

Restoring Ebbing Hormones May Slow Aging

Researchers hope supplements may have rejuvenating effects.

By JANE E. BRODY

Why do some people in their 80's look, act and feel vigorous and energetic while others need help just to get through the chores of daily living? A good part of the answer may lie in their hormones. If studies now under way bear out their initial promise, hormone treatments for people over 60 may help to turn back the clock and, though without extending life, greatly enhance its quality.

Researchers are exploring the rejuvenating effects of several hormones that are known to undergo rather striking declines with age. These include, but go beyond, replacing estrogen, which declines sharply in women after menopause. The safety of estrogen replacement, particularly with regard to the risk of breast cancer, is hotly debated and raises a cautionary note about the wisdom of replacing other hormones that fall with age.

A major focus of the new research is growth hormone, a product of the pituitary gland that gradually declines with age and until recently was not thought important to older people. Researchers are considering replacing testosterone loss in older men. There is also keen interest in a hormone of the adrenal cortex called DHEA or dihydroepiandrosterone, which is said to enhance immune function and life span in rats.

Whether or not nature has some hidden agenda for the ebbing of these various hormones with age, for example in slowing people down as the life span wanes, it is now recognized that as people live to their 80's and beyond, the effect of declining hormones may contribute significantly to chronic, debilitating and costly illnesses.

"For every major hormone system that's been studied, we find age-related changes that suggest they could have meaning to the aging process," said Dr. Marc R. Blackman, chief of endocrinology at the Johns Hopkins Bayview Medical Center in Baltimore. Among the well-known attributes of aging that hormone loss may bring about are the loss of muscle mass and strength, an increase of body fat, particularly fat around the abdomen; a weakening of the bones; a decline in immune responses and a general loss of energy.

While no one expects to turn a frail 80-year-old into an iron man, the hormonal effects under study could help to save old people from some of the burden of illness and to preserve their independence. More than seven million Americans now need long-term care costing tens of billions of dollars a year because they are no longer able to perform daily activities without help. Without an antidote for age-associated disabilities, by the year 2030 nearly 14 million people will need such care.

Several years ago, the National Institute on Aging in Bethesda, Md., made

The Fountain, Not of Youth, but Possibly of a Longer Prime

Some hormones that decline sharply with age are being studied for clues to aging and how to counter it. Some researchers wonder if replacing these hormones might help ward off diseases as more and more people live into their 80's and beyond. Another approach might use molecules to stimulate the aging body to increase its own output of pituitary hormones.

Where Some Hormones Come From ...

Main sources: many hormones have multiple origins as well as complex effects and feedback systems

GROWTH HORMONE RELEASING HORMONE (GHRH)
Hypothalamus



IGF-1 (an insulin-like growth factor)
The liver

DHEA (dihydroepiandrosterone)
Cortex of adrenal glands above kidneys

ESTROGEN
Ovaries before menopause in women

TESTOSTERONE
Sex glands

... and What They Might Affect.

For men and women unless otherwise noted.

GROWTH HORMONE RELEASING HORMONE Triggers release of **GROWTH HORMONE**, which in turn influences things like muscle mass and strength, bone strength, cholesterol metabolism, body fat and psychological well-being.

IGF-1 (in animals)
Can stimulate production of immune cells by the thymus, which normally shrinks with age.

DHEA May benefit the heart and immune function, improve sleep and mobility and lessen joint pain.

ESTROGEN Helps protect against heart disease and osteoporosis. A possible link to breast cancer is still under study.

TESTOSTERONE Replacement may improve men's muscle mass and strength, bone density, sense of well-being, cognitive function and balance.

available some \$2 million for exploring hormone replacement in people 60 and older. Nine research teams are now midway through their studies, which focus on growth hormone and other "trophic factors," substances that promote growth or maintenance of tissues. "Trophic factors may not be the 'fountain of youth,' as some have suggested, but they may have promise for halting or reversing degenerative changes in bones, muscles, nerves and cartilage, which lead to 'frailty,'" said Dr. Stanley Slater, deputy associate director for geriatrics at the institute. Some form of growth hormone therapy,

A decline in hormones may contribute to debilitating illnesses.

If its early promise is sustained, might help people "stay stronger, leaner and more mobile" in their later years, he said.

But it would be wrong to make too much of these early findings, researchers caution. Dr. David Clemmons, an endocrinologist who studies growth hormone at the University of North Carolina in Chapel Hill, said: "Just because you make a person's hormone profile more youthful does not mean you will arrest or reverse aging. You'll still have wrinkles and gray hair."

Growth hormone, along with the special factors that trigger its release or carry out its effects on the tissues, are the stars of current anti-aging studies. The hormone was once thought to be important in making the body reach its final stature, though of no great consequence afterward. But several impor-

Source: "Hormones: From Molecules to Disease," E. E. Baukhu and P. A. Kelly (Hermann Publishers/Chapman & Hall)

Charles M. Blow/The New York Times

Restoring Hormones May Help Slow Aging

Continued From Page B5

tant studies have showed this is not the whole picture.

European researchers, following up patients who had lost their pituitary glands, found that when growth hormone was added as well other pituitary hormones, there was a much greater improvement in muscle, bone and psychological well-being. The hormone also promoted a healthful loss of body fat, especially belly fat, which raises the risk of heart disease.

In this country, a team led by the late Dr. Daniel Rudman at the Medical College of Wisconsin in Milwaukee gave growth hormone three times a week to 12 healthy men aged 61 to 81 for six months. They found that the men gained muscle, lost fat and developed thicker skin, while a comparison group did not.

The interest in growth hormone picked up significantly after advances in genetic engineering made it possible to synthesize the hormone in bacteria. Until then it had to be extracted from the pituitary glands of cadavers and was in very short supply. As a result of recent studies, much has been learned about the physiology of this potent natural messenger.

"A gradual but inexorable decline in growth hormone release starts in one's 30's and 40's and by the time people reach 70 and beyond, two-thirds to three-fourths of them have experienced a substantial decline in growth hormone," Dr. Blackman said.

Many factors contribute to this loss, including changes in sleep pat-

Growth hormone therapy may help people stay stronger and leaner.

terns with age, he explained. Growth hormone is secreted in pulses predominantly during the evening hours and especially during the phase of sleep known as slow-wave, or deep, sleep. This is just the phase that becomes truncated with age and can also be disrupted by medications and illness.

Another contributing factor is the tendency for older people to become sedentary, he said. Physical activity, particularly aerobic exercise, sets off the release of growth hormone in people of all ages and, Dr. Blackman said, "sedentary people who become physically active frequently have bursts of growth hormone release." In fact, it may be no coincidence that the known benefits of physical exercise mimic those now observed for growth hormone.

But what might such changes mean to overall well-being? Will supplements of growth hormone and other factors lead to greater independence, fewer fractures and heart attacks and more of a zest for life? And can the hormone treatments be administered in a way that is safe, convenient and cost-effective? These are some of the questions the National Institute on Aging is addressing.

In one of its nine projects, at the Johns Hopkins Bayview Medical Center, Dr. Blackman, Dr. Mitchell Hartman and their colleagues are

treating men and women over 65 with one of four regimens for six months: growth hormone alone, growth hormone plus the appropriate sex hormone (testosterone for men, estrogen for women) and an inactive dummy medication.

In another project, Dr. Mark L. Hartman and colleagues at the University of Virginia Health Sciences Center in Charlottesville are looking into the interactive effects in people over 60 of a year of growth hormone treatment with and without aerobic exercise or strength training. Perhaps most telling, Dr. Hartman said, will be the effects on everyday function, like how well the participants climb stairs, walk at a normal pace and maintain their balance.

At the University of Washington in Seattle, Dr. Robert S. Schwartz, Dr. George Merriam and their colleagues are looking at growth hormone releasing hormone, or G.H.R.H., the brain chemical that prompts the pituitary gland to release growth hormone into the bloodstream.

"Our preliminary findings include significant changes in body composition — a decrease in body fat and increase in lean body mass due to the hormone and in some cases to exercise — and a complete absence of side effects," Dr. Merriam said.

Treating a person with the brain's releasing factor for growth hormone instead of with growth hormone itself, he explained, should better mimic the body's natural pulsed output of the hormone and diminish possible side effects, like swelling of tissues and aggravation of diabetes and congestive heart failure. "We're still learning how to give growth hormone to older adults," Dr. Hartman said. "The original dose, based on body weight, turned out to be too high."

Other researchers are looking at the effects of the sex steroids testosterone and estrogen in older people. Dr. Peter J. Snyder of the University of Pennsylvania School of Medicine explained that although men did not experience the precipitous decline in sex hormones that women did at menopause, "by age 80, healthy men have roughly one-half to one-third the amount of free testosterone they had at age 20."

In a study of 100 normal, healthy men over 65, he and his colleagues are testing the effects of skin patches that raise the blood level of free testosterone to that of men in their 30's and 40's. After three years of treatment with either a testosterone or a placebo patch, the researchers will look for hormone-related improvements in muscle mass and strength, bone calcium and sense of well-being.

A different and more mysterious hormone, the DHEA produced by the cortex of the adrenal gland, is being studied by Dr. Samuel S. Yen at the University of California in San Diego. Production of DHEA starts at about age of 7 and peaks between the ages of 25 and 30. It then slowly declines to 10 to 15 percent of peak levels by the age of 70.

In a small study of 16 middle-aged to elderly people who received either DHEA or a placebo for one year, Dr. Yen said there was a 75 percent increase in overall well-being among those receiving the hormone. He reported at a conference held in Washington last month that his subjects coped better with stress, got around more easily and slept better. Men, but not women, also gained muscle and bone and lost body fat, although



Dr. Marc R. Blackman, chief of endocrinology at the Johns Hopkins Bayview Medical Center, studies age-related hormone changes.

neither reported any change in libido.

