Medicine Grand Rounds November 10, 1994

GROWTH HORMONE: NORMAL PHYSIOLOGY AND CHANGES DURING AGING

Michael J. McPhaul, M.D.

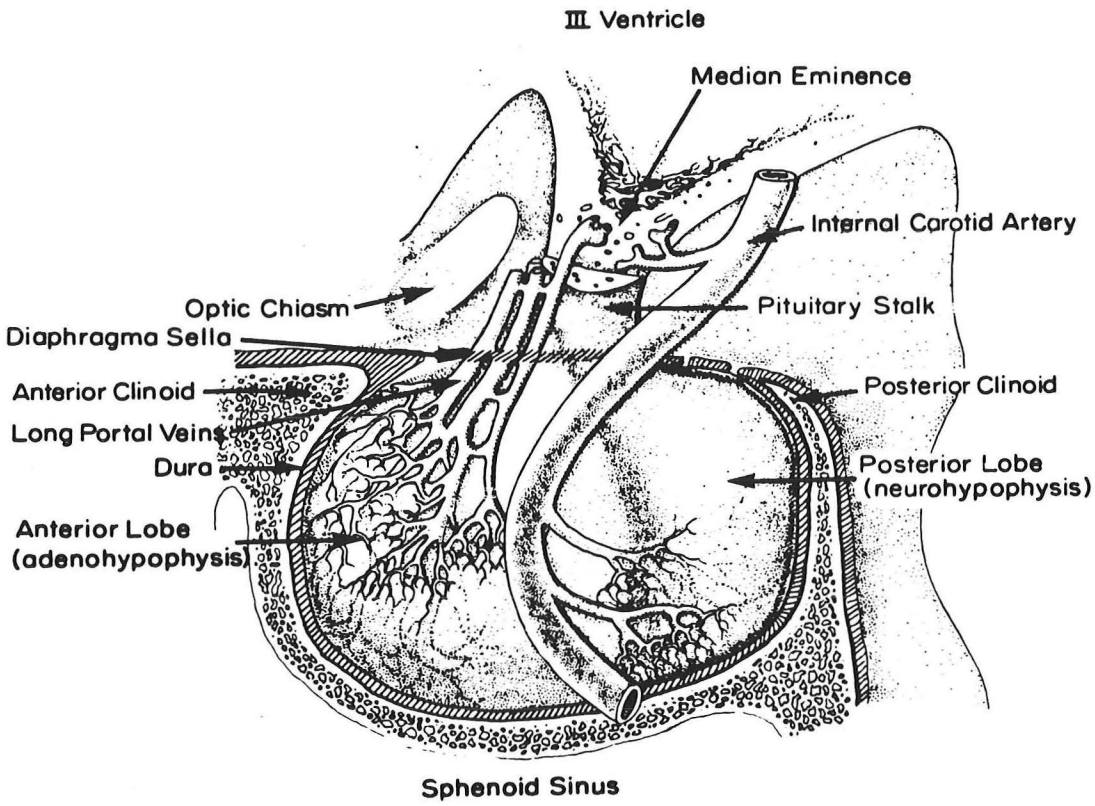


Fig. 1

The normal pituitary gland is quite small, usually approximately 0.6 grams, yet effectively functions as the master controller of endocrine function in the body. Its six major hormone products are secreted by five distinct cell types and act to regulate the synthesis of release of hormones from the adrenal glands, thyroid gland, and the gonads. The hormones produced by the pituitary are also crucial to normal lactation and to the normal growth and development of the adult phenotype.

Growth hormone is a single polypeptide hormone, 191 amino acids long, that is produced by the somatotropes, which comprise the largest hormone-producing cell type in the pituitary (~50% of the total). Although several distinct forms of this hormone have been described in humans, no distinctive functions have been ascribed to the different 'variants.' This hormone bears a significant relatedness to two other hormones, prolactin

and placental lactogen, and thus comprise a family of hormones believed derived from a common ancestral gene.

TABLE I

Cell Type	Hormone (properties)	Size	Comments
Corticotropes	Adrenocorticotropin (ACTH)	39 amino acids	(Also synthesize α MSH, β lipotropin and β endorphin from a single precursor)
Somatotropes	Growth Hormone (GH)	191 amino acids	
Mammotropes	Prolactin (PRL)	198 amino acids	
Thyrotropes	Thyrotropin (TSH)	α subunit: 89 β subunit: 112	- TSH, FSH, & LH share a common α subunit
Gonadotropes	Luteinizing Hormone (LH)	α subunit: 89 β subunit: 115	- LH and FSH are produced by the same cells
	Follicle-stimulating Hormone (FSH)	α subunit: 89 β subunit: 115	- LH and FSH are produced by the same cells

The growth hormone axis is among the most complicated and confusing systems in human endocrinology. An understanding of the subjects to be reviewed later requires a brief review of several crucial aspects of growth hormone physiology.

The Regulation of Growth Hormone Secretion by the Pituitary: Control by the Hypothalamus

Multiple signals control the level of growth hormone secreted by the pituitary somatotrophs. A vast amount of experimental work can be distilled down to the information contained in Fig. 2 and reviewed in Ref. 4. A principal control is the secretion of the peptide GHRH by the GHRH expressing cells within the hypothalamus. GHRH released by these cells travels to the pituitary via the long portal vessels. The release of GHRH is pulsatile, and it is believed that periods of elevated release of GHRH are coordinated with a decrease in tonic negative influences exerted by somatostatinergic neurons. A final additional subtlety pertains to cholinergic interneuron or interneurons that have been inferred from experimental studies demonstrating the effects of cholinesterase inhibitors that profoundly stimulate growth hormone release, presumably by inhibiting somatostatin release and stimulating GHRH release. Many tests of growth hormone secretion, particularly in children, employ cholinesterase inhibitors, such as pyridostigmine to stimulate maximal growth hormone secretion hinge upon this realization.

