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The Growing of Growth Ho

By Carol Kahn

Studies and real-life stories from everyday people show that growth hormone replacement therapy can have a dramatic effect on regaining youthful vitality, increasing muscle mass, improving immune function, bettering learning and memory, and lowering blood pressure.

Carol Kahn is a longtime science writer and, with Dr. Ronald Klatz, co-author of the new book on growth hormone, "Grow Young With HGH."

On July 5, 1990, the New *England Journal* of *Medicine* published a clinical study on a drug that sent shock waves throughout the world. The drug-human growth hormone, HGH for short, or simply GH, a substance produced naturally by the pituitary gland-was hailed as a fountain of youth. Injections of synthetic human growth hormone had turned 12 men, ages 61 to 81, and with flabby, frail, fat-bulging bodies, into sleeker stronger, younger selves.

After just six months of treatment, the men gained an average of 8.8 percent in lean body mass, and lost an average of 14.4 percent in fat mass. In addition, their skin thickened by 7.1 percent, the bone density of their lumbar spines increased by 1.6 percent, their livers grew by 19 percent, and their spleens by 17 percent. In language rarely used in conservative medical journals, Daniel Rudman, M.D., and his colleagues at the Medical College of Wisconsin, wrote, "The effects of six months of human growth hormone on lean body mass and adipose-tissue mass were equivalent in magnitude to the changes incurred during 10 to 20 years of aging."

Rudman's study opened the floodgates to thousands of subsequent studies documenting the benefits of growth hormone therapy in GH-deficient adults. The National Institute on Aging is funding a five-year, multimillion-dollar study in nine medical centers to test whether human growth hormone and nutrition-related factors can retard or reverse aging. However, thousands of persons worldwide are not waiting for these results, but are injecting themselves with GH in the hopes of preventing or reversing the downward course of aging.

In addition. growth hormone received the Food and Drug Administration's imprimatur in 1996 for use in adults with GH deficiency due to pituitary or hypothalamic disease, injury, surgery or radiation therapy. This now allows doctors to prescribe growth hormone as an anti-aging treatment for adults with low levels of IGF-1, which indicates a failure of the pituitary gland to produce adequate amounts of growth hormone.

The most abundant hormone made by the pituitary gland is growth hormone. Pituitary cells, called somatotrophs, make growth hormone, which also is known as somatotrophin (from the Greek, turning towards the body). Fully 50 percent of the cells of the pituitary are somatotrophs.

Secretion in Brief Bursts

Growth hormone hits its peak when the body grows rapidly during adolescence: hence, the hormone's name. Most growth-hormone secretion occurs in brief bursts, or pulses, that take place during the early hours of the deepest sleep. Indeed, the old adage that you grow during your sleep appears to have a basis in fact.

The hormone lingers in the bloodstream for only a few minutes, but that is long enough to stimulate its uptake into the liver, where it is converted into growth factors. The most important of these is insulin-like growth factor 1 (IGF-1), also known as somatomedin C. IGF-1 is directly responsible for most of the positive benefits of growth hormone, although GH does exert some action on a local tissue level.

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Remarkable results from GH therapy ware experienced by this aging couple, left and below, who underwent treatment for six months. The results, right, show dramatic physical improvement.

Growth hormone declines with age in every animal species tested to date. In humans. the amount of growth hormone after age 21 to 31 falls about 14 percent per decade, so that total 24-hour growth hormone production is cut in half by the age of 60. In numerical values. we produce on a dally basis about 500 micrograms of GH at 20 years of age, 200 micrograms at 40 years, and 25 micrograms at 80. The fall in IGF-I with age mirrors that of growth hormone

Rudman considered a plasma IGF-1 level under 350 international units (IU) as evidence of deficiency. Between 20 and 40 years of age, less than 5 percent of healthy men have GH readings lower than 350 IU. But after age 60, 30 percent of apparently healthy men have this low amount of GH. And after age 65, about half the population is partially or wholly deficient in growth hormone.

