymorphism (SNP) analyses in approximately 80,000 individuals of European ancestry (UK, Scandinavia, Holland, Iceland), these 3 investigative groups have identified more than 30 chromosomal sites and the potential genes that appear to be partially involved in the regulation of adult stature in humans (Table). Gudbjartsson et al divided the candidate genes into 3 functional groups—those associated with skeletal development (eg, *BMP2*, *BMP6*), those that encode zinc-dependent metalloproteinases (*ADAMTS10*) and glycoproteins (eg, *FBN1*) that affect cartilage composition, and those that are involved with the processes of chromosome segregation and mitosis (eg, *CDK6*, *HMG2*). The gene most frequently associated with stature in all 3 studies was *ZBTB38*. This zinc-finger protein binds methylated DNA—specifically the methylated allele of the differentially methylated region of *H19/IGF2*.¹ This is the site at which epigenetic errors of imprinting result in either the Beckwith-Wiedemann syndrome (OMIM 130650) of somatic overgrowth or the growth retardation syndrome of Russell-Silver (OMIM 180860).² *ZBTB38* represses transcription of methylated regions. Thus, it is interesting to speculate that *ZBTB38* might affect adult stature through regulation of the production of insulin-like growth factor (IGF)-II, perhaps during in utero development when IGF-II is known to be one of the determinants of fetal growth. Independent of its effect on methylated DNA, *ZBTB38* also regulates transcription of *TH*, the gene encoding tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. Other commonly identified gene candidates were *HMG2* encoding a chromatin architectural factor and *CDK6* encoding a cyclin dependent kinase regulator of the cell cycle.

While each of these candidate genes has only a small effect upon adult height (estimated 0.4 cm), collectively they can exert significant influence and account for only approximately 4% of adult stature. The more “tall” alleles one has, the taller the individual (Figure). In the study of Weedon et al, there was a 5 cm difference in adult stature between subjects with 17 or fewer “tall” alleles compared to those with 27 or more.

Gudbjartsson DF, Walters GB, Thorleifsson G, et al. Many sequence variants affecting diversity of adult human height. *Nat Genet*. 2008;40:609-15.

Lette G, Jackson AU, Gieger C, et al. Identification of 10 loci associated with height highlights new biological pathways in human growth. *Nat Genet*. 2008;40:489-90.

Weedon MN, Lango H, Lindgren CM, et al. Genome-wide association analysis identifies 20 loci that influence adult height. *Nat Genet*. 2008;40:573-83.

First Editor's Comment: *These reports are of great interest as they dramatically illustrate just how many genes must be involved in the determination of adult stature. They also illustrate the quantitative problem that the clinician will face in identifying the “cause” of genetic short stature in a specific patient. However, it was difficult to critically examine the data because some of it was derived by meta-analysis of previously published reports. Thus, it was unclear whether or not there may have been some overlap between analytical data utilized in the 3 reports. The reports are also difficult to interpret because the investigators employed different probes for similar or related SNP sites. For example, ZBTB38 was identified as SNP rs724016 in the report of Lettre et al, as SNP rs6440003 in the report of Weedon et al, and as SNP rs6763931 in the report of Gudbjartsson et al. [A brief expository review of genome-wide association studies and SNPs has been written by Christensen and Murray.³]*

Allen W. Root, MD

Second Editor's Comment: *Fisher proposed in 1918 that many genetic factors, each having an individually*