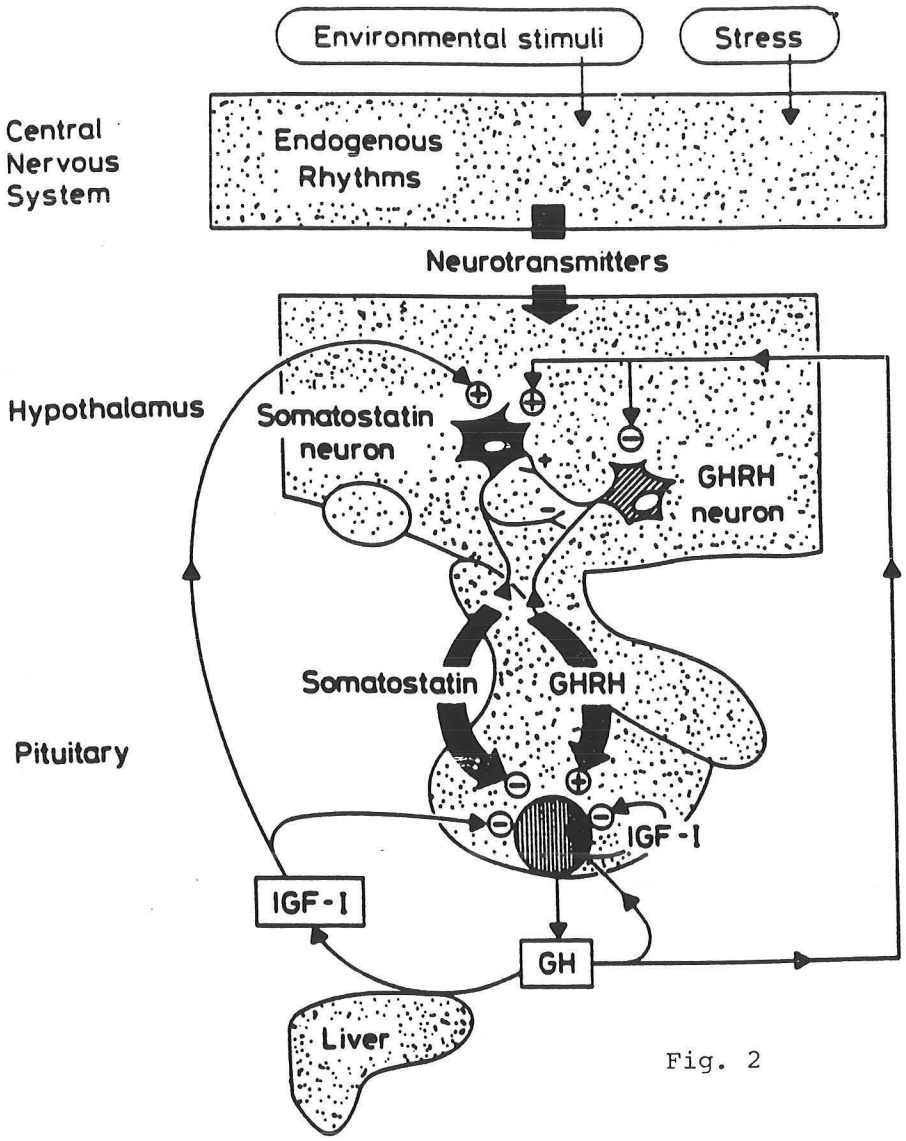
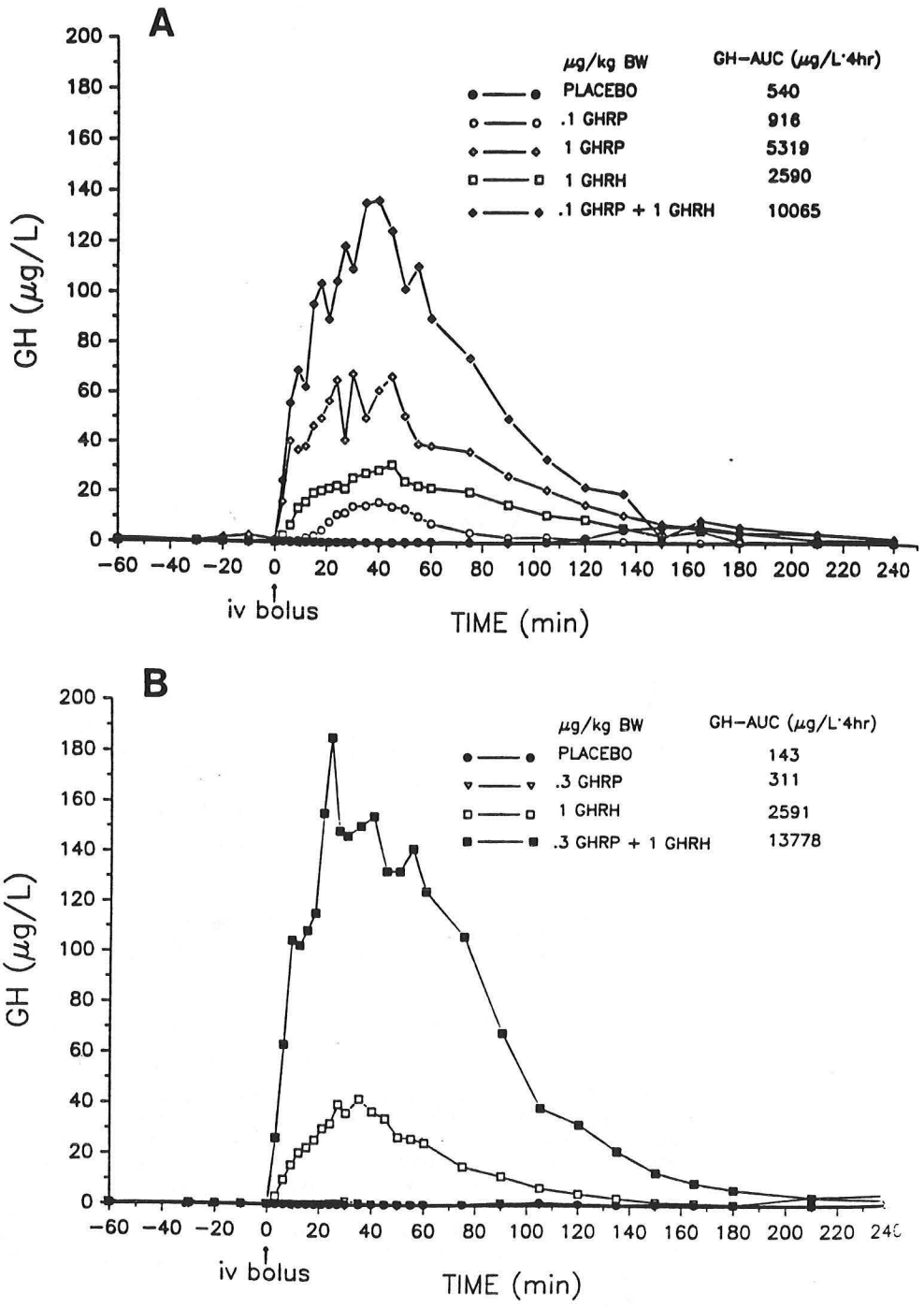


Fig. 2

A very interesting and somewhat underappreciated aspect of the hormonal control of growth hormone secretion is contained in the literature pertaining to a substance termed Growth Hormone Releasing Peptide or GHRP-6. This search apparently grew out of studies that examined the effects of peptide enkephalin analogues on pituitary hormone secretion (97). A large amount of investigation has resulted in the following conclusions. First, this compound appears to act at both the hypothalamus and pituitary levels of stimulate growth hormone secretion. Second, it appears to act via a receptor distinct from that which binds GHRH. Third, it appears to act within the cell via mechanisms distinct from those implicated in GHRH action. Finally, it appears to have the ability to amplify the effects of other growth hormone secretagogues. For example, a large synergism is observed when GHRH and GHRP are administered, compared to the levels observed when either is administered individually. It is postulated that GHRP is a synthetic

analogue of a substance that is a normal hormonal modulator of growth hormone secretion.



Comparative GH responses in individual subjects. GH responses to various doses of GHRP, GHRP plus GHRH, and 1.0 μg/kg GHRH in two normal men.