We do not yet have the answer to why this happens. Studies have shown that the aging pituitary somatotroph cell can still release as much growth hormone as the young cell if it is adequately stimulated. This means that the fault must lie in the factors that regulate its release.

Some researchers believe the problem lies with somatostatin, the natural inhibitor of growth hormone. Somatostatin has been found to increase with age and may act to block the secretion of growth hormone. When researchers knocked out somatostatin action in old rats, they found GH pulses as large as those in young rats. Other researchers believe the precursor hormone, growth hormone-releasing hormone (GH-RH), which stimulates GH release, becomes less sensitive to feedback signals. The latest thmking is that, not only does the growth hormone that is available to tissues decline with age. but that our tissues become more resistant to the action of the growth hormone that is there. In this view, aging can be considered a dis-

ease of growth hormone resistance in the same way that Type II diabetes is a disease of insulin resistance.

The most recent research shows that whatever causes the decline of growth hormone, it is neither irreparable nor permanent. William Sonntag, professor of physiology, and his colleagues at Bowman Gray School of Medicine in Winston-Salem, NC, has just completed an experiment showing that the decline in growth hormone secretion with age is reversible. Old rats (like old people) have a decline in the bursts of growth hormone secreted. But when Sonntag took old rats (26 months) and restricted their caloric intake, growth hormone secretion came back after two months.

The Take-Home Message

The take-home message is that the decline of growth hormone with age can be reversed. Even if growth-hormone releasing hormone activity declines, or somatostatin increases, or receptors become less responsive to growth hormone, it can all be overcome by the administration of growth hormoe or growth-hormone releasers. Clinical trials now are being funded by major drug companies, such as Merck & Co. and Wyeth-Ayerst Laboratories, on oral drugs that stimulate the pituitary to release normal youthful levels of growth hormone.

Those who produce little or no growth hormone because they have pituitary tumors, other diseases, or have had their pituitary gland removed often seem like doddering old people. They consistently show mental and physical changes that are characteristics of aging, including a reduced sense of well-being, plus lower energy, vitality and capacity for work. In addition, they also exhibit mood swings, anxiety, depression and increased social isolation. Important physical signs are an increase in body fat, especially around the waist (apple-shaped rather than pear-shaped), a decrease in muscle mass, and thin, wrinkled, or prematurely damaged skin.

Bengt-Ake Bengtsson. M.D., and his colleagues at Salgrenska Hospital in Gothenburg, Sweden, studied 333 patients between 1956 and 1987 who were diagnosed with pituitary insufficiency. The patients were given pituitary-hormone replacement, including cortisone, thyroid hormones and sex hormones. The one hormone not replaced was GH. The GH-deficient patients died at twice the expected rate-107 deaths compared to 57 in the overall population, matched for age and sex. The primary cause of death was cardiovascular disease, which showed an almost two-fold increase (60 deaths vs. 31) over the general population.

Three pioneering studies in Sweden, Denmark and England found that four to six months of growth hormone replacement in adults who had low GH levels that was due to pituitary insufficiency had beneficial effects on body composition, cardiac function, exercise capacity, renal function and quality of life. Bengtsson went on to show that 12 to 18 months of GH therapy increased bone mineral density.

Some of the most striking effects were in quality of life. Before treatment, many of the patients said they were struggling with low self-esteem, anxiety and depression. But after a short tune on GH therapy, the difference was like night and day.

"We called it the Lazarus effect," he says. "We woke them up. With some patients, it was like giving them a kick in the back. Their lives changed within a few weeks."

Dr. L. Cass Terry's high-frequency, low-dose GH treatment is aimed at reducing side effects.

The treatment went on to change the lives of everyone who participated in the program, according to Dr. Lena Wiren, a psychologist who evaluated the patients. "Nobody wants to stop treatment," she says. "Sometimes it is not even the patient who notices the difference it is making. Rather it is their wives or children or friends at work."