Dr. Blackman said that other research had pointed to important effects of DHEA on cardiovascular function and the risk of heart disease, especially among men, and on immune function, which normally declines significantly with age.

One of the messengers of growth hormone, too, may have important immunological benefits. Dr. Ross Clark, an endocrinologist, and Dr. Paula Jardieu, an immunologist, at Genentech Inc. in San Francisco, are finding that an insulin-like growth factor called I.G.F.-1, produced in the liver and elsewhere, can stimulate production of both B cells and T cells, which are vital to producing antibodies to infectious organisms and to fighting off cancers.

In animal studies, Dr. Clark found, "the thymus gland, which shrinks to one-half to one-quarter of its youthful size with age, can be made to bloom again by I.G.F.-1." The thymus is a major source in the production of immune cells.

There are, to be sure, a few nay-sayers among hormone cognoscenti about stoking the healthy elderly with hormones. For example, Dr. Clemmons of the University of North Carolina believes the most effective use of growth hormone therapy will be on a short-term basis to speed recovery in elderly people who have sustained injuries or suffered illnesses that result in a prolonged convalescence. He pointed out that like all drugs, hormone treatments had side effects, and the risks would be more acceptable in people who have a lot to gain.

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FILE Growth Hormone

GROWTH HORMONE TO REVERSE AGING
to appear in the June 1995 edition of Alternative Medicine

By Elmer M. Cranton, M.D. and James P. Frackelton, M.D.

Hormones are tiny chemical messengers continuously secreted into the blood stream by endocrine glands to regulate the activities of vital organs. The word, hormone, is derived from a Greek word meaning "to stimulate." Hormones stimulate a multitude of life-giving processes throughout the body which maintain health, harmony, growth, healing and repair.

Probably the best known hormone is insulin, produced in the pancreas. When production declines or ceases, diabetes results. Scientists long ago discovered a way to duplicate insulin and administer periodic injections to control the symptoms of diabetes. The discovery of insulin and the process of injecting man-made insulin made control of diabetes possible.

Growth hormone, secreted by the pituitary gland, is a small protein-like hormone (peptide), similar to insulin. Commonly referred to as human growth hormone or "hGH", it is difficult to measure directly. HGH is secreted in very brief pulses during the early hours of sleep and remains in the circulation for only a few minutes. It is quickly taken into the liver and converted into somatomedin-C, another small peptide hormone (also known as insulin-like growth factor-one or IGF-1). Somatomedin-C is then responsible for most of the activity of growth hormone in the body. Somatomedin-C levels in the blood are much more stable and can be measured in the laboratory.

During adolescence, when growth is most rapid, production of hGH is very high. That is why it was named "growth hormone." Even after growth stops, growth hormone must continue to be present (at somewhat lower levels) throughout life to maintain physical and mental health and well-being. Tissue repair, healing, cell replacement, organ integrity, bone strength, brain function, enzyme production, integrity of hair, nails, and skin all require the ongoing availability of adequate growth hormone. After age 20, growth hormone production falls progressively at an average rate of about 14% per decade. By age 60, it is not uncommon to measure a growth hormone loss of 75% or more. Physical decline with age correlates directly with decreased secretion of growth hormone by the pituitary gland.

Children who develop a pituitary deficiency of growth hormone at a young age will never grow normally and are destined to become dwarfs in adulthood if untreated. Growth hormone therapy was initially developed to treat such children so they could grow to become normal adults. Initially, supplies were very limited, expensive and sometimes contaminated. There was not enough growth hormone available to treat all the children who needed it. With the development of recombinant DNA technology, human growth hormone has recently become more available and in very pure form - but it is still

expensive. The increasing availability of growth hormone now provides a new dimension in health care.

Approximately every three years 90% of the cells in the human body are made anew. The body is composed of more than 100 trillion cells which are continuously dying and being replaced. Only in the brain and nervous system are the original cells (neurons) retained but proteins are continuously being made in the brain to store memories of each new experience. Learning, memory and intelligence all depend on adequate growth hormone. As growth hormone falls with age, functions of all vital organs decrease.

Human growth hormone replacement therapy is now available to reverse and slow the age-related symptoms of physical and mental decline. By measuring blood levels of growth hormone (somatomedin-C) in older adults, and also in younger who are not doing well despite other therapies, a new advance in health care and preventive medicine is now available. If somatomedin-C is at a normal level for a healthy young adult, the use of supplemental growth hormone is not warranted. If, however, growth hormone is low, then supplementation can offer the potential for great benefit.

Benefits from growth hormone replacement which are reported in the scientific literature include increased muscle mass, improved physical strength, reduced fatigue, decreased fat (especially abdominal fat), increased bone strength, and revitalization of liver, kidney, spleen, and brain functions. Skin regains a more youthful appearance with fewer wrinkles and sexual functioning improves. Cholesterol decreases, cartilage in joints becomes stronger, and osteoporosis and Alzheimer's disease are improved. A markedly improved quality of life has also resulted for AIDS patients receiving growth hormone.

Like insulin, growth hormone is given by injection. A small syringe with a tiny 27-gauge needle is used to give self-administered injections just under the skin, usually on 4 days each week. Benefits come on slowly during the first few months of therapy. The following statements were made by people who benefited from this therapy.

H.T., a 62 year-old businessman, has been giving himself daily injections of growth hormone for the past 3 years. In his own words, "My energy, stamina and sex drive are like a 30 year-old. Muscle tone is fantastically improved. My waist went from 42 inches to 34 and I went from 28 percent fat to 12 percent. I look in the mirror in the morning and can't believe that guy is me - it looks like me when I was 30. The palsy in my hand is gone, I discarded my bifocal glasses and my skin went from tissue-thin to youthful."

J.H., a 40 year old businesswoman, suffered for many years with chronic fatigue and constant pain in her jaw and head from degeneration in the temporal-mandibular joints (TMJ syndrome). After taking daily growth hormone injections, she states, "I was a 40 year old woman in a 60 year old body. On growth hormone therapy my TMJ pain is gone, completely, my energy and stamina are increased, fat is decreased, and I feel much more alive, blossoming inside, almost euphoric."

Dr. Daniel Rudman conducted a scientific research project at the Medical College of Wisconsin in 1991 giving growth hormone injections to elderly men. The results of the study were published in the *New England Journal of Medicine*. Dr. Rudman stated in an interview, "We reversed 10 to 20 years of the aging process...fat diminished, muscle tissue increased."

Another important benefit from growth hormone replacement is strengthening of the immune system. Infections decrease, recovery from illness is aided, allergies improve and immune related diseases such as arthritis become less bothersome. The immune system is an important defense against cancer and it seems logical that cancer might, to some extent, be prevented by growth hormone. Although it has been speculated that growth hormone might speed the spread of cancer, that has not been seen in clinical practice. In fact, improved immunity might logically be expected to reduce the risk of malignancy and speed healing from a treated cancer.

Side-effects reported in medical research were mostly associated with very large doses. Research doses of growth hormone were as much as eight times the amount normally produced by the pituitary gland. Such overdosage caused carpal tunnel syndrome, decreased glucose tolerance (increased tendency to diabetes), breast enlargement (even in males), and fluid retention.

As tissue repair, healing and cell replacement are speeded up by growth hormone replacement, the need for nutrients of all types increases. Protein intake must be adequate to build new tissues. Vitamins, minerals and trace elements are all utilized in higher amounts, as the metabolic rate increases. If the body is deficient or borderline in essential nutrients, an increase in cell growth can aggravate or create deficiencies. For that reason, it is wise to seek out a physician skilled in clinical nutrition and preventive medicine to obtain growth hormone therapy.

If a person is deficient in an essential micronutrient, such as vitamin B-6, it is no surprise that growth hormone can, in some cases, cause carpal tunnel syndrome, which is related to B-6 deficiency. Side effects can thus be caused by the poor nutritional status of patients.

Low-dose growth hormone therapy (4 to 8 units per week) is now known to be clinically effective and free of significant side effects. Side effects which do occur, such as mild fluid retention, usually pass within a few weeks as the body readjusts to a younger metabolic rate.

Longevity and health are extremely complicated goals with many contributing or detracting factors such as heredity, stress, nutrition, antioxidants, life-style, harmful habits, tobacco, excessive alcohol, and exposure to chemicals and environmental pollution - in addition to the usual decline in hormone production with age. Standard "health care" is largely oriented toward drug or surgical attacks against disease, which is a negative approach which usually does not include nutritional and hormonal support or removal of

toxins in order to stimulate natural healing and repair. Growth hormone supports health and healing and mediates cell repair.

A sound program of growth hormone therapy should be built on a foundation of clinical nutrition, vitamin, mineral and trace element supplementation, chelation therapy, assessment and replacement of other deficient hormones (thyroid, DHEA, etc.) and free-radical antioxidants for optimum results.

The present cost of approximately \$13,000 per year remains expensive for many people and medical insurance will only reimburse for treatment of dwarfism in children. Hopefully the cost will come down in the future as generic products become available and as usage increases.

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GROWTH HORMONE REPLACEMENT THERAPY IN ADULTS

Though less true than in the past, frailty and age seem to go together. Must that continue to be the case?

The United States National Institute on Aging is funding studies to confirm earlier findings that human growth hormone (HGH) and other hormones, including DHEA (an adrenal hormone) and sex hormones, can slow, stop, and/or possibly reverse the changes associated with aging.

The levels of a variety of hormones drop substantially with age. Hormones are protein messengers that tell the cells what to do (such as protein synthesis and cell replication and repair). One of the hormones that declines sharply is human growth hormone. Human growth hormone (HGH) is a hormone synthesized by the pituitary gland in the human brain. It is responsible for the physical growth in childhood and puberty periods. The circulating levels fall by more than 50 percent from the peak during puberty and reaches "older" levels by age 33 to 40.