Fig. 3

Human Growth Hormone - Transport in Blood

Although hGH is a soluble molecule, a substantial proportion of the hormone circulates in blood complexed to a binding protein derived from the same gene as the growth hormone receptor (see below). Although is has been demonstrated that the half-life and clearance rates of the complexed and uncomplexed forms of growth hormone differ, different biological activities have not been demonstrated (84).

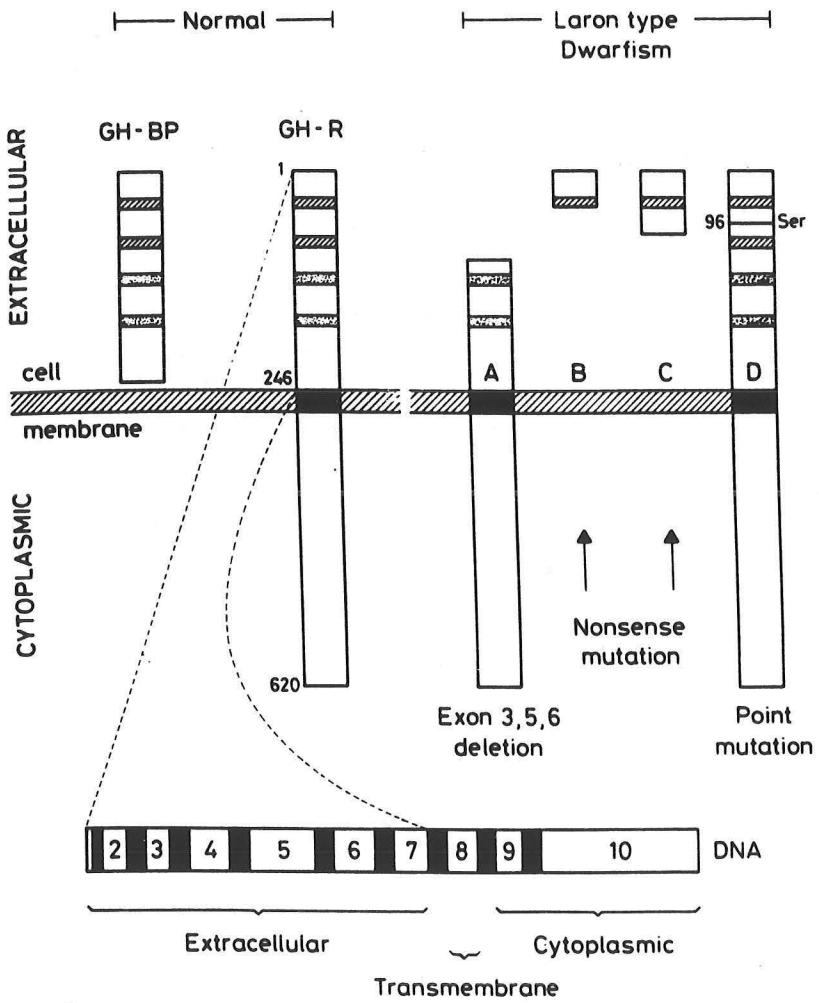


Figure 4 - *Left side,* Schematic representation of the GH receptor (GH-R), the GH-binding protein (GH-BP), and the GH-receptor gene. The transmembrane domain is shown in black and the numbers refer to amino acids of the mature protein. The numbered rectangles represent the exons for the receptor, and the black rectangles represent the introns (not to scale). *Right side,* Various receptor mutations identified in Laron type dwarfism, A = deletion of extracellular domain corresponding to exons 3,5,6; B and C = nonsense mutations with stop codons; and D = point mutation that leads to changing the phenylalanine in position 96 for a serine. (*Adapted* from Kelly PA, Djiane J, Postel-Vinay M-C: The prolactin/growth hormone receptor family. Endocrine Rev 12:235, 1991; © The Endocrine Society.)

Human Growth Hormone Receptor

Growth hormone exerts its effects by binding to specific receptors present on the surface of target cells. Two aspects of this receptor deserve comment. First, following the elucidation of the structure of the growth hormone receptor, it became clear that the circulating growth hormone binding protein is derived from the same gene as the growth hormone receptor itself. Second is the mechanism by which intracellular signalling is effected by the receptor following ligand binding. The intracellular segment did not contain prototypical kinase domains, although it was well known that receptor activation resulted in increased tyrosine kinase activity. Recent studies have demonstrated that the signalling mechanism is distinct and resides in a family of kinases, termed JAK kinases, that associate with the intracellular segment of the growth hormone receptor and are activated following binding of ligand (5). It appears that these kinases activated in individual cell types may represent a level at which substantial diversity in response to a single hormonal signal may be effected.

Growth Hormone - Effects on Cells and Tissues

Table II

SOMATOMEDIN HYPOTHESIS

1. Hypophysectomized rats demonstrate defective incorporation of [^{35}S] sulfate into cartilage matrix proteins.

2. When studied in vitro, this defect could not be repaired by the addition of growth hormone to the culture medium.

3. Rapid reversal of the defect was observed following the addition of serum from normal but not hypophysectomized rats.

The term paracrine is used to describe those biological effects that are induced by a hormonal signal which is not itself the final mediator. The actions of growth hormone represent one of the clearest examples of this type of physiology. A summary of the experiments that have led to the promulgation of the 'somatomedin hypothesis' are shown in Table II. These experiments suggested that normal serum would stimulate the growth of cartilage in culture, that serum from growth hormone deficient animals would not produce this effect, and that the addition of growth hormone would not replace the effect

of serum from growth hormone deficient animals treated with growth hormone. A large body of work now supports the concept that growth hormone acts to stimulate the production of IGF-I (somatomedin C) in many tissues (1). It is believed that in this way, IGF-I is directly responsible for many of the actions regulated by growth hormone. It should be pointed out, however, that many tissues contain growth hormone receptors. For this reason it is quite likely that growth hormone exerts its actions via a combination of endocrine and paracrine effects.

Somatomedin-C (IGF-I) as a Marker of Growth Hormone Status

Numerous studies have demonstrated the utility of plasma IGF-I measurements as an indicator of growth hormone secretion. These levels show a good correlation with estimates of integrated 24-h growth secretion (48). It is important to realize that IGF-I, its binding proteins, and their assays represents a complex area where much is still incompletely understood. The most important point to appreciate is that the level of IGF-I detected in the blood of patients varies widely depending on the age and sex of the individual. Thus, the normal range for age and sex must be used to interpret the results of any IGF-I assay. In addition to the differences due to age and sex, major differences are possible depending on the assay method employed. For this reason, extreme caution must be used when interpreting the significance of any IGF-I assay results.