Dramatic Improvement Seen

L. Cass Terry, M.D., Ph.D., has completed a preliminary study of patients treated with what he calls the high-frequency, low-dose (HF-LD) method. This is about one-quarter to one-half the weekly dosage used by Rudman, whose patients experienced side effects such as carpal tunnel syndrome and gynecomastia. The HF-LD regimen uses about 0.3 to 0.7 IU of GH twice daily.

According to the authors, it is well tolerated and there have been no adverse side effects. At the same time, the average somatomedin C (IGF-I) levels increased by 61 percent, from a mean of *238.8* to 384.5 after treatment. On self-assessment questionnaires from 202 patients, more than 75 percent of the respondents reported body-fat loss, muscle-mass gain, greater strength, exercise-tolerance and energy levels, and improved quality of life. A large majority also reported better skin texture, and greater skin thickness and elasticity.

Growth-hormone therapy may be effective in preventing or treating many common diseases and conditions of aging. In fact, it appears that hormone replacement, which includes growth hormone, may be one of the most effective methods of maintaining health and vigor for people in their 80s, 90s and beyond. Here are some of the areas in which growth hormone has already shown considerable benefit:

- *Immune* function. In 1985, Keith Kelley, M.D., a research immunologist at the University of Illinois at Urbana-Champaign, showed that injections of cells that secrete high amounts of growth hormone could regrow the shriveled thymus gland in old rats until it was as large and robust as in young rats. Kelley's work was confirmed by

Israel scientists who used bovine growth hormone to reverse thymus shrinkage in mice, and similar results have been demonstrated in dogs. Immune activities that growth hormone improves are the manufacture of new antibodies; increased production of T-cells and interleukin 2; greater proliferation and activity of lymphocytes; higher activity of natural killer cells; stimulation of macrophages; increased maturation of neutrophils; and increased production of red blood cells.

*** Cardiac** *function*. GH therapy improves cardiac function and protects against cardiovascular disease in a number of ways. It reduces body fat, particularly in the abdominal region, which has been shown to be highly correlated with increased risk of heart attack. Growth hormone also improves blood cholesterol profiles, raising high-density lipoproteins (HDL) and lowering low-density lipoproteins (LDL), and reduces diastolic blood pressure by about 10 percent, without affecting systolic pressure.

Treatment with growth hormone has reversed heart failure. In a 1996 study in *the New England Journal of Medicine,* growth hormone given to seven patients-five men and two women with moderate-to-severe heart failure-increased the thickness of the left ventricular wall, enhanced the ability of the heart to contract and pump blood, reduced the oxygen requirement of the heart, improved exercise capacity and enhanced quality of life.

* Lung Function. Human growth hormone injections have improved heart-lung function by increasing the ability of patients to exercise, raising their maximum oxygen uptake, and increasing then stroke volume and cardiac output. David Clemmons, chief of endocrinology at the University of North Carolina School of Medicine in Chapel Hill, found that three weeks of GH injections in patients in the latter stages of chronic obstructive pulmonary disease raised maximum inspiratory force by 10 to 12 mm on average, and increased maximum expiratory force.

"If you were as impaired as these patients, going from 25 mm to 38 nun would be quite a help," says Clemmons, who believes that growth hormone is a promising treatment for emphysema and other forms of chronic obstructive pulmonary diseases.

* Osteoporosis. While GH therapy is used to grow the skeletal bones of children who are deficient in the hormone, results in adults have been inconsistent. Rudman found that six months of GH treatment increased the density of the lumbar vertebrae by 1.6 percent in men over 65, but there was no increase in the bone density of the radius bone in the arm or the femur of the leg. Several groups have reported an increase in bone mineral content.