Research in human growth hormone (HGH) in healthy human subjects prior to the 1980s was restricted due to scientists inability to synthesize the complex molecule, made up of 191 amino acids. However, scientific DNA recombinant technological break-throughs in the early 1980s finally gave scientists the ability to synthesize the human growth hormone in large quantities. The human growth hormone molecule, so synthesized by the DNA-recombinant technique, is identical to the one produced by the pituitary gland in the human brain. This led the Federal Food and Drug Administration (FDA) to promptly approve growth hormone for human consumption and experimentation in healthy individuals in the late-1980s.

One of the scientists who jumped into human growth hormone research was Daniel Rudman, M.D. at the Medical College of Wisconsin in Milwaukee. For many years, Dr. Rudman had asked the world these questions: "Do hormone levels control the aging process? If they do, then does replacing the hormone levels to the youthful range in humans reverse the effects of aging?" Up until the 1980s, no scientist in the world could give him an answer, especially with human growth hormone (which drops the most drastically), because human growth hormone research could not be done on healthy individuals due to the lack of FDA approval in this country.

Once this hormone became FDA approved, Dr. Rudman and his colleagues promptly entered into a double blind study using twelve healthy elderly men, ages 61 to 81, from a nearby Veterans Administration Hospital. These volunteer subjects were given human growth hormone three times a week for six months to restore the circulating insulin growth factor (IGF) levels to the youthful range—above 350µg/ml. IGF is a protein synthesized mostly by the liver, and its level is regulated by the measurement of the circulating levels of growth hormone, since the secretion of growth hormone in the human brain is in a pulsatile fashion and is difficult to measure accurately during any period.

When compared with the controlled subjects who received the placebo, the growth hormone treated subjects showed changes that were "equivalent in magnitude to the changes incurred during 10 to 20 years of aging. He reported his discovery and was promptly published in the prestigious *New England Journal of Medicine*, July 1990.

Following his landmark discovery, scientists from all over the world commenced research on replacing growth hormone in elder persons. The results were astonishing. Additional beneficial findings were discovered. Growth hormone was shown to increase bone mass in osteoporosis, to reverse declining cardiac function, to reverse declining pulmonary function, to reverse the decline in immune function associated with aging, increase lean muscle mass, decrease the percentage of body fat, increase capacity for exercise, hence, vitality, prevent illness, and reduce sleeping disorders. The Scandinavian scientists even eliminated the minor side effects seen in the Rudman Study—namely problems associated with the water retention effects of the growth hormone. By changing Rudman's three times weekly method of injecting growth hormone to twice daily injection of smaller doses of growth hormone, the water retention side effect from growth hormone (though reversible) were completely eliminated. Between the years of 1990 and 1992, hundreds of scientific studies were conducted on growth hormone's effect on age-associated changes in the human body. The findings concluded that growth hormone replacement therapy can be safe with proper doses and proper methods of administration. That is good news for advanced aged men and women with medical problems related to aging and growth deficiencies who want to reverse the effects of aging.

After examining the various studies that show growth hormones ability to reverse changes associated with aging, the Stanford University Medical Researchers concluded in 1992 that "It is possible that physiologic growth hormone replacement therapy might REVERSE or prevent some of the 'inevitable' sequelae of aging," (Psychoneuro-endocrinology, Volume 17, No. 4, Pages 327-333, 1992).

Unfortunately, growth hormone has received many "bad raps" lately in many lay journals because of its abuse by athletes for its performance-enhancing effects. These athletes abused growth hormone in large doses which led to a condition called acromegaly—the overgrowth of many bodily parts. When one compares growth hormone to insulin hormone, the growth hormone is much more forgiving, as an overdose of insulin hormone can cause instant DEATH!

Medical research is often trapped in a paradox. For example, fetal tissue research for the treatment of Parkinson's Disease, in vitro fertilization for infertile couples, and the use of growth hormone for reversing aging are all examples of science working to improve lives. But these scientific endeavors are often criticized by skeptics who believe we are treading into uncharted intellectual and moral areas where humankind is not intended to go. Still, it seems imprudent to limit growth hormone research and replacement therapy simply because a few skeptics disagree or because of abuse by a few athletes.

Drs. Rowen, Johannson, and Bengtson of the University Hospital of Goteborg, Sweden, had this to say, "When one does not abuse or overdose human growth hormone, there is simply NO evidence suggesting that human growth hormone replacement therapy causes ANY LONG TERM side effects." (Hormone Research, 43, Pages 93-99, 1995).

Dr. Eve VanCauter, a human growth hormone researcher at the University of Chicago Medical Center, has this perspective on human growth hormone replacement therapy for elderly people. "All of these ideas about treating people with growth hormone have been directed toward people 65 and older. If you look at the data, people have so-called 'elderly' levels by age 40. Perhaps we should be giving human growth hormone replacement therapy earlier rather than attempting to treat tissues that have seen little or no growth hormone for decades." (Personal communication to David L. Lewin, 1995).

Impaired Growth Hormone Secretion in the Adult Population

RELATION TO AGE AND ADIPOSITY

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ABSTRACT Growth hormone (GH) release was studied in adults of normal stature, ages 21-86 yr. The subjects were 85-115% of ideal body weight, between the 5th and 95th percentiles in height, and free of active or progressive disease. 9 to 12 individuals in each decade from third to ninth were evaluated. The following criteria of GH status were measured: serum GH concentration, analyzed by radioimmunoassay at half-hour intervals for 4 h after onset of sleep, and at 1-h intervals from 8 a.m. to 4 p.m. in 52 subjects; daily retention of N, P, and K in response to 0.168 U human (h)GH/kg body wt^{2/3}/day in 18 subjects; and plasma somatomedin C (SmC) level before and during exogenous hGH treatment in 18 subjects.

All 10 individuals, 20-29 yr old, released substantial amounts of endogenous GH during both day and night (average peak serum GH obtained during day and night was 7.3 and 20.3 ng/ml, respectively); average plasma SmC was 1.43 U/ml (95% tolerance limits, 0.64-2.22 U/ml). There was no significant effect of exogenous hGH on elemental balances or on plasma SmC. In contrast, 6 of 12 individuals 60-79 yr old showed the following evidences of impaired GH release: peak waking and sleeping serum GH < 4 ng/ml; plasma SmC < 0.38 U/ml; a significant retention in N, P, and K; and a significant rise in plasma SmC, in response to exogenous hGH.

Plasma SmC, serum GH during sleep, serum GH during the day, retentions of N, P, and K in response to exogenous hGH, and rise in plasma SmC in response to hGH were all intercorrelated ($P < 0.05$). Plasma SmC < 0.38 U/ml corresponded to peak nocturnal serum GH < 4 ng/ml. The prevalence of plasma SmC < 0.38 U/ml

increased progressively from age 20 to 90: third decade, 0%; fourth, 11%; fifth, 20%; sixth, 22%; seventh, 42%; eighth, 55%; and ninth, 55%. Within each decade, plasma SmC was inversely related to adiposity.

INTRODUCTION

In children and adolescents, serum growth hormone (GH) levels rise to peak values of 20-50 ng/ml during the first 4 h of sleep (1-3). In adulthood, the nocturnal peaks of serum GH are less pronounced (4-7). Some individuals over age 40 release little GH (4, 5) during sleep. Two easily measured consequences of impaired GH secretion are subnormal levels of circulating somatomedins (8, 9), and hyperresponsiveness to the anabolic effects of exogenous human (h) GH, reflected by retention of abnormally large amounts of N, P, and K during treatment with a standard dose of hGH (10-12).