Alterations in Growth Hormone Secretory Pattern in Aging Humans

By 1972, two groups had independently demonstrated that the normal nocturnal surges of growth hormone and the cumulative 24-h secretion of growth hormone declined as a function of age (47, 17). These observations were confirmed and extended in 1981 when Daniel Rudman and coworkers examined the levels of growth hormone, a serum marker of growth hormone action (somatomedin-C), and the responsiveness of the subjects to exogenous growth hormone in 94 healthy individuals spanning seven decades (122) (Fig. 5). The observations made by these authors can be summarized as follows: 1) Serum growth hormone levels were substantial in both waking and sleep. Exogenous (purified native) growth hormone administration in these individuals had no discernible effect on elemental balances or on plasma somatomedin-C levels. 2) Levels of somatomedin-C declined as a function of age. In the most carefully studied groups (20-29 and 60-79 year old age groups) these levels paralleled the quantities of nocturnal growth hormone released. 3) The levels of somatomedin-C in the 60-79 y/o age group segregated into two groups: in one group, the levels of somatomedin-C was higher and approached that observed for the younger aged individuals. In these patients, little response was observed (elemental balances or somatomedin-C) in response to exogenous growth hormone. The second group, however, characterized by low somatomedin-C levels and low nocturnal secretion of growth hormone, were seen to respond appreciably (using both parameters) to exogenous growth hormone. 4) Within each age group, the level of somatomedin-C was correlated, negatively, with the level of adiposity (expressed as wt/h^2).

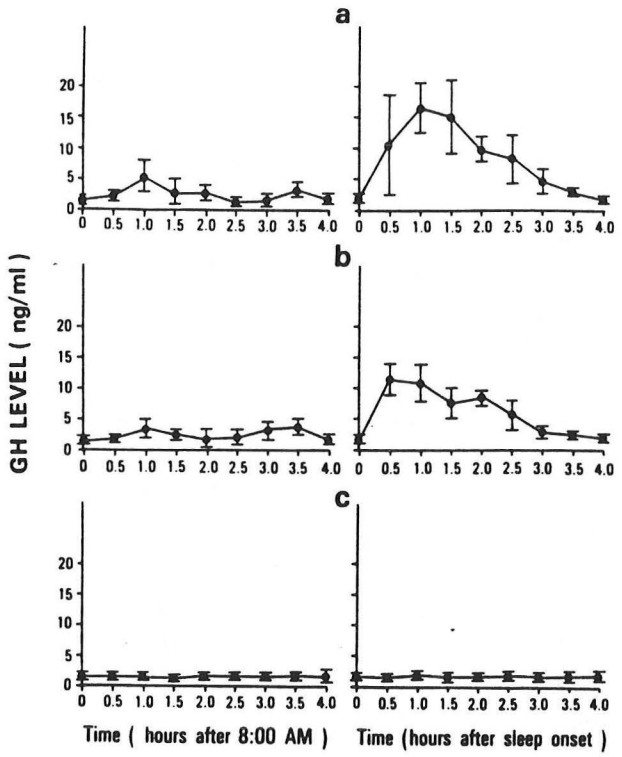


FIGURE 5A (a) Average serum GH concentration curves for six subjects ages 20–29 in both the waking (left) and sleeping (right) state. (b) Average serum GH concentration curves for six subjects ages 60–79 with SmC ≥ 0.64 U/ml in both the waking (diurnal) and sleeping (nocturnal) state. (c) Average serum GH concentration curves for six subjects ages 60–79 with SmC < 0.64 U/ml in both the waking (diurnal) and sleeping (nocturnal) state. Bars represent ± SD.

Data of Phase A: Comparison of Plasma SmC, Diurnal and Nocturnal Release of Endogenous GH, and Response to Exogenous hGH in Subjects of Third, Seventh, and Eighth Decades

	Age group (yr)		
	20–29 (n = 6)‡	60–79* (n = 12)	
		(n = 6) SmC < 0.64	(n = 6) SmC ≥ 0.64
SmC, *U/ml*	1.38 (0.42)	0.27 (0.04)	0.98 (0.15)
GH release§			
Peak day, *ng/ml*	7.27 (1.48)	3.25 (0.57)‖	5.39 (1.09)
Peak night, *ng/ml*	20.38 (5.51)	3.18 (0.47)‖	14.10 (3.31)
Ave area/h day, *ng/ml*	2.84 (0.37)	1.55 (0.13)‖	2.49 (0.35)
Ave area/h night, *ng/ml*	8.64 (1.48)	1.57 (0.11)‖	6.45 (1.00)
Elemental balances			
ΔN, $g/kg\ BW^{3/4} \times 10^{-1}/d$	0.13 (0.21)	1.31 (0.21)‖	0.10 (0.12)
ΔP, $g/kg\ BW^{3/4} \times 10^{-1}/d$	0.060 (0.078)	1.15 (0.17)‖	0.066 (0.080)
ΔK, $meq/kg\ BW^{3/4} \times 10^{-1}/d$	1.90 (1.06)	4.68 (2.45)‖	1.03 (1.58)
ΔSmC, *U/ml*	0.100 (0.153)	0.642 (0.112)‖	0.096 (0.085)

* For the 60–79-yr group, average (±SD) SmC was 0.62 (±0.39) U/ml. This group was subdivided on the basis of SmC level above or below 0.64 units/ml because this value represents the lower 2.5% limit for SmC in the 20–29 yr group.

‡ Phase A; combined SmC for phases A + B (n = 10) averaged 1.43 U/ml (0.34) in the 20–29-yr group.

‖ $P < 0.001$ when compared with age 20–29.

§GH concentration by time curves were quantitated by (i) measuring the peak serum GH value, and (ii) calculating the area under the serum GH concentration curve and dividing it by the length of the time interval to obtain the ave/hr.

Fig. 5B

The nature and cause of these changes in growth hormone secretory patterns have been the subject of a great deal of investigation. The data pertaining to even the observations themselves are confusing and at times even contradictory. In most investigations (47, 17, 122, 48) normal elderly subjects have been found to have decreased total and pulsatile growth hormone secretion, although this observation has not been uniform. A possible explanation for such discrepancies is that the analyses, focused on age groups, neglected one or more variables (e.g., obesity, nutrition) that affected growth hormone levels independent of age. This possibility was assessed in studies by Iranmanesh et al, who used deconvolution analysis to examine the effects of age and adiposity (separately and together) on rates of growth hormone secretion and clearance (77). The results of this study can be summarized as shown in Table III. Most important was the finding that daily growth hormone secretion was negatively correlated, independently, with age and BMI. Notably, the combination of these two variables produced had a dramatic effect. Both of these variables also had a significant, independent effect on growth hormone half-life. Of note, these investigators also noted significant correlations between free and total serum testosterone and all aspects of growth hormone secretion and half-life.

