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**Analysis of Faulty Data Yields Inaccurate Results:  
Thousands Benefit from Growth Hormone Replacement Therapy  
for Aging-Related Disorders –  
Proven, Real-World Track Record of Benefits  
of Adult Growth Hormone Deficiency Therapy**

Issued 15 January 2007

*Official Response to Liu H, Bravata D, Olkin I, Nayak S, Roberts EB, Garber A, and Hoffman A,  
"Systematic Review: The Safety and Efficacy of Growth Hormone in the Healthy Elderly,"  
Annals of Internal Medicine, 2007:146; 104-115.*

The American Academy of Anti-Aging Medicine (A4M; [www.worldhealth.net](http://www.worldhealth.net)) is a non-profit medical society dedicated to the advancement of technology to detect, prevent, and treat aging related disease and to promote research into methods to retard and optimize the human aging process. A4M is also dedicated to educating physicians, scientists, and members of the public on biomedical sciences, breaking technologies, and anti-aging issues.

The A4M has reviewed the findings of the Liu et al meta-analysis concerning adult growth hormone (GH; HGH) replacement therapy published in the January 15, 2007 issue of the *Annals of Internal Medicine*, and refutes the paper's findings. Observes Ronald Klatz, M.D., D.O., President of the A4M: "The Liu et al paper is flawed, as it is based on an incomplete compilation of clinical studies of GH replacement in healthy adults. The A4M submits that thousands of published studies on hundreds of thousands of patients have demonstrated the clear benefits of adult GH replacement therapy, when utilized under proper clinical guidelines and at proper physiological dosages. Real-world results must take precedence over academic hypotheses as to benefits and risks."

The A4M finds that the Liu et al paper is flawed for the following reasons.

**1. Meta-Analysis Conducted on Incomplete Compilation of GH Therapeutics Studies**

The Editors of *Annals of Internal Medicine* state that "The researchers reviewed all clinical trials of GH to determine if it is safe and effective in the healthy elderly. "

However, Liu et al state in the Methods - Study Selection, that "We excluded studies that: ... evaluated GH as a treatment for a specific illness (for example, adult GH deficiency ...". To exclude data from studies conducted to treat adult GH deficiency from the meta-analysis flaw the Liu et al review as incomplete. As stated by Savine: "If mean IGF-1 of 300 is mean normal for 20-30 year olds, almost all men and women over the age of 40 have an IGF-1 deficit." [Savine R. et al. Growth hormone replacement for the somatopause. *Horm Res* 2000;53 Suppl 3:37-4]. It is the position of the A4M that we submit that the empirical data suggests that when treating adult GH deficiency, physicians are treating a documented deficiency disease. In fact, HGH deficiency is associated with significantly decreased longevity in human siblings. Longevity and healthy aging are directly related to GH/IGF-1 levels. [Wuster C, Melchinger U, Eversmann T, Hensen J, Kann P, von zur Muhlen A, Ranke MB, Schmeil H, Steinkamp H, Tuschy U. Reduced incidence of side-effects of growth hormone substitution in 404 patients with hypophyseal insufficiency. Results of a multicenter indications Study. *Med Klin* 1998 Oct 15;93(10):585-91.]

The A4M further submits that the Liu et al compilation of studies on which their meta-analysis was conducted, is incomplete. We have compared the Liu et al compilation with the results of MEDLINE literature searches independently conducted by the A4M, and find the following studies absent from the Liu compilation. These missing studies specifically advocate on behalf of the benefits of GH therapeutics in adults:

*Northwestern University Feinberg School of Medicine, Chicago, IL USA, April 2006:* Dr. Molitch and colleagues found that: "GH therapy offers benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures .... The risks of GH treatment are low." [Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Shalet SM, Vance ML; Endocrine Society's Clinical Guidelines Subcommittee; Stephens PA. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2006 May;91(5):1621-34. Epub 2006 Apr 24. ]

*Christie Hospital, Manchester, U.K., April 2002* — Dr. Murray and colleagues administered low-dose GH regimen administered to 67 growth-hormone deficient (GHD) adults. Significant improvements in total cholesterol, LDL, triglycerides, and ratio of total cholesterol to HDL were seen. The researchers commented that "Growth hormone deficiency in adult life is associated with a number of adverse biological changes ... Most of these changes can be reversed by growth hormone replacement therapy." [Murray RD, Wieringa GE, Lissett CA, Darzy KH, Smethurst LE, Shalet SM. Low-dose GH replacement improves the adverse lipid profile associated with the adult GH deficiency syndrome. *Clin Endocrinol (Oxf).* 2002 Apr;56(4):525-32.]