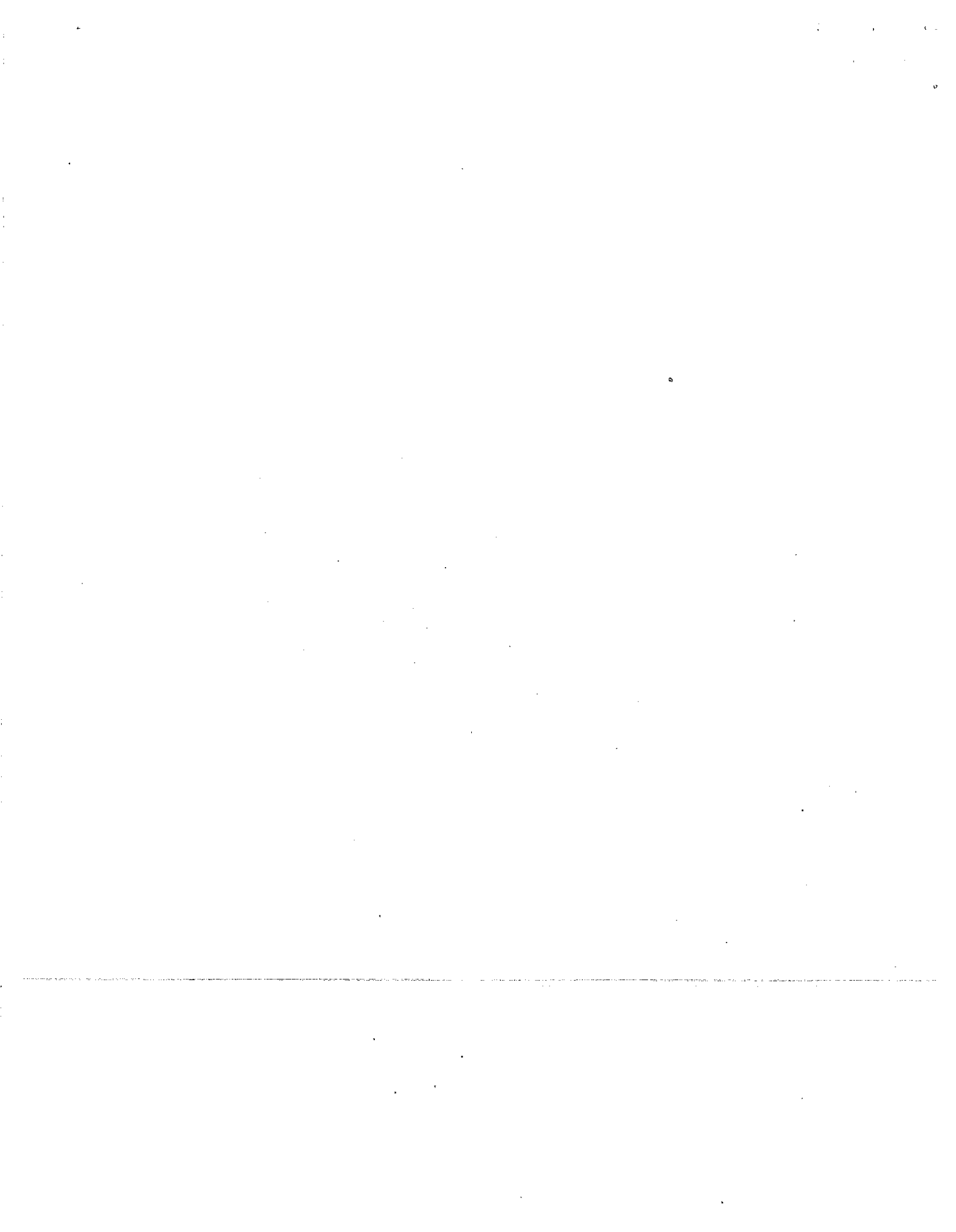
The object of this study was to investigate the prevalence of impaired GH release in the adult population of normal stature by measuring waking and sleeping release of endogenous GH, plasma concentration of somatomedin C (SmC), and anabolic responsiveness to exogenous hGH. Because endogenous GH release is influenced by nutritional state (13-19) and by disease (20-23), we confined the study to ambulatory adults who were within 15% of ideal body weight and free of progressive or active disease.

METHODS

Subjects. 94 ambulatory individuals, 21-86 yr old, of average height and without overt obesity, were recruited by a

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Abbreviations used in this paper: BW, body weight; GH, growth hormone; h, human; RIA, radioimmunoassay; SmC, somatomedin C; T₃, triiodothyronine; T₄, thyroxine.



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EFFECTS OF HUMAN GROWTH HORMONE IN MEN OVER 60 YEARS OLD

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Abstract Background. The declining activity of the growth hormone—insulin-like growth factor I (IGF-I) axis with advancing age may contribute to the decrease in lean body mass and the increase in mass of adipose tissue that occur with aging.

Methods. To test this hypothesis, we studied 21 healthy men from 61 to 81 years old who had plasma IGF-I concentrations of less than 350 U per liter during a six-month base-line period and a six-month treatment period that followed. During the treatment period, 12 men (group 1) received approximately 0.03 mg of biosynthetic human growth hormone per kilogram of body weight subcutaneously three times a week, and 9 men (group 2) received no treatment. Plasma IGF-I levels were measured monthly. At the end of each period we measured lean body mass, the mass of adipose tissue, skin thickness (epidermis plus dermis), and bone density at nine skeletal sites.

Results. In group 1, the mean plasma IGF-I level rose into the youthful range of 500 to 1500 U per liter during treatment, whereas in group 2 it remained below 350 U per liter. The administration of human growth hormone for six months in group 1 was accompanied by an 8.8 percent increase in lean body mass, a 14.4 percent decrease in adipose-tissue mass, and a 1.6 percent increase in average lumbar vertebral bone density ($P < 0.05$ in each instance). Skin thickness increased 7.1 percent ($P = 0.07$). There was no significant change in the bone density of the radius or proximal femur. In group 2 there was no significant change in lean body mass, the mass of adipose tissue, skin thickness, or bone density during treatment.

Conclusions. Diminished secretion of growth hormone is responsible in part for the decrease of lean body mass, the expansion of adipose-tissue mass, and the thinning of the skin that occur in old age. (N Engl J Med 1990; 323:1-6.)

IN middle and late adulthood all people experience a series of progressive alterations in body composition.¹ The lean body mass shrinks and the mass of adipose tissue expands. The contraction in lean body mass reflects atrophic processes in skeletal muscle, liver, kidney, spleen, skin, and bone.

These structural changes have been considered unavoidable results of aging.¹ It has recently been proposed, however, that reduced availability of growth hormone in late adulthood may contribute to such changes.^{1,2} This proposal is based on two lines of evidence. First, after about the age of 30, the secretion of growth hormone by the pituitary gland tends to decline.^{1,3,4} Since growth hormone is secreted in pulses, mostly during the early hours of sleep, it is difficult to

measure the 24-hour secretion of the substance directly. Growth hormone secretion can be measured indirectly, however, by measuring the plasma concentration of insulin-like growth factor I (IGF-I, also known as somatomedin C), which is produced and released by the liver and perhaps other tissues in response to growth hormone.⁵ There is little diurnal variation in the plasma IGF-I concentration, and measurements of it are therefore a convenient indicator of growth hormone secretion.⁵ Plasma IGF-I concentrations decline with advancing age in healthy adults.^{1,4,6} Less than 5 percent of the healthy men 20 to 40 years old have plasma IGF-I values of less than 350 U per liter, but the values are below this figure in 30 percent of the healthy men over 60.⁴ Likewise, the nocturnal pulses of growth hormone secretion become smaller or disappear with advanced age. If the plasma concentration of IGF-I falls below 350 U per liter in older adults, no spontaneous circulating pulses of growth hormone can be detected by currently available radioimmunoassay methods.⁴ The concomitant decline in plasma concentrations of both hormones supports the view that the decrease in IGF-I results from diminished growth hormone secretion.^{4,6} Second, diminished se-

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cretion of growth hormone is accompanied not only by a fall in the plasma IGF-I concentration, but also by atrophy of the lean body mass and expansion of the mass of adipose tissue.¹ These alterations in body composition caused by growth hormone deficiency can be reversed by replacement doses of the hormone, as experiments in rodents,⁷ children,^{8,9} and adults 20 to 30 years old¹⁰⁻¹³ have shown. These findings suggest that the atrophy of the lean body mass and its component organs and the enlargement of the mass of adipose tissue that are characteristic of the elderly result at least in part from diminished secretion of growth hormone.¹⁻³ If so, the age-related changes in body composition should be correctable in part by the administration of human growth hormone, now readily available as a biosynthetic product.¹⁴

In this study we administered biosynthetic human growth hormone for six months to 12 healthy men from 61 to 81 years old whose plasma IGF-I concentrations were below 350 U per liter, and we measured the effects on plasma IGF-I concentration, lean body mass, adipose-tissue mass, skin (dermal plus epidermal) thickness, regional bone density, and mandibular-height ratio (the height of the alveolar ridge divided by the total height of the mandible). The measurement of the mandible was included to test the hypothesis that the age-related involution of dental bone results in part from the loss of stimulation by growth hormone.¹ In addition, the men were monitored for possible adverse effects of the hormone by means of interviews, physical examinations, and standard laboratory tests. Nine men matched for age and with similar plasma IGF-I concentrations served as controls.

METHODS

Subjects

Healthy men who were 61 or older and living in the community were recruited through newspaper advertisements followed by an interview. Entry criteria (available from the authors on request) included body weight of 90 to 120 percent of the standard for age, the ability to administer growth hormone to oneself subcutaneously, and the absence of indications of major disease. Ninety-five men who answered the advertisements met criteria that could be ascertained by interview. Their plasma IGF-I concentrations were then determined twice at an interval of four weeks. Consistent with the results of a previous study,¹³ the plasma IGF-I values in these men ranged from 100 to 2400 U per liter, with an average of 500 U per liter. Thirty-three of the men had plasma IGF-I values of less than 350 U per liter on both occasions. These 33 men were then further evaluated by a medical-history taking, physical examination, differential blood count, urinalysis, blood-chemistry tests, chest radiography, and electrocardiography. Twenty-six subjects (11 black and 25 white) met all the entry criteria and were enrolled in the 12-month protocol summarized in Table 1.

Study Periods

The men were seen at regular intervals and tested as shown in Table 1 during the first week of the first, third, and sixth months of the base-line period. Five men dropped out of the study during these six months (four for personal reasons and one because carcinoma of the prostate was detected).

Table 1. Schedule of Tests during the Base-Line and Treatment Periods.

Test	Base-Line Period			Treatment Period					
	1	3	6	7	9	10	11	12	
Physical examination	x	x	x	x	x	x	x	x	
Hematology*	x	x	x	x	x	x	x	x	
Urinalysis*	x	x	x	x	x	x	x	x	
Blood chemistry*	x	x	x	x	x	x	x	x	
Chest radiography	x	x							
Electrocardiography	x	x							
Echocardiography	x	x							
Total body potassium†			x						
Skin thickness‡			x						
Bone density§			x						
Mandibular-height ratio¶			x						
Plasma IGF-I	x	x	x	x	x	x	x	x	
Biosynthetic growth hormone**				x	x	x	x	x	

*Tests included a complete blood count, sedimentation, blood urea nitrogen, and the measurement after an overnight fast of plasma glucose, urea nitrogen, creatinine, urea acid, sodium, potassium, calcium, carbon dioxide, phosphorus, chloride, and protein. All other tests were used according to standard methods. Urine chemistry included protein, glucose, ketones, and leukocytes. Hematology included hemoglobin, hematocrit, and erythrocyte sedimentation rate. Tests were performed in the North Chicago Veterans Affairs Medical Center laboratory.