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Improved Bone Density

Recently, Swedish scientists led by Gudmundur Johannson, M.D., studied 44 men and women between 23 and 66 who were severely deficient in growth hormone. Two years of growth hormone therapy caused significant increases in the density of the bones that form the hip joint and the vertebrae of the lower spine. The studies also showed an increase in calcium, a calcium-binding bone protein called osteocalcin, *as well* as two types of collagen, which are markers of bone formation. The researchers estimate that they have reduced the possibility of fracture so that it now equals that of normal healthy controls.

- *Brain function*. **Growth** hormone raises energy levels, improves slow-wave sleep, and elevates mood. In a startling report, Johannsson's team found that growth hormone actually changed the levels of certain neurotransmitters in the human brain, raising the level of B-endorphin, which has been called the brain's own opiate, and lowering the level of dopamine, which is associated with feelings of agitation. This is similar to the concentrations of these neurotransmitters one sees in antidepressants, says Bengtsson, who was part of the research team.

In other reports, GH appears to reduce stress, improve focus and concentration, and build self-esteem and self-confidence. Growth hormone can reverse decline in memory and cognitive performance. In a study of adult male patients deficient in GH, Dutch researchers headed by Jan Berend Deijem, M.D., found that GH deficiency is associated with impairments in iconic memory (the ability to process flashes of information), short-term memory, long-term memory, and perceptual-motor skills such as hand-eye coordination. Interestingly, the lower the levels of IGF-I, the lower the patient's IQ and education level.

Growth hormone, IGF-1, and nerve-growth factors in the brain show promise in the treatment of neurodegenerative disease and injury. IGF-1, which is also available in recombinant drug form, has been shown to repair and reconnect severed nerve endings of up to 6 mm, a feat previously unheard of, and has increased motor neuron activity in spinal cord cultures. Some of the diseases for which IGF-I may be useful are amyotrophic lateral sclerosis (Lou Gehrig's disease), and peripheral neuropathies and muscle-atrophy problems such as Charcot-Mane-Tooth disease. It also may allow more aggressive chemotherapy for certain cancers, since drugs like vincristine and cisplatin can cause peripheral neuropathies at high doses.

Growth hormone normalizes the impaired motor activity of dwarfed mice, suggesting that it may be of value in treating Parkinson's patients. It also helps motor activity by stimulating the growth of the myelin sheath on neurons, making it a potential treatment for multiple sclerosis. In Alzheimer's disease,

there is a loss in a number of neurotransmitters.. especially acetylchohne and noradrenaline, which stimulate growth hormone. Belgian physician Thierry Hertoghe is treating several Alzheimer's patients with multihormone replacement, including growth hormone. Other benefits of GH therapy for the brain include restoration of slow wave sleep, a particular problem among the elderly. There also have been anecdotal reports of improved vision, both near and far in daytime as well as nighttime.

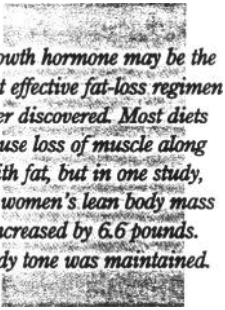
- *Sexual function.* The decline of male potency parallels the decline of growth hormone release in the body, with GH levels and sexual potency at their peak during puberty and already decreasing in young manhood, until, by age of 80, 75 percent of men are incapable of getting or sustaining erections.

Although there have been no clinical studies looking at the effects of growth hormone on sexual function, people who are growth-hormone deficient due to pituitary disease have decreased libido and sexual function. After treatment with GH replacement, they experience increased sexual drive and function, according to their responses on the Nottingham Health Profile.

Terry, in a study of 202 aging adults, found that 75 percent of the men reported improvement in sexual potency and frequency, and 62 percent had longer-lasting erections. In fact, in interviews with people who have used GH for anti-aging purposes, almost everyone, male and female, reports improvements in libido and sexual function. A typical case is that of a 63-year-old divorced doctor who hadn't had sexual relations with a woman in five years and was no longer interested in sex. After four weeks on GH, he felt a surge of sexual energy He started dating again and now has sex an average of twice a week.