Clinical features of healthy aging men

Clinical parameters	Age tertiles		
	Young (n = 8)	Middle-aged (n = 5)	Older (n = 8)
Age (yr)	25 ± 1.5[a]	47 ± 3.8[b]	66 ± 3.8[c]
Somatomedin-C (U/ml)	0.94 ± 0.15[d]	0.73 ± 0.06	0.57 ± 0.22
Mean serum GH conc. (μg/L)	1.4 ± 0.3[a]	0.59 ± 0.22[b]	0.38 ± 0.10[b]
Body mass index (kg/m²)	23 ± 0.61[a]	29 ± 1.5[b]	26 ± 1.2[a,b]
Serum testosterone conc. (nmol/L)			
Total	2420 ± 230[a]	1630 ± 220[b]	1290 ± 110[b]
Free	109 ± 9.1[a]	70 ± 10[b]	74 ± 4.6[b]
Serum estradiol conc. (pmol/L)	125 ± 11[d]	103 ± 13	128 ± 17

Data are the mean ± SEM. n, Number of subjects per group.
[a–c] Means without common superscripts differ significantly by analysis of variance and Duncan's multiple range.
[d] $P > 0.05$.

Table IIIa

Multiple linear regression analysis of the effects of age and/or body mass index on specific parameters of GH secretion and clearance in healthy men

Parameter	Age	BMI	Age and BMI
GH secretory burst frequency (no./24 h)	0.0005	NS	0.0003 (−0.80)
Secretory burst half-duration (min)	NS	NS	NS
GH half-life (min)	0.024	0.045	0.0048 (−0.70)
Mass of GH secreted/burst (μg/L)	NS	NS	0.047 (−0.57)
Daily GH secretion rate (μg/L·24 h)	0.0031	0.027	0.00056 (−0.78)
GH secretory burst amplitude (μg/L·min)	NS	0.031	0.026 (−0.61)
Interburst interval (min)	0.01	NS	0.0197 (−0.62)
Somatomedin-C/IGF-I (U/mL)	0.03	0.01	<0.01 (−0.68)

BMI, Body mass index (kilograms per m²). *P* values are given for the null hypothesis of no relationship. Correlation coefficients are given in parentheses. Age and BMI were not significantly correlated in this subject group. NS = $P < 0.05$.

Table IIIb

The mechanisms that underlie the alterations in growth hormone secretion in aging adults remains incompletely characterized. Numerous investigators have examined the levels of growth hormone secretion in young and aged individuals in basal conditions and in response to a variety of provocative stimuli. In most instances, low basal growth

hormone levels have been reported. In most instances, it has been demonstrated that responsiveness to each of the provocative stimuli is detectable but is often diminished in elderly subjects. The overall impression that one is left with is not one of global hyporesponsiveness, but instead, a picture of altered responsiveness to most stimuli emerges. As a result of these studies, it has been hypothesized that as the result of aging that a state of increased 'somatostanergic tone' evolves, dampening the release of endogenous GHRH and the response to exogenous GHRH. In addition to their importance as far as mechanisms are concerned, these studies point to possible methods by which these trends might be reversed: 1) interference with the presumed increased levels of somatostatinergic tone (e.g., as has been observed following treatment with anticholinergic agents); 2) alternatively, administration of growth hormones secretagogue, such as GHRH, might be employed to counteract the observed decline in growth hormone secretion in aged individuals.

Measurements of Body Composition and Metabolism

Table IV Mean percentage body fat for the subject groups (M=male, F=female) using different methods.

Subject groups	mean percentage fat								
	IRI	BIA	SF	BMI	KJE	MODEL	TBN	TBW	TBK
16M[a]	15.9	16.8	17.8	19.5	20.7	21.9	22.4	22.4	22.9
SEM	1.4	1.6	1.4	0.9	1.2	1.7	2.1	1.6	1.9
17F[a]	27.6	31.5	30.3	28.2	32.0	35.8	36.0	36.3	32.3
SEM	1.0	2.1	1.0	0.9	1.4	1.5	1.9	1.5	2.2
10F[b]	31.6	43.3	40.0	43.4	62.7	44.6	49.6	43.8	40.2
SEM	2.3	2.5	0.8	1.8	4.1	2.0	1.7	2.1	2.3

a = BMI <30 kg m^{-2}, b = BMI >30 kg m^{-2}, SEM = standard error of the mean

IRI is near-infrared interactance, BIA is bioelectric impedance, SF is skin-fold anthropometry, TBN is total body nitrogen (measured using in vivo neutron activation analysis, TBK is total body potassium measured by whole-body counting, TBW is total body water measured by tritiated water dilution. MODEL refers to a method for estimating body fat using a 5-compartment model. BMI and KJE refer to estimates of body fat using two prediction equations.

Prior to a discussion of the effects of growth hormone in humans, a few comments need to be made regarding the methods that investigators use to study body composition. A list of commonly employed methods that can be used for such studied is listed in

Table IV (45, 142). Grossest of the methods are measurements such as skin-fold measurements which infer the quantity of adipose tissue by measurement of skin thickness at specific sites on the body. Such measurements are very crude and that changes in these values can represent alterations in other tissue compartments besides adipose tissue. Very commonly, measurements of body composition utilize isotope dilution techniques, such as radiolabeled water or potassium. The validity of these measurements, however, depends on the volumes of distribution of these materials: for example, if a compound alters the relative amount of total body water between intracellular and extracellular compartments, if measurements are made and interpreted based on the ratios present under basal (untreated) conditions, the changes detected may not in fact represent the alterations that are inferred. Underwater weighing is very exact and precise but gives little information except as it relates to total body densities. Radiographic techniques in some instances offer greater degrees of precision (e.g., areas of muscle, thickness of subcutaneous tissue) but are often insensitive to subtle changes in density.

For these reasons, although a variety of modalities are available to monitor body composition, each has its drawbacks. One can only feel truly confident about reports that employ multiple different techniques to demonstrate changes in body composition.

The Effects of Growth Hormone Administration - Children

The effects of growth hormone on the growth rates of growth hormone deficient children have been known since 1957. Only in later reports were the effects of other body composition described. Cheek et al (21) and Collipp et al (29) reported changes in skin-fold thickness and in total body potassium which were interpreted as a decrease in total body fat and an increase in lean body mass that accompanies the increase in linear growth

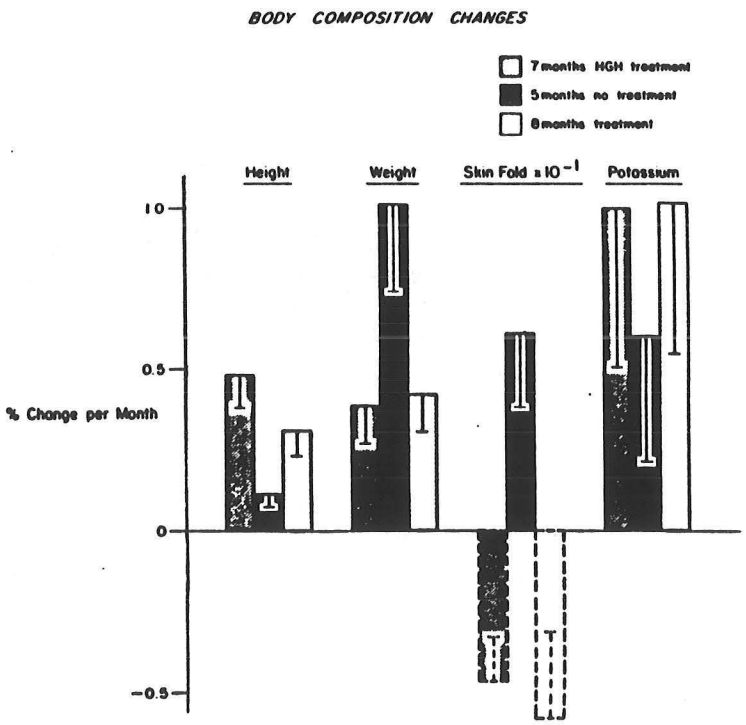


Fig. 6 Changes in height, weight, triceps skinfold thickness, and total body potassium in nine children receiving human growth hormone are presented. Mean per cent change per month (± 1 SD) are indicated during the three study periods.

resulting from growth hormone administration. These inferences have been confirmed in several other studies (100, 101) using metabolic, dilutional, and anthropomorphic measurements. Interestingly, in these studies of patients deficient in growth hormone, cessation of growth hormone therapy was associated with decreased lean body mass and increases in estimates of total body fat.