†Total body potassium levels (from body mass and administered doses) were measured according to the method of Flynn et al.¹¹

‡Calculated as the sum of the skin thickness of the right and left dorsal hand and right and left lower forearm combined with a Harpenden caliper according to the method of L'Herminier and Dumas.¹²

§Measured according to the method of Nagay et al.¹⁷

¶Measured according to the method of Goldberg et al.¹⁸

**Obtained at National Laboratory, Los Angeles, according to the method of Fortmann et al.¹⁹

** Administered to group 1 only.

At the beginning of the seventh month, the 21 men who had completed the base-line period were randomly assigned to group 1 (growth hormone group) or group 2 (control group) in a ratio of 3 to 2. The randomization table was generated by a computer program such that in each group of five men, three would be assigned to the growth hormone group and two to the control group. All 21 men (12 in group 1 and 9 in group 2) completed the treatment period and constitute the study group for this report. Their clinical characteristics are summarized in Table 2. During the first week of the seventh month, the men in group 1 were instructed in the subcutaneous administration of recombinant biosynthetic human growth hormone (2.6 IU per milligram of hormone; Eli Lilly). The initial dose was 0.03 mg per kilogram of body weight, injected three times a week at 8 a.m., the interval between injections being either one or two days. A sample of venous blood for plasma IGF-I assay was obtained each month 24 hours after a growth hormone injection. If the IGF-I level was below 500 U per liter, the dose of hormone was increased by 25 percent; if the IGF-I level was above 1500 U per liter, the dose was reduced by 25 percent. The men in group 2 received no injections. The schedule of tests for both groups during the treatment period is shown in Table 1.

At the start of the base-line period, the project dietitian instructed each man to follow a diet that furnished 25 to 30 kcal per kilogram. The distribution of kilocalories among protein, carbohydrate, and fat was approximately 15 percent, 50 percent, and 35 percent, respectively. At each scheduled visit shown in Table 1, the dietitian analyzed each man's diet on the basis of a 24-hour dietary recall and instructed the subjects again about the standard diet. The men were told not to alter their lifestyles (including their use of tobacco or alcohol and their level of physical activity) during the 12-month study period.

The study protocol was carried out with the informed consent of each subject and with the approval of the human-research commit-

Table 2. Clinical Characteristics of the Study Subjects.

CHARACTERISTIC	GROUP 1 (N = 12)	GROUP 2 (N = 9)
Median age (range)	67 (61-73)	68 (65-81)
Percent of ideal body weight — median (range)	103 (94-120)	105 (94-117)
Medical conditions (no. of subjects)		
Degenerative joint disease	5	2
Benign prostatic hypertrophy	3	1
Glaucoma	1	1
Cataract	2	1
Atherosclerotic heart disease*	3	1
Gallstones	0	1
Kidney stone	1	1
Hipertension	0	1
Medications (no. of subjects)		
Nonsteroidal antiinflammatory drug	1	1
Pharmacologic eyedrops	1	1
Cimetidine	0	1

*Defined as a history of myocardial infarction or electrocardiographic abnormality ascribed to coronary artery disease.

tees of the Medical College of Wisconsin, the Chicago Medical School, and the Veterans Affairs Medical Centers in North Chicago and Milwaukee.

Statistical Analysis

The methods used to measure each response variable and the locations where the tests were performed are described in Table 1. The interassay coefficients of variation for the response variables were as follows: plasma IGF-I, 7.2 percent; lean body mass, 3.6 percent; adipose-tissue mass, 6.9 percent; skin thickness, 5.4 percent; and bone density, 2.3 percent (average of nine measured sites).

P values based on two-tailed, matched-pair t-tests were calculated for the comparisons between the 6-month and 12-month values in group 1 and group 2. In addition, for each response variable the 6-month value was subtracted from the 12-month value to represent the change in each subject. P values based on two-tailed, unequal-variance, independent-sample t-tests were then calculated for the comparison of the changes in response variables between groups 1 and 2.

RESULTS

Clinical Observations

All the men remained healthy, and none had any changes in the results of differential blood count, urinalysis, blood-chemistry profile, chest radiography, electrocardiography, or echocardiography during the 12-month protocol. Specifically, none had edema, fasting hyperglycemia (>6.6 mmol of glucose per liter), an increase in blood pressure to more than 160/90 mm Hg, ventricular hypertrophy, or a local reaction to

human growth hormone, nor did their serum cholesterol or triglyceride concentrations change significantly. In group 1, however, both the mean (\pm SE) systolic blood pressure and fasting plasma glucose concentration were significantly higher ($P < 0.05$ by matched-pair t-test) at the end of the experimental period than at the end of the base-line period (127.2 ± 5.2 vs. 119.1 ± 3.6 mm Hg and 5.8 ± 0.2 vs. 5.4 ± 0.2 mmol per liter, respectively).

Plasma IGF-I Concentration

In group 1, the mean plasma IGF-I concentration ranged from 200 to 250 U per liter throughout the base-line period (Table 3). Within one month after the administration of growth hormone had been initiated, the mean IGF-I level rose to 830 U per liter ($P < 0.05$), and it remained near this value for the next five months. Eight of the 12 men in group 1 required no adjustment in their initial dose of growth hormone. Two required an upward adjustment of 25 percent, and two required a downward adjustment of 25 percent. The mean plasma IGF-I concentration in group 2 remained in the range of 180 to 300 U per liter throughout the base-line and treatment periods.

Lean Body Mass, Adipose-Tissue Mass, Skin Thickness, Bone Density, and Mandibular-Height Ratio

Table 4 shows the mean values for the other response variables at the end of the base-line period (6 months) and the end of the treatment period (12 months). There was no significant change in weight in either group. In group 1, several response variables had changed significantly after 12 months. Lean body mass and the average density of the lumbar vertebrae increased by 8.8 percent ($P < 0.0005$) and 1.6 percent ($P < 0.04$), respectively, and adipose-tissue mass decreased by 14.4 percent ($P < 0.005$). The sum of skin thicknesses at four sites increased 7.1 percent ($P = 0.07$). The small average change in lumbar vertebral bone density (only 0.02 g per square centimeter) was statistically significant because of very little variability in individual results. The bone density of the radius and proximal femur and the ratio of the height of the alveolar ridge to total mandibular height did not change significantly. In group 2 none of these variables changed significantly. The change in the lean body mass was significantly greater in group 1 than in group 2 ($P < 0.018$), but the differences in

Table 3. Effect of the Administration of Human Growth Hormone on Plasma IGF-I Concentrations in Healthy Older Men.*

GROUP	BASE-LINE PERIOD				TREATMENT PERIOD				
	mo 1	mo 3	mo 6	mo 7	mo 8	mo 9	mo 10	mo 11	mo 12
	units per liter								
Group 1	240 \pm 86	230 \pm 97	230 \pm 66	830 \pm 139†	680 \pm 180†	720 \pm 150†	810 \pm 205†	810 \pm 192†	910 \pm 312†
Group 2	240 \pm 64	240 \pm 126	240 \pm 108	200 \pm 126	220 \pm 123	240 \pm 177	180 \pm 126	240 \pm 186	300 \pm 201

*Values are means \pm SD.

† $P < 0.05$ for the comparison between groups.

Table 4. Effect of the Administration of Human Growth Hormone on Weight, Lean Body Mass, Adipose-Tissue Mass, Skin Thickness, and Bone Density in Healthy Older Men.*

VARIABLE	GROUP	End of BASE-LINE PERIOD	End of TREATMENT PERIOD	P VALUE†	DIFFERENCE IN CHANGE‡
Weight (kg)	1	77.2±11.4	78.3±12.1	0.26	+1.0 (-1.4 to +3.4)
	2	83.3±11.1	83.3±9.7	0.97	
Lean body mass (kg)	1	53.0±7.4	57.7±9.1	0.0005	+3.7 (+0.7 to +6.6)
	2	54.2±7.1	55.2±7.3	0.17	
Adipose-tissue mass (kg)	1	24.1±5.0	20.6±5.6	0.05	-2.4 (-5.7 to +0.8)
	2	29.0±6.4	28.0±4.0	0.43	
Sum of skin thickness at four sites (mm)	1	9.9±1.2	10.6±1.5	0.07	+0.8 (-0.1 to +1.7)
	2	9.3±0.9	9.23±0.80	0.69	
Bone density (g/cm ³)					
	1	0.74±0.10	0.74±0.12	0.85	-0.04 (-0.02 to +0.10)
Mid-shaft radius	2	0.76±0.10	0.71±0.07	0.09	
	1	0.37±0.07	0.36±0.08	0.12	-0.004 (-0.03 to +0.02)
Distal radius	2	0.34±0.04	0.33±0.05	0.26	
	1	1.23±0.12	1.25±0.13	0.04	-0.006 (-0.04 to +0.02)
Average lumbar vertebrae L ₁₋₄	2	1.29±0.25	1.29±0.26	0.64	
	1	0.70±0.14	0.69±0.13	0.15	-0.018 (-0.08 to +0.03)
Ward's triangle	2	0.70±0.17	0.70±0.17	0.69	
	1	0.85±0.13	0.85±0.13	0.72	-0.007 (-0.05 to +0.03)
Greater trochanter	2	0.81±0.15	0.81±0.13	0.55	
	1	0.92±0.15	0.91±0.14	0.53	-0.029 (-0.08 to +0.03)
Femoral neck	2	0.89±0.14	0.85±0.14	0.14	
	1	0.45±0.15	0.46±0.11	0.87	-0.003 (-0.07 to +0.06)
Mandibular height ratio	2	0.47±0.12	0.47±0.12	0.98	

*Values are means ±SD.