* Obesity and body composition. Growth hormone does something no other weight-loss regimen does: It recontours the body melting away fat and building muscle. In many cases, people look like they've shed years away along with the fat they've lost. Even better the greatest loss occurs in deep belly fat-the area associated with increased risk of heart attack. In every study of growth hormone's effects on "normal" people who are aging, GH reduced body fat and increased lean body mass. In a six-month placebo-controlled trial at Thomas Hospital in London of 24 adults with GH deficiency, the hormone-treated group had no net change in weight, but lost an average of 12.5 pounds of fat and gained an average of 12.1 pounds of lean body mass.

Growth hormone may be the most effective fat-loss regimen ever discovered. In a double-blind, placebo-controlled, crossover study on overweight women, GH caused an average loss of more than 4.6 pounds of body fat, mostly in the abdomen. Most diets cause loss of muscle along with fat, but in this study, the women's lean body mass increased by 6.6 pounds. In two double-blind, placebo-controlled studies by David Clemmons, M.D., at the University of North Carolina in Chapel Hill, growth hormone and dieting caused a 25-percent acceleration in the rate of fat loss, above and beyond the effect of dieting alone. In the 11-week treatment period, the GH-treated subjects lost 30 to 32 pounds, compared with 20 to 25 pounds in the controls. And, while the controls lost muscle along with their fat, the treated group maintained their body tone.



Loss of abdominal fat also has implications for Type II diabetes, since there is a close association between central obesity and insulin resistance. While some early studies showed increased blood sugar and insulin resistance in GH-treated subjects, later studies showed that after six months of treatment, insulin sensitivity returned to baseline. While proof is still lacking, it is reasonable to assume that, over the long run, stimulation of growth hormone could help to prevent Type II diabetes or even reverse the disease process.

A question remains: Can human growth hormone extend life span?

In 1990, two scientists at North Dakota State University, David Khansari and Thomas Gustad, attempted to answer this question. They gave growth hormone injections to 26 mice that were more than three-quarters through their life span, while another 26 mice received placebo injections of saline solution. After 13 weeks, 16 animals, or 61 percent of the controls, had died, while all but two, or 97 percent, of the growth-hormone treated animals were still alive. In other words, the vast majority of the treated animals had already lived longer than the average lifespan for that species.

The results, said the researchers, "suggest that long-term GH therapy prolongs the average life expectancy of the hormone-treated mice significantly."

Unfortunately, the researchers did not have enough growth hormone to determine what the maximum life span of the treated animals would have been. There are indications that the animals might have lived far longer. The most consistent extension of life span comes from experiments in which animals have their food intake restricted. In well-conducted experiments, animals on calorie-restricted diets have lived to ages that would be comparable to 150 in humans!

Determining Maximum Lifespan

Could growth hormone be a significant factor in these animals' ability to defy death? The Bowman Gray School of Medicine's Dr. Sonntag has examined what happens to growth hormone and IGF-1 secretion in animals that are diet-restricted. Normally when we age, the amount of growth hormone and IGF-1 decreases along with protein synthesis in cells and tissues. But Sonntag and his associates found just the opposite in the

diet-restricted animals. Young rats on a moderate food-restricted diet actually had their growth-hormone secretion go down, but by the time they reached 26 months - old age for a rat - their growth hormone pulses were the same as that of a young control rat.

"What we have tried to relate that to is that the calorically restricted animals at that age have a higher capacity to synthesize protein in their tissues," say Sonntag. While the rates of protein synthesis went down in old control rats, the aged restricted rats had a 70-percent increase of new protein in the heart and a 30-percent increase in the diaphragm, compared with unrestricted animals. Interestingly, the level of IGF-1 did not rise, but the number of receptors in the cells for IGF-1 increased by 60 to 100 percent.

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