The Effect of Growth Hormone Administration in Growth Hormone Deficient Adults

Internists are often faced with the necessity of devising and implementing a hormone replacement regimen for patients with multiple hormonal deficiencies as the result of prior surgery or irradiation in the region of the pituitary. These regimens are invariably focused on the administration of thyroid hormone, glucocorticoids, and gonadal steroids. Growth hormone is ignored.

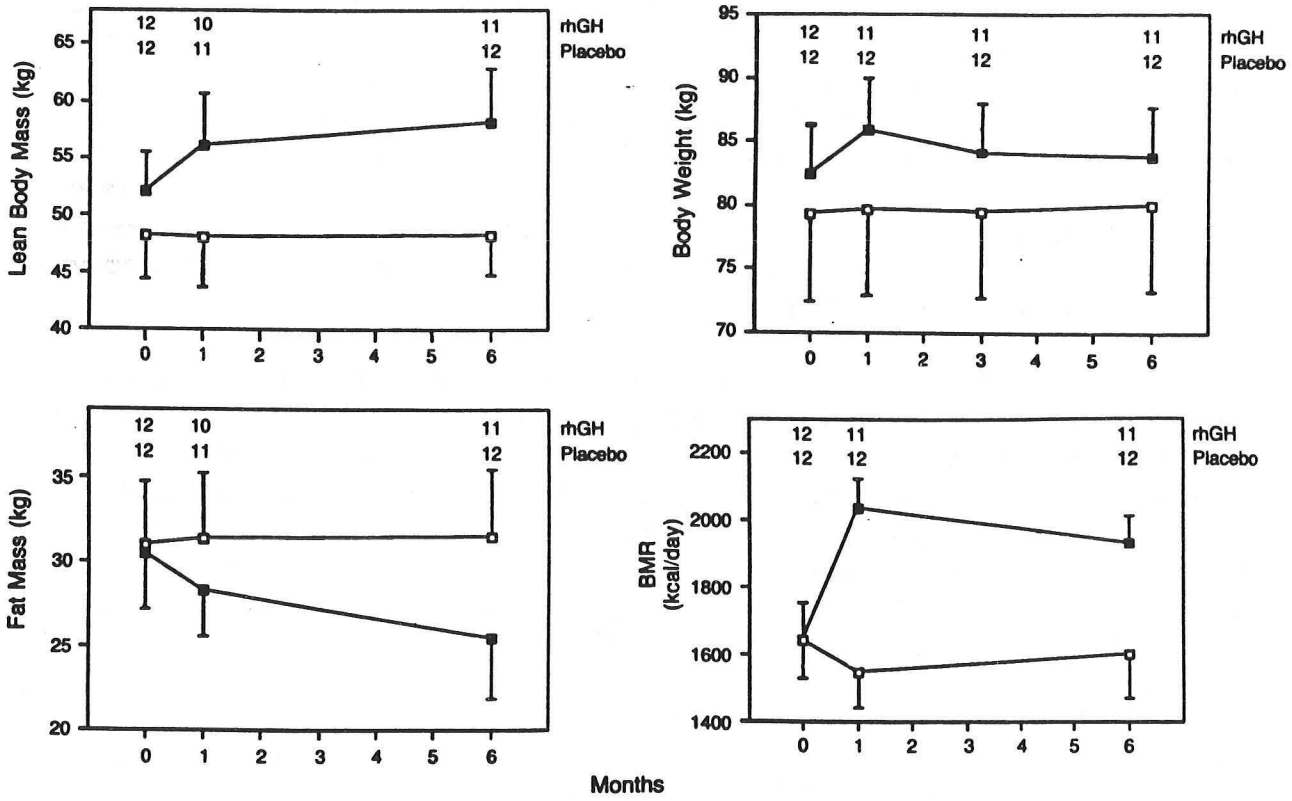


Figure 7 Mean Body Weight, Lean Body Mass, and Fat Mass during the Administration of rhGH (■—■) or Placebo (□—□) in Adults with Growth Hormone Deficiency.

The number of patients studied at each time in each group appears at the top of each panel. The horizontal bars indicate the SE for the mean values shown.

In 1989 two very interesting reports appeared by Jorgensen et al (81) and Salomon et al (124). These authors examined the effect of growth hormone administration to patients with documented deficiencies of growth hormone. The studies of Salomon et al studied 24 patients, aged 21-51 years, who had acquired the deficiency of growth hormone as adults as a consequence of a pituitary tumor or its treatment. The effects of the administration of rhGH or placebo was studied for a period of six months. Lean body mass was estimated by measurements of total body potassium. Measurements of skin-fold thickness and basal metabolic rate were made in parallel. The results can be summarized as follows: 1) serum IGF-I levels rose from the lower limits of normal into the high normal or slightly elevated range, compared to normal controls; 2) the body mass of patients did not change significantly during the course of the study period; 3) the group receiving rGH demonstrated an 11% increase in lean body mass; and 4) adipose tissue mass decreased from 30±3 kg to 28±3 kg at one month and 26±4 kg (a decrease of approximately 20%) at six months. These latter changes (in lean and adipose tissue mass) were in parallel with changes of skin-fold thickness (-24±3 mm) and decreases in the waist-to-hip ratio (0.89±0.06 to 0.87±0.04). These changes in the growth hormone-treated group were also reflected in a significant increase in urine creatinine excretion (+18%). These alterations were statistically significant in the growth hormone, in contrast to insignificant changes in the placebo treated group. 5) Basal metabolic rate increased from 1664±78 Kcal to 2035±86 (one month) to 1931±84 (six months) Kcal/day in the growth hormone treated group. BMR did not change significantly in the placebo group during the study period.

These results suggest that the growth hormone deficiency documented in these individuals has demonstrable effects (subnormal lean body mass, increased adipose tissue mass) on body composition.