†P values are for the change from base line, by matched-pair *t*-test.

‡The difference in change (12-month value minus 0-month value) is the average change in group 1 minus the average change in group 2. Values in parentheses are 95 percent confidence intervals, obtained by matched-pair *t*-test.

changes in skin thickness and adipose-tissue mass between groups did not reach statistical significance in this small series ($P = 0.10$ and 0.13 , respectively).

DISCUSSION

The 21 men studied were representative of the approximately one third of all men 60 to 80 years old who have plasma IGF-I concentrations of less than 350 U per liter (as compared with a range of 500 to 1500 U per liter in healthy men 20 to 40 years old).⁴ Our findings cannot be generalized to the approximately two thirds of all men over 60 who have plasma IGF-I concentrations of more than 350 U per liter or to women of a similar age. Furthermore, our entry criteria focused the study on an overtly healthy subgroup of older men.

In the absence of obesity,⁴ below-normal weight,²³ or liver disease,²⁴ a plasma IGF-I concentration of less than 350 U per liter in older men generally signifies that they secrete very little growth hormone.⁴ To verify this explanation for the low plasma IGF-I concentration in these men, it would be necessary to measure serum growth hormone levels at frequent intervals for 24 hours or to determine the 24-hour urinary excretion of growth hormone. We did not do this, but Ho et al. found that the 24-hour integrated serum growth hormone level was markedly lower in the men over 55 than in men 18 to 33 years old.²⁵ An alternative explanation for a low plasma IGF-I concentration is decreased production of plasma IGF-I binding proteins.

Most of the IGF-I plasma is bound to these proteins, but their concentrations vary little in healthy people who eat a normal diet.

In the 12 men in group 1, initially low plasma IGF-I concentrations were raised to the normal range for young adult men by the dose of growth hormone administered, with no evidence of tachyphylaxis or hormone resistance. The dose, approximately 0.03 mg per kilogram three times a week, was based on published estimates of the rate of growth hormone secretion in young men²⁶ and was comparable to or smaller than doses given previously to children with growth hormone deficiency^{21,22} and young adults.¹⁰⁻¹³ The plasma IGF-I responses to this dose in these older men were similar in magnitude to those in younger people. That "replacement" rather than pharmacologic doses were being administered was confirmed by the plasma IGF-I measurements, which remained within the range for healthy young adults (500 to 1500 U per liter) throughout the treatment period

(Table 3). We conclude that in aging men with low plasma IGF-I concentrations hepatic responsiveness to human growth hormone is not impaired, and the decline in plasma IGF-I concentrations in such men results from growth hormone deficiency rather than growth hormone resistance. The increase in plasma IGF-I levels that occurs when growth hormone is administered to children with growth hormone deficiency reflects not only augmented hepatic production of IGF-I, but also increased production of one of the binding proteins that transport IGF-I.²⁶ The extent to which the production of IGF-I binding protein is increased by the administration of growth hormone has not yet been studied in adults.

At the beginning of our study, adverse reactions to human growth hormone were thought to be unlikely because physiologic doses were being used. Furthermore, similar or larger doses have not caused undesired reactions in children or young adults.^{10-14,26} Nevertheless, it remained possible that this dose, when given for six months to older subjects, might cause some manifestation of hypersomatotropism, such as edema, hypertension, diabetes, or cardiomegaly.²⁷⁻²⁹ Although none of these conditions developed, there were small increases in the mean systolic blood pressure and fasting plasma glucose concentration of the group of men who received growth hormone.

The magnitude of the increases in lean body mass and the decreases in adipose-tissue mass (8.8 and -14.2 percent above and below base line, respective-

ly) in the aging men who received human growth hormone for six months was similar to the magnitude of these responses in children^{4,9} and young adults^{10,11} treated with similar or lower doses for three to six months, a comparison that provides further evidence that tissue responsiveness to growth hormone and IGF-I is not altered in older men. Until now, the evidence for such a conclusion came only from short-term nitrogen-balance experiments.^{14,20-22}

Salomon et al. reported that the administration of human growth hormone in a dose of 0.49 unit per kilogram per week (0.19 mg per kilogram per week) for six months to adults 20 to 30 years old who had growth hormone deficiency lowered the serum cholesterol concentration significantly.¹³ Serum cholesterol concentrations did not change in our study, in which the dose of growth hormone was about half as large (0.9 mg per kilogram per week). The divergent results could reflect differences in the subjects' ages, the degree of growth hormone deficiency, the dose of hormone, or all three.

In rodents, the increase in lean body mass in response to growth hormone is due to increases in the volume of skeletal muscle, skin, liver, kidney, and spleen.^{1,7} In young human subjects, an enlargement of muscle and kidney induced by growth hormone has been documented^{8,12}; other organs have not yet been assessed. The reduction in adipose-tissue mass when children with growth hormone deficiency are treated with human growth hormone is associated with a redistribution of adipose tissue from abdominal to peripheral areas.²¹ It is not known, however, whether the increase in lean body mass and the decrease in adipose-tissue mass are qualitatively as well as quantitatively similar in old and young human subjects.

Biosynthetic human growth hormone had no detectable effect on the bone density of the radius or proximal femur in the aging men, but it increased the density of the lumbar vertebrae by about 1.6 percent. Although the decrease in bone density with advancing age in men may be due in part to diminished secretion of growth hormone,^{1,23} longer periods of administration of human growth hormone will be required before a final conclusion can be drawn regarding its efficacy in reversing that decrease. A similar interpretation applies to the lack of increase in the mandibular-height ratio.

The findings in this study are consistent with the hypothesis that the decrease in lean body mass, the increase in adipose-tissue mass, and the thinning of the skin that occur in older men are caused in part by reduced activity of the growth hormone-IGF-I axis, and can be restored in part by the administration of human growth hormone.^{1,2} 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.^{1,24,25} Among the questions that remain to be addressed are the following: What will be

the benefits and what will be the nature and frequency of any adverse effects when larger numbers of elderly subjects and other doses of human growth hormone are studied? What organs are responsible for the increase in lean body mass, and do their functional capacities change as well? Only when such questions are answered can the possible benefits of human growth hormone in the elderly be explored. Since atrophy of muscle and skin contributes to the frailty of older people, the potential benefits of growth hormone merit continuing attention and investigation.

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Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance

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Growth hormone (GH) replacement therapy in several controlled short-term trials have shown unanimous beneficial effects on body composition and other features. To evaluate more long-term effects we report data from 3 years of uninterrupted GH therapy in 10 GH-deficient adults who had all completed a previous double-blind placebo-controlled study and who also had been studied after 16 months of open GH therapy. No further increase in linear height was observed. The initial increase in thigh muscle volume was maintained after 3 years of GH therapy. A slight increase in body weight and thigh fat volume was recorded. Exercise capacity and isometric muscle strength were increased significantly compared to the initial placebo period. This was associated with stabilized levels of resting heart rate and blood pressure. Glycosylated hemoglobin levels were normal and did not change during the study. A standard oral glucose tolerance test performed at the end of the study revealed no evidence of glucose intolerance. No side-effects were reported. Compared to an age- and sex-matched group of healthy untreated subjects, thigh muscle volume, exercise capacity and isometric muscle strength had become normalized from subnormal levels after 3 years of GH therapy. We conclude that long-term GH replacement therapy in GH-deficient adults is associated with preserved beneficial effects on body composition and physical performance, resulting in a near normalization of several previously abnormal features and adding new merits to this treatment modality.

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Within the last 4 years several studies on growth hormone (GH) treatment in GH-deficient adults have been published (1, 2). This in turn has prompted surveys on the epidemiological and clinical features of hypopituitary adults (3-9). It has become evident that untreated GH deficiency in adulthood is associated with abnormal body composition in terms of increased fat mass (4, 5, 7, 9), decreased lean body mass (5, 8), decreased extracellular water (5, 7, 9) and decreased bone mineral content (4, 6). In addition, there is suggestive evidence of a substantially increased mortality in these patients due to cardiovascular disease (3, 4). Growth hormone treatment in adult patients has shown unequivocal beneficial effects as regards part-normalization of body composition (10-16). Furthermore, GH therapy has been shown to improve exercise capacity (10, 12, 14, 16, 17) and muscle strength (12, 18) from distinctly subnormal levels. Additional potentially beneficial effects of GH therapy on several other features also have been reported (10, 11, 13, 15, 19-24). So far, the only substantial side-effect has been subjective discomfort related to fluid retention, which in

most instances is a transient dose-dependent occurrence. Still, the well-known insulin antagonistic actions of GH may cause concern.

The duration of GH therapy in presently published trials has not exceeded 16 months. Therefore, we have found it relevant to report in this paper the data on 3 years of uninterrupted GH therapy in GH-deficient adults.

Patients and methods

The present study is an extension of a protocol involving an initial double-blind placebo-controlled crossover phase (4 months of GH/placebo therapy) and a subsequent open phase (10, 12). The present paper comprises 10 patients (three females and seven males), who have completed the initial double-blind study and thereafter have continued with 37.6 (1.5) months (mean (SEM)) of uninterrupted GH therapy in an open design. The variables measured after 37.6 months are compared to those obtained from the same 10 patients during their participation in the double-blind study and

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Consequences of Growth Hormone Deficiency in Adults and the Benefits and Risks of Recombinant Human Growth Hormone Treatment

A Review Paper

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Key Words

Growth hormone deficiency
Body composition
Bone
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Abstract

Growth hormone deficiency (GHD) in adults is now recognized as a specific clinical syndrome with characteristic symptoms and signs. Thus, the patients are overweight, have an abnormal body composition (excess body fat and a decrease in the extracellular water volume) and a low bone mineral content compared to normals. Furthermore, the GHD patients have lipid abnormalities, decreased insulin sensitivity and a decreased fibrinolysis. Finally, the 'quality of life' is low in terms of energy and social life. Short- and long-term studies with recombinant human GH (rhGH) treatment have shown normalization of body composition, increase in the lipid pattern and marked improvement of the psychological well-being. The treatment seems safe with no serious side effects reported. In analogy with other hormonal replacement therapies, the rhGH dose should be individualized.