*KIGS/KIMS Outcomes Research, Pharmacia AB, Stockholm, Sweden, November 2001* — Data concerning visits to the doctor, number of days in hospital, and amount of sick leave were obtained from patients included in KIMS (Pharmacia International Metabolic Database), a large pharmacoepidemiological survey of hypopituitary adults with GHD, for 6 months before GH treatment and for 6-12 months after the start of treatment. Assistance required with normal daily activities was recorded at baseline and after 12 months of GH therapy. Quality of life (QoL) (assessed using a disease-specific questionnaire, QoL-Assessment of GHD in Adults) and satisfaction with physical activity during leisure time were also assessed. For the total group (n = 304), visits to the doctor, number of days in hospital, and amount of sick leave decreased significantly ( $P < 0.05$ ) after 12 months of GH therapy. Patients also needed less assistance with daily activities, although this was significant ( $P < 0.01$ ) only for the men. QoL improved after 12 months of GH treatment ( $P < 0.001$ ), and both the amount of physical activity and the patients' satisfaction with their level of physical activity improved after 12 months ( $P < 0.001$ ). In conclusion, GH replacement therapy, in previously untreated adults with GHD, produces significant decreases in the use of healthcare resources, which are correlated with improvements in QoL. [Hernberg-Stahl E, Luger A, Abs R, Bengtsson BA, Feldt-Rasmussen U, Wilton P, Westberg B, Monson JP; KIMS International Board., KIMS Study Group. Pharmacia International Metabolic Database, "Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency," *J Clin Endocrinol Metab.* 2001 Nov;86(11):5277-81]

## II. Benefits and Side Effects of GH Therapeutics

The Editors of *Annals of Internal Medicine* state that "The researchers reviewed all clinical trials of GH to determine if it is safe and effective in the healthy elderly. They found that GH had no important effects on body composition but led to frequent adverse effects."

However, once again, the A4M submits that the Liu et al study neglected to include in its meta-analysis several key studies finding that GH therapy in adults is beneficial and tolerated without side effects, as follows:

*Research Centre for Endocrinology and Metabolism, University Hospital, Goteborg, Sweden, October 2001:* In this 1-center study, including 118 consecutive adults (70 men and 48 women; mean age, 49.3 yr; range, 22-74 yr) with adult-onset GH deficiency, the effects of 5 yr of GH replacement on body composition, bone mass, and metabolic indices were determined. The mean initial GH dose was 0.98 mg/d. The dose was gradually lowered, and after 5 yr the mean dose was 0.48 mg/d. The mean IGF-I SD score increased from -1.73 at baseline to 1.66 at study end. A sustained increase in lean body mass and a decrease in body fat were observed. The GH treatment increased total body bone mineral content as well as lumbar (L2-L4) and femur neck bone mineral contents. BMD in lumbar spine (L2-L4) and femur neck were increased and normalized at study end. Total cholesterol and low density lipoprotein cholesterol decreased, and high density lipoprotein cholesterol increased. At 5 yr, serum concentrations of triglycerides and hemoglobin A(1c) were reduced compared with baseline values. In conclusion, 5 yr of GH substitution in GH-deficient adults is safe and well tolerated. The effects on body composition, bone mass, and metabolic indices were sustained. The effects on body composition and low density lipoprotein cholesterol were seen after 1 yr, whereas the effects on bone mass, triglycerides, and hemoglobin A(1c) were first observed after years of treatment. [Gotherstrom G, Vensson J, Koranyi J, Alpsten M, Bosaeus I, Bengtsson B, Johannsson G, "A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices," *J Clin Endocrinol Metab.* 2001 Oct;86(10):4657-65]