Although conducted on a much different patient population, the study of Jogensen et al (81) was conducted using a similar design. Patients were growth hormone deficient adults who had previously received growth hormone therapy. In this study the effects of four months of growth hormone administration on muscle and adipose tissue volume, isometric muscle strength, exercise capacity, and renal function were assessed. Interestingly, these investigators employed CT of the thighs to assess muscle and adipose area, a method quite different from the preceding study. The results, tabulated in Table V, demonstrate significant changes in muscle and adipose volume, while the overall thigh volume itself did not change. These investigators also demonstrated concordant changes in skin-fold thickness. Interestingly, they also noted a significant increase in exercise capacity and a slight, but insignificant increase in isometric strength. Similar effects were observed in a study conducted by Moller et al (96).

Taken together, these studies clearly suggest that growth hormone administration to growth hormone deficient adults results in substantial changes in body composition, with increases in lean body mass and decreases in adipose tissue mass. While many caveats should be applied to individual indirect measurements of body composition, the concordant

TABLE V—EFFECT OF GH ON PHYSIOLOGICAL FEATURES

—	Mean (SEM)		
	GH	Placebo	p
*Thigh volume**			
Muscle	70·0 (3·7)	66·3 (3·1)	<0·01
Adipose tissue	36·5 (4·7)	39·3 (4·7)	<0·05
Total	105·2 (6·4)	104·7 (6·3)	NS
Subscapular skinfold thickness (mm)	14·1 (6·7)	16·4 (7·1)	<0·01†
Isometric strength (Nm)	86·8 (7·2)	80·3 (5·9)	NS (0·08)
Exercise capacity (kJ)	60·8 (7·2)	54·2 (6·6)	<0·05
Blood pressure (mm Hg) at rest			
Systolic	108 (3)	102 (2)	NS
Diastolic	71 (2)	69 (2)	NS
Blood pressure (mm Hg) on exercise			
Systolic	161 (2)	160 (5)	NS
Diastolic	70 (2)	74 (2)	NS
Ventricular wall mass (g)	203 (15)	200 (15)	NS

*Mean of right and left thigh, ml /0·8 cm cross-sectional slice. Three volumes (muscle, adipose, total) measured independently by scanner.
†After correction for period effect, skinfold being thicker after first period ($p < 0·05$).

results observed using dilutional techniques, anthropomorphic techniques, biochemical measurements, and radiographic methods suggest that these changes are in fact real and not simply complicated artifacts. An additional intriguing aspect of this latter study is the suggestion that these changes can have discernible functional consequences.

Growth Hormone Administration to Elderly Subjects

While the possibility that growth hormone administration to selected patients with specific deficiencies of growth hormone due to pituitary disease is of potential significance to those patients, it does not necessarily have broad implications for the larger group of aging humans.

In 1990 Daniel Rudman and his associates published a paper that stimulated an enormous amount of interest (121). In this study, Rudman identified 21 men aged 61-81 and randomized them to treatment with growth hormone or no treatment. The characteristics of these two groups of patients are summarized in Table VI. These groups were well matched for age and body composition, as well as somatomedin-C levels less than 350 U/L. As shown in Table VII, treatment with growth hormone resulted in a rise to a mean of 830 U/L and remained at this level throughout the course of the treatment period. No change was observed in the control group.

Table VIIClinical 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 (99–117)
Medical conditions (no. of subjects)		
Degenerative joint disease	5	2
Benign prostatic hypertrophy	3	1
Glaucoma	1	1
Cataract	2	1
Arteriosclerotic heart disease*	3	1
Gallstones	0	1
Kidney stone	1	1
Hiatus hernia	0	1
Medications (no. of subjects)		
Nonsteroidal antiinflammatory drug	3	1
Pilocarpine eyedrops	1	1
Cimetidine	0	1

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

Table VII

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 CHANGES‡
Weight (kg)	1	77.2±11.4	78.2±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^2)					
Mid-shaft radius	1	0.74±0.10	0.74±0.12	0.85	+0.04 (−0.02 to +0.10)
	2	0.76±0.10	0.71±0.07	0.09	
Distal radius	1	0.37±0.07	0.36±0.08	0.12	−0.004 (−0.03 to +0.02)
	2	0.34±0.04	0.33±0.05	0.26	
Average, lumbar vertebrae 1–4	1	1.23±0.12	1.25±0.13	0.04	+0.006 (−0.04 to +0.05)
	2	1.29±0.25	1.29±0.26	0.64	
Ward's triangle	1	0.70±0.14	0.69±0.13	0.15	−0.018 (−0.08 to +0.05)
	2	0.70±0.17	0.70±0.17	0.69	
Greater trochanter	1	0.85±0.13	0.85±0.13	0.72	+0.007 (−0.05 to +0.03)
	2	0.81±0.15	0.81±0.13	0.55	
Femoral neck	1	0.92±0.15	0.91±0.14	0.53	−0.029 (−0.08 to +0.03)
	2	0.89±0.14	0.85±0.14	0.14	
Mandibular-height ratio	1	0.45±0.15	0.46±0.11	0.87	−0.003 (−0.07 to +0.06)
	2	0.47±0.12	0.47±0.12	0.98	

*Plus–minus values are means ±SD.

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

‡The difference in changes (12-month value minus 6-month value) is the average change in group 1 minus the average change in group 2. Values in parentheses are 95 percent confidence intervals, calculated by independent-sample, unequal-variance t-tests.

These treatment groups showed several significant differences. Measurements of lean body mass increased and adipose tissue mass decreased in the growth hormone treated group. These changes are of a similar magnitude to those observed in growth hormone deficient children and in growth hormone deficient adults (see above). Of the other parameters measured, trends toward increased bone density were observed in the lumbar vertebrae and increased skin thickness.

Following this first report, the cohort of patients has been enlarged and followed longitudinally. The most recent summary of results was published in 1993 (119) and are depicted in Table VIII. These results are in general agreement with the results obtained earlier in the trial, although the increase in lumbar bone density that was originally reported (121) has not been maintained. This report also includes preliminary results from the first time point after stopping growth hormone. These results, obtained at three months post therapy suggest that the changes in LBM and adipose tissue mass have begun reverting toward the pretreatment values.

Table VIII

Outcome Variables as Percentage of Initial Baseline Value

	Month	0	6	12	18	21
Lean body mass	**Group I**	**100%**	**99.0%**	**104.8%***	**105.7%***	**102.7%***
	Group II	**100%**	**99.8%**	**99.1%**	**96.0%***	**91.7%***
Adipose mass	**Group I**	**100%**	**96.8%**	**86.9%***	**84.8%***	**90.1%***
	Group II	**100%**	**98.2%**	**102.2%**	**97.8%**	**105.5%**
Skin thickness (sum of four sites)	**Group I**	**100%**	**98.9%**	**106.4%***	**104.3%***	
	Group II	**100%**	**99.0%**	**98.0%**	**93.9%***	
Liver size	**Group I**	**100%**	**99.2%**	**119%***	**108%***	
	Group II	**100%**	**98.6%**	**98.3%**	**93.3%**	
Spleen size	**Group I**	**100%**	**95.1%**	**116.6%**	**123.0%**	
	Group II	**100%**	**95.2%**	**101.9%**	**93.2%***	
Sum of 10 muscle areas	**Group I**	**100%**	**101.7%**	**111.3%***	**110.6%**	
	Group II	**100%**	**104.2%**	**96.7%**	**98.3%**	

*P < .05 for change from initial baseline value by paired t-test.