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Historical Review

Growth hormone deficiency (GHD) has only recently been recognized as a specific clinical syndrome. Routine replacement therapy with corticosteroids, L-thyroxine and sex hormones has been considered as sufficient therapy for pituitary deficiency for the last 30-40 years, although it has been recognized for many years that growth hormone (GH) continues to be secreted in adult life [1].

Some of the physiological consequences of GHD in adults have been known for many years. In 1963, the

pathophysiological effects of hypophysectomy in adult patients who were hypophysectomized because of metastatic mammary carcinoma, diabetes mellitus or acromegaly were described [2]. Despite replacement therapy for deficient adrenal, thyroid and gonadal function, there was a decrease in basal metabolism, renal function, blood volume and cardiac function within 1 month postoperatively. It was postulated that the observed changes were due to the abolished or reduced GH secretion caused by the hypophysectomy.

Table 1. The symptoms and signs of GHD in adults [modified from 3]

Symptoms	Signs
Impaired psychological well-being and quality of life with	Reduced lean body mass
Poor general health	Reduced extracellular fluid volume
Impaired self-control	Reduced bone mineral density
Lack of positive well-being	Increased body fat
Depressed mood	Increased waist-hip ratio
Increased anxiety	Decreased plasma HDL cholesterol
Reduced vitality	Increased plasma LDL cholesterol
Reduced energy	Reduced glomerular filtration rate
Impaired emotional reaction	Reduced renal plasma flow
Increased social isolation	Reduced basal metabolic rate
	Reduced muscle bulk
	Reduced muscle strength
	Reduced exercise performance
	Reduced anaerobic threshold

Consequences of GHD in Adults

GHD in adults is manifested as a number of characteristic symptoms and signs (table 1) [3].

Body Composition

GH has profound effects on body composition through its anabolic, lipolytic and antinatriuretic effects. In acromegaly, these effects result in an increase in body weight, body cell mass and extracellular fluid volume [4]. Also GHD is associated with characteristic changes in body composition. Typically, the adult GHD patient is found to be heavier than normal subjects of the same age, sex and body height. The increase in weight is explained by an increment of body fat with a simultaneous reduction of total body water, especially extracellular water (ECW) [5].

In a study from Gothenburg of 106 patients with multiple pituitary deficiencies, including GHD acquired in adult life, body composition was estimated according to the four-compartment model from body weight, total body water (TBW) and total body potassium [5]. There was an increase in body weight both in male (7.5 kg) and female (3.6 kg) patients compared to the predicted normal weights. A similar increase in body weight was noted in 24 patients with GHD ($1.26 \pm 5\%$ of their ideal body weight) [6]. Thus, the increase in body weight can be explained by an increase in body fat. In the Gothenburg study the increase in body fat was 2.4 kg in men and 3.3 kg in wom-

en, compared with controls of the same weight, and Salomon et al. [6] found a 7% increase in body fat as a percentage of body weight, compared with that predicted from age, sex, height and weight. The extra adipose tissue is typically situated in the abdominal and visceral fat depots, resulting in an increase in the waist-hip ratio compared with controls.

There is also a reduced lean body mass or fat-free mass in the adults with GHD. In a study of 24 patients with GHD, the mean lean body mass was $92.6 \pm 2.0\%$ of the predicted value [6]. In another study of 13 adult GHD patients, bio-impedance analysis showed a reduced fat-free mass compared with controls [7]. Furthermore, a reduction of the muscle:fat ratio of the thigh has been noted in patients with GHD [8], and the thigh muscle area is shown to be decreased compared with controls [9].

Dehydration is another characteristic feature of adult GHD patients. In the Gothenburg study comprising 106 patients with GHD, extracellular fluid was reduced in both men (2.4 kg; $p < 0.001$) and women (2.8 kg; $p < 0.001$), compared with controls of the same weight. This corresponds to a decrease in extracellular fluid volume of about 15% [5].

Bone Mass

Bone formation and resorption occur continuously in adults, and GH seems to affect bone metabolism throughout life. In recent years, GH receptors have been found on osteoblast-like cell lines, thus indicating a direct effect by GH on osteoblast proliferation [10]. GH also increases the availability of minerals and enhances the intestinal absorption of calcium and phosphate [11]. A few studies have shown low bone mineral content in adults with GHD of both childhood and adult onset. In a study of 30 men with GHD of childhood onset, a significant decreased bone mineral content was found in both the lumbar spine and the forearm [12]. Similar findings have been reported in other studies [13-15]. The cause of osteopenia in these subjects could be a deficient build-up of bone mass during childhood and adolescence.

In a retrospective study of 122 adult patients with pituitary deficiency of adult onset, a low bone mass was found in the lumbar spine and proximal forearm of 51 and 73% of patients, respectively [16]. Interestingly, these patients had more osteoporotic fractures than predicted. Furthermore, in a study of 95 patients with GHD of adult onset, a low bone mineral content, measured with dual-photon absorptiometry, was found in the third lumbar vertebra, compared with matched controls [17].

Cardiac Function and Physical Performance

Recent studies have revealed an impaired cardiac function in GHD patients. Adults with GHD have been found to have a reduction in both maximal oxygen uptake [18, 19] and in maximal heart rate [18] when compared with normals. Furthermore, reductions in left ventricular wall thickness and interventricular septum thickness in adult GHD patients have been shown compared with normals [20, 21]. Moreover, in a study of 21 adults with GHD a significant correlation was found between left ventricular mass and the serum insulin-like growth factor I (IGF-I) concentration [22].

Renal Function

In 1963, it was shown that glomerular filtration rate and renal plasma flow decreased after hypophysectomy, in spite of replacement therapy for deficient adrenal, thyroid and gonadal function [2]. In a recent study of 22 adults with GHD, it was also found that glomerular filtration rate and renal plasma flow were reduced in patients with GHD compared with matched controls [8]. This might be explained by the combined effects of reduced extracellular volume and decreased cardiac output.

Cardiovascular Risk Factors

The early findings of hyperlipidaemia in patients with hypopituitarism [23] or isolated GHD [24] suggested a role for GH in the regulation of lipoproteins [25]. Increases in LDL and total cholesterol levels, with an increase [26] or a decrease in HDL cholesterol [27], have recently been reported in adult GHD patients [26, 27]. In a study of 104 patients with GHD of adult onset, the serum triglyceride concentration was higher ($p < 0.001$) and the serum HDL cholesterol concentration was lower ($p < 0.001$) in the patients than in the controls, but the total cholesterol concentration did not differ [28]. Moreover, the prevalence of treated hypertension was higher ($p < 0.05$) in the GHD patients, but there were fewer smokers ($p < 0.001$) among the patients compared with the controls.

In a retrospective study of 122 adult patients with pituitary deficiency, the frequency of hyperlipidaemia (77%) and hypertension (18%) among the patients was found to be higher than expected [16]. Furthermore, a significant increase in the intimal thickness and in the number of atheromatous plaques has been found in the femoral and carotid arteries of patients with hypopituitarism compared with controls [29]. Also, a reduced distensibility of the aorta has been noted among hypopituitary patients [30].

Interestingly, a recent study has shown that adult GHD patients had higher serum concentrations of both fibrinogen and plasminogen activator inhibitor I than healthy controls matched for age, sex and body mass index [31], thus indicating a decreased fibrinolysis in adult GHDs. Also, GHD patients seem to be insulin-resistant; a clamp study from our unit showed a reduced glucose infusion rate in GHD patients compared to controls, although the fasting blood glucose was lower and the fasting insulin similar to that in controls [32]. Thus, these studies on cardiovascular risk factors and fibrinolysis in adult GHD patients suggest a connection between the syndrome X or metabolic syndrome [33] and the syndrome of GHD in adults. Both syndromes include abdominal obesity, decreased insulin sensitivity, decreased fibrinolysis and lipid abnormalities.

Long-Term Prognosis

In a retrospective study of 333 patients with hypopituitarism diagnosed between 1956 and 1987, cardiovascular mortality was found to be almost doubled (60 observed deaths compared with 31 expected) [34]. The hazard function for death was independent of age at diagnosis, sex, or degree of pituitary insufficiency. It can be assumed that most patients were GH-deficient, as loss of GH secretion is an early event in pituitary failure. According to the known effects of GH on lipid metabolism and cardiac function, unsubstituted GHD might be a major factor in explaining the increased rate of cardiovascular mortality.

Quality of Life

The clinical impression is that patients with GHD often complain of fatigue, lack of concentration, memory difficulties and irritability. This causes a reduction of their working capacity and might influence their professional career and social status. With self-rating questionnaires such as the Nottingham Health Profile (NHP) and the Psychological General Well-Being Index (PGWB) quality of life and psychological well-being have been analyzed in adult patients with GHD. In a study of 24 adult GHD patients McGauley [33] found the patients to be more labile, socially isolated and less energetic than their controls. In our study of 86 adult patients with GHD, it was found that these patients had a poorer quality of life in terms of energy, social isolation, emotional distress and sex life compared with normals [36]. There was also a tendency to a higher frequency of early retirement among the patients.