*Department of Medical Sciences, University Hospital, Uppsala, Sweden, October 2001:* The safety and effects of a fixed low dose of growth hormone (GH), 0.17 mg/day was evaluated for 3 months, on glucose metabolism, serum lipids, body composition and cardiac function in 53 GH deficient adults aged 18-78 years. At 3 months, serum levels of insulin-like growth factor (IGF)-I, IGF binding protein (IGFBP)-3 and lipoprotein (a) and lean body mass were increased ( $P<0.05$ ). Total and low density lipoprotein cholesterol levels and fat mass were reduced ( $P<0.05$ ). There was an increase in the serum glucose value at 120 min after an oral glucose tolerance test performed at 3 months ( $P<0.05$ ), no other changes in glucose metabolism or in cardiac function were noted. Side-effects were few and mild. This fixed low-dose regime resulted in improvements in body composition and lipid profile, without causing serious side effects. This is therefore a valid method to institute GH replacement in adults. [Gillberg P, Brammert M, Thoren M, Werner S, Johannsson G, "Commencing growth hormone replacement in adults with a fixed low dose. Effects on serum lipoproteins, glucose metabolism, body composition, and cardiovascular function," *Growth Horm IGF Res.* 2001 Oct;11(5):273-81]

*Department of Diabetes & Endocrinology, Royal Liverpool University Hospital, UK, June 2001:* Dr. Ahmad and colleagues found that: "Low-dose GHR improves body composition and QoL as early as 1 month after commencement and the beneficial effects continue at 3 months. Most importantly, these changes occur in the absence of side-effects. We therefore suggest the use of low-dose GH therapy." [Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP.

Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. *Clin Endocrinol (Oxf)*. 2001 Jun;54(6):709-17.]

In the anti-aging clinical setting, adult GH replacement therapy employs doses of GH that are 1/3 of that used in the individual studies analyzed by Liu et al, which utilized doses at 1/3 to 1/2 that used in the pediatric setting for the treatment of dwarfism. The attenuated low-dose therapies have been proven effective in more than ten years of application by physician members of the A4M. The side effect profile does not apply to clinical treatment where low doses are used initially and doses are slowly ramped up and decreased if side effects occur. Significant side effects are rarely seen in clinical practice. Also, when the same total dose is divided daily over a week-long period (instead of administering 3 days a week) side effects are diminished or absent. If side effects do occur, it has been clinically demonstrated that they disappear with cessation of treatment. When the proper dosing customized to the anti-aging patient is reached, and coupled with regular laboratory testing and clinical examination, our member physicians are able to limit adverse effects of GH replacement therapy in adult patients.

It is the position of the A4M that the side effect profile of GH therapy is nominal when the dosage is properly determined and monitored by a qualified endocrinologist or anti-aging physician. Laboratory testing is essential to the safe and scientific application of anti-aging hormone replacement therapy. Safe optimization of essential hormone levels in the deficient and symptomatic patient is the goal of anti-aging endocrinology. This requires careful monitoring of bio-available hormone levels. This also requires establishment of baseline laboratory data and regular analysis on at least a semi-annual basis in order to achieve the safest and most effective hormonal balance at the lowest possible dose.

To deny the benefit of HGH and other essential hormonal regulators of metabolism in deficient patients based on age may be considered a heinous act of malpractice which will prove to be erroneous and short-sighted in the years to come, and may in fact lead to unnecessary morbidity in the form of diminished healthspans, as well as excess mortality in the form of reduced lifespans. In the future, the replacement of essential hormones that decline with age may be seen as important as insulin replacement in diabetics today.

The safety and clinical value of GH replacement in aging adults is proven to decrease weight and body fat mass; increase lean body mass; increase exercise capacity; increase muscle mass and strength; improve cardiac performance; improve bone density and decrease fracture rate; improve poor sleep; and improve an impaired sense of well being. As the master regulating hormone, HGH is a pacemaker for all the other rejuvenative (anti-aging) hormones such as estrogen, testosterone, DHEA, and melatonin, and as a result is an essential component of physiologic replacement therapy.

In conclusion, it is the position of the A4M that adult GH replacement therapy is safe and efficacious when administered judiciously by a qualified endocrinologist or anti-aging physician. Thousands of controlled research studies conducted over the course of the past fifteen years document the safety and efficacy of adult GH replacement therapy. HGH has an extensive history of rigorous scientific trials and practical clinical application. The American Association of Clinical Endocrinologists has stated that: "The usefulness of GH treatment in adults who have completed their statural growth is based on the roles of GH in: increasing bone density; increasing lean tissue; decreasing adipose tissue; bolstering cardiac contractility; improving mood and motivation; increasing exercise capacity." [AACE Guidelines for Growth Hormone Use, *Endocrine Practice* 4(3):165-173]. Many clinical studies have demonstrated the value of HGH replacement in healthy adults, associated with negligible side effects, when acquired from a reliable, safe, approved pharmaceutical supplier and administered judiciously by a qualified physician.