In recent years, a number of other reports have emerged using different treatment regimens to treat a variety of subject populations, including two recent studies of the effects in healthy elderly women (71, 131). Each has shown similar effects on lean body weight and adipose tissue mass.

Effects of Growth Hormone Administration on Muscle Function

The observation that growth hormone administration increases indices suggesting increased muscle mass has prompted several studies to examine the effects on muscle strength or on exercise performance. These studies have examined either growth hormone deficient subjects or otherwise normal elderly men.

TABLE IX *Results of muscle strength and fatigue tests expressed as z-scores*

	Treatment	Baseline	3 mo	6 mo	Δ
1st dorsal interosseus	rhGH	0.42±0.29	1.79±0.41	0.98±0.43	0.62±0.24
	Placebo	0.12±0.33	0.35±0.37	0.27±0.38	0.15±0.19
Abductor digiti minimi	rhGH	1.64±0.42	2.68±0.53	2.29±0.58	0.57±0.21
	Placebo	0.91±0.35	1.18±0.27	1.08±0.27	0.17±0.29
Abductor pollicus brevis	rhGH	−0.82±0.27	0.14±0.35	−0.15±0.26	0.66±0.21
	Placebo	−0.92±0.27	−0.76±0.31	−0.47±0.29	0.45±0.27
Elbow flexion	rhGH	0.32±0.41	0.56±0.38	0.80±0.58	0.54±0.49
	Placebo	−0.71±0.49	−0.57±0.40	−0.30±0.44	0.42±0.37
Shoulder abduction	rhGH	−0.65±0.39	−0.29±0.44	0.08±0.40	0.73±0.26
	Placebo	−0.78±0.30	−0.39±0.38	−0.31±0.33	0.47±0.21
Hip flexion	rhGH	0.19±0.35	1.19±0.47	1.47±0.44	1.25±0.27*
	Placebo	0.44±0.34	0.37±0.31	0.70±0.36	0.26±0.12
Hip abduction	rhGH	−0.22±0.50	0.67±0.41	0.54±0.63	0.85±0.44
	Placebo	−0.61±0.48	−0.81±0.42	−0.50±0.45	0.11±0.30
Knee extension	rhGH	0.71±0.41	0.69±0.44	0.99±0.44	0.23±0.23
	Placebo	0.18±0.30	0.31±0.28	0.38±0.30	0.20±0.16
Neck flexion	rhGH	0.26±0.44	0.24±0.34	0.36±0.39	0.25±0.16
	Placebo	0.02±0.65	0.40±0.72	0.21±0.55	0.31±0.32
Mean *z*-score	rhGH	0.22±0.29	0.81±0.30	0.81±0.37	0.62±0.15
	Placebo	−0.17±0.28	0.08±0.26	0.13±0.30	0.30±0.14
Fatigue index	rhGH	−0.97±0.47	−1.40±0.52	−1.45±0.50	−0.67±0.86
	Placebo	−1.94±0.39	−1.81±0.23	−1.97±0.55	−0.40±0.58

Values are means ± SE for all patients tested (n = 12 in rhGH data at entry and all placebo data and n = 11 for subsequent rhGH data; neck flexion data at entry limited to n = 7 in both groups and thereafter n = 11 in each group). Mean *z*-score is an average of all muscle groups. No significant differences existed between groups before treatment. * P = 0.004.

TABLE X *Maximal O_2 uptake expressed per body weight, lean body mass, and cross-sectional area of thigh muscle*

	Treatment	Baseline	3 mo	6 mo	P
$\dot{V}O_{2\,max}$/body wt, ml/kg	rhGH	22.7±1.5	27.5±1.8	27.8±1.6	0.05
	Placebo	24.2±2.3	26.4±2.2	25.8±1.7	
$\dot{V}O_{2\,max}$/lean body mass, ml/kg	rhGH	35.9±1.7		40.5±1.6	0.88
	Placebo	38.9±3.0		41.7±1.8	
$\dot{V}O_{2\,max}$/thigh muscle area, ml/cm^2	rhGH	14.5±0.6	16.4±0.9	16.6±0.9	0.96
	Placebo	15.4±1.1	17.8±1.5	17.1±1.0	

Values are means ± SE. Lean body mass was measured by total body potassium content (^{40}K) and cross-sectional area of thigh muscle by computerized tomography of dominant midthigh. Comparisons of differences from baseline to 6-mo values of 2 groups (P) performed with analysis of covariance. No significant differences existed between groups at baseline.

The studies of Cuneo et al (37, 38) examined the effects of growth hormone administration to 24 growth hormone deficient adults, the deficiency caused by tumor or previous radiotherapy. These subjects were randomized into two groups and received either placebo or growth hormone in a blended fashion. In this study, as in other studies, lean muscle mass increased and body fat decreased. In several of the limb girdle muscles

(shoulder abduction, hip flexion, hip abduction) a trend toward increased strength was noted. The authors suggested that these changes did not achieve significance due to the small number of subjects. Interestingly, when the exercise performance of these same patients was studied, significant changes in anaerobic threshold and Vo_2 max were observed.

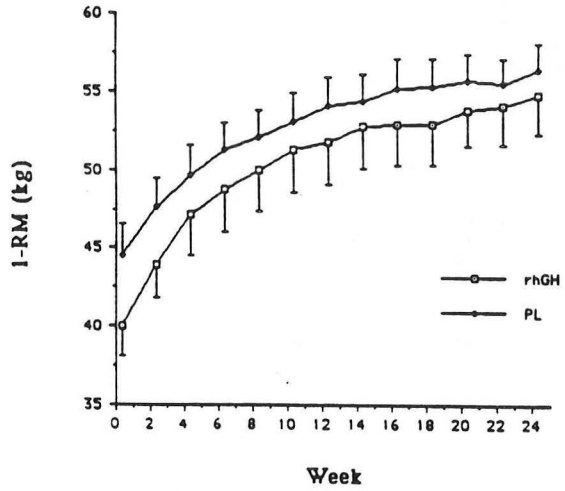


FIG. 8 Average muscle strength for the 10 exercises between 0-24 weeks. No difference exists at any time point between the rhGH (n = 9) and PL (n = 7) groups.

A different approach was employed by Taaffe and coworkers (128). These authors examined the hypothesis that diminished growth hormone secretion in elderly men limits the strength gains observed during exercise testing regimens. For this reason, 18 subjects were divided into two groups (growth hormone treated and placebo) and then examined during the ensuing 14 weeks of treatment during which time both groups underwent progressive weight training.

Growth Hormone Administration in Adults: Side Effects

The normal secretory pattern of growth hormone is characterized by discrete pulses. The plasma levels of growth hormone following growth hormone administration is decidedly not pulsatile. The regimens employed have attempted to walk a thin line between growth hormone administration in doses adequate to effect 'replacement' and doses that induce complications due to growth hormone excess. The complications observed in studies of growth hormone administration to older adults in one study (27) are depicted in Fig. 9.