Effects of Recombinant Human GH Treatment

In 1989, the first two major studies of GH therapy in GHD adults were published [6, 8]. They both demonstrated that recombinant human GH (rhGH) treatment for a period of 4–6 months had beneficial effects on body composition, cardiac function, exercise capacity, renal function and quality of life. These results have then been confirmed by short- and long-term studies with rhGH treatment in recent years [14, 19, 37–39].

Effects on Body Composition

The effects of GH on body composition are mediated through its anabolic, lipolytic and antinatriuretic actions. In summary rhGH treatment causes a decrease in body fat (mainly in the abdominal depots) and an increase in body cell mass and extracellular water volume. Normally, no change in body weight is observed.

The effects of GH on fat mass and lipolysis are complex, and have only recently been elucidated. GH increases the number of adipocytes by recruiting cells from the preadipocytes [40]. Furthermore, except for an initial phase of 2–3 h, GH has an anti-insulin effect on the adipocytes. Thus, GH increases fat mobilization by hydrolysis of triglycerides into glycerol and free fatty acids. GH also promotes redistribution of body fat from an abdominal (android) to a more peripheral (gynoid) distribution [37, 41]. These changes have been associated with GH-induced inhibitions of the anti-insulin effect of insulin, which differs in different adipose tissue regions [42].

In a study from our unit comprising 25 adult GHD patients body fat mass was decreased by 23.1% ($p < 0.001$) after 6 months and by 15.5% ($p < 0.001$) after 12 months of treatment, according to the four-compartment model [39]. Also the waist-hip ratio was reduced, thus showing that GH preferentially decreases abdominal fat. These GH-induced reductions in fat mass and fat distribution could be beneficial with respect to the long-term prognosis of these patients.

Already in 1958, it was shown that GH treatment caused nitrogen retention in normal subjects [43]. Recent studies have shown that GH increases the protein synthesis without affecting proteolysis [9, 44], which is in contrast with the effects of insulin and IGF-1 [45, 46]. Furthermore, GH stimulates muscle growth by increasing the number of muscle cells, rather than the size of the muscle cell [47].

In our study of 25 adult GHD patients an increase in body cell mass by about 6% after 12 months of rhGH treatment was noticed. This increase is in agreement with

the results from previous studies [6, 19]. Furthermore, an increase in muscle volume by about 5% measured with the CT scan has been observed after both short-term and long-term rhGH treatment studies [8, 19, 37, 38].

GH has long been known to increase sodium retention [48]. The mechanisms are not yet clearly elucidated, but recent studies have suggested that the antinatriuretic effect of GH is a tubular effect and that GH acts by increasing the sodium pump activity [49]. Moreover, supraphysiological doses of GH to healthy subjects have been shown to stimulate the renin-angiotensin system with a simultaneous increase of the ECW volume [50].

rhGH treatment typically causes an increase in total body water, and especially the ECW volume. In one study there was an increase in TBW and ECW by 3.7 and 3.0 kg, respectively, after 26 weeks of rhGH treatment [37]. In our recent study comprising 25 adult GHD patients there was an increase in TBW by 2.4 kg ($p < 0.01$) after 12 months of treatment, but there was no significant increase in the ECW volume [39]. This might be due a lower starting dose compared with other studies, and due to a subsequent reduction of the dose because of side effects.

Effects on Cardiovascular Risk Factors

Previous short-term studies of rhGH treatment of adult GHD patients have shown a decrease [6, 9] or no change [19, 51] in total cholesterol, and no effect on triglycerides [6, 19, 51]. However, an increase in HDL cholesterol has been noted in both short-term [51] and long-term studies [39]. It is known that GH increases the hepatic VLDL triglyceride production [52] and probably also the VLDL turnover [53]. Furthermore, GH increases the LDL cholesterol clearance through activation of the hepatic LDL receptor [54]. These changes might explain the favourable increase in HDL concentration, which in turn might have a beneficial effect on the long-term cardiovascular morbidity in these patients [55, 56].

Moreover, long-term studies with rhGH treatment of GHD adults have not revealed evidence of glucose intolerance secondary to the rhGH treatment [38, 39].

A favourable decrease in diastolic blood pressure, but no change in the systolic pressure was noted in a 26-week rhGH study comprising 10 patients with GHD [57]. The decrease in diastolic blood pressure was explained by a simultaneous decrease in total peripheral resistance.

Effects on Cardiopulmonary Functions

GH-deficient patients show improvement in their exercise capacity [18, 38] and maximum oxygen uptake [18] in response to rhGH treatment. This might be due to posi-

tive effects on the cardiac muscle mass and cardiac function. In a study from our unit including 10 adult patients with GHD a significant increase in left ventricular mass, mainly due to an increase in cardiac dimensions, was found after 26 weeks of rhGH treatment [57]. There was also an increase in stroke volume and cardiac output. Similar beneficial findings on left ventricular myocardial mass and function have been observed in other studies [18, 20].

Cuneo et al. [18] observed an increase in mean O_2 uptake, but no change in vital capacity or FEV_1 after 6 months rhGH treatment. In our long-term study, however, an improvement in maximum expiratory pressure was noted after 12 months of rhGH treatment, indicating that rhGH treatment might have long-term beneficial effects on the pulmonary function [39].

GH also has positive effects on the muscle strength [9], which seems to be correlated to the increase in muscle mass. Thus, Jørgensen et al. [8] found that the increase in the muscle volume of the quadriceps was highly correlated with an increase in isometric strength, in a study of 22 GHD adults treated with GH for 4 months. Thirteen of these patients were followed in an open study for an additional year of rhGH treatment. At the end of this period a significant increase in the isometric strength of the quadriceps muscle was found, which was not noted during the initial 4-month double-blind study. This suggests that the benefits of GH resulted from its long-term use [8].

Effects on Bone Metabolism and Bone Mineral Density

rhGH treatment has marked effects on bone metabolism, which is illustrated by the increase in serum concentrations of bone markers in several studies [7, 19, 37]. The increase in the osteocalcin and procollagen-III concentrations indicates an increase in bone turnover. Adult patients with GHD of childhood onset have been shown to increase both forearm and lumbar bone mineral content after 12–18 months of rhGH treatment [14, 58, 59]. Recently, we have shown that also GHD patients of adult origin had increased their bone mineral density in the femur neck and at the trochanter region by about 4–5% compared with baseline after 18 months of rhGH treatment [39]. Interestingly, a decrease in total body bone mineral density was seen after both 6 and 12 months. Thus, it seems that rhGH treatment during the initial phase increases bone resorption, causing an expansion of the 'remodelling space' [60].

Effects on Psychological Well-Being

Several studies in recent years have shown significant improvement in psychological well-being subsequent to rhGH treatment in patients with GHD [35, 37]. Above all, there is an increase in the energy level, mood, concentration, memory and in general vitality. The effects are often visible within only a few weeks, and sometimes the improvement is remarkable. The mechanism causing this beneficial effect of GH is unclear. One explanation might be the change in body composition and exercise performance caused by the GH treatment. It is also possible that GH has CNS effects, as GH receptors and IGF-I receptors are present in the brain. In a double-blind placebo-controlled trial with 20 adult GHD patients the effect of 1 month of rhGH treatment on the cerebrospinal fluid concentrations of GH, IGF-I, IGF-BP3, monoamine metabolites, neuropeptides and opioid peptides was measured [61]. In the rhGH group there was a mean 10-fold increase of GH in the CSF indicating that rhGH passes the blood-CSF barrier. Also the concentrations of IGF-I and the β -endorphin immunoreactivity increased. These changes might possibly explain the improvement in psychological well-being during rhGH treatment.

Side Effects and Risks of rhGH Treatment

Some epidemiological reports suggest that acromegalic patients have a general increase in the risk of malignancy, especially from colonic cancer and colonic polyps [62, 63]. It seems inappropriate, however, to extrapolate these data from the acromegalic patients to the GHD patients being replaced with rhGH, as the production rate of GH in a GH-producing pituitary adenoma exceeds the ordinary rhGH substitution dose by 10–1,000 times.

From the (KABI) Pharmacia International Growth Study (KIGS), a long-term surveillance study of paediatric patients treated for short stature, knowledge is emerging concerning adverse effects during rhGH treatment of children. In summary, rhGH treatment of short stature children, who were operated on and/or irradiated for craniopharyngioma, does not cause a higher relapse rate than that observed among patients not having rhGH treatment. Furthermore, there does not seem to be an increased risk of development of leukemia during rhGH treatment.

In contrast to the child, the most common causes of GHD in the adults are pituitary and peripituitary tumours and their associated therapy. Isolated cases of tumour recurrence (especially macroprolactinomas) have

been observed in adult GHD patients on rhGH therapy, but there is not enough data to determine whether the recurrence rates of the operated pituitary tumours are influenced by the rhGH treatment. Only a thorough surveillance programme comparing the recurrence rates among the rhGH-treated and the non-treated patients might bring light into this matter.

In the early adult rhGH treatment studies, where rhGH doses of 0.50 mU/kg/week were given, a considerable portion of the patients had side effects due to fluid retention (such as swelling of hands and feet, arthralgias and joint stiffness). However, by starting with 0.10 mU/kg/week and slowly increasing the dose to 0.15–0.25 mU/kg/week while watching side effects, these problems can be avoided. It is our opinion that, in analogy with other

hormonal replacement therapies, the dose of rhGH should be individualized. It seems that the dose of 0.25 U/kg/week is too high for some of the patients. The two factors now determining the rhGH dose are the side effects and the IGF-I concentration, which should be kept within the normal range even if no side effects occur. Long-term studies have shown no serious side effects and only very few patients have withdrawn from studies because of the inconvenience of the daily injections.

In conclusion, untreated GHD in adults causes several severe symptoms and signs. Most of these symptoms and signs are reversed during GH replacement therapy. There is no evidence suggesting that this replacement therapy causes any unfavourable long-term side effects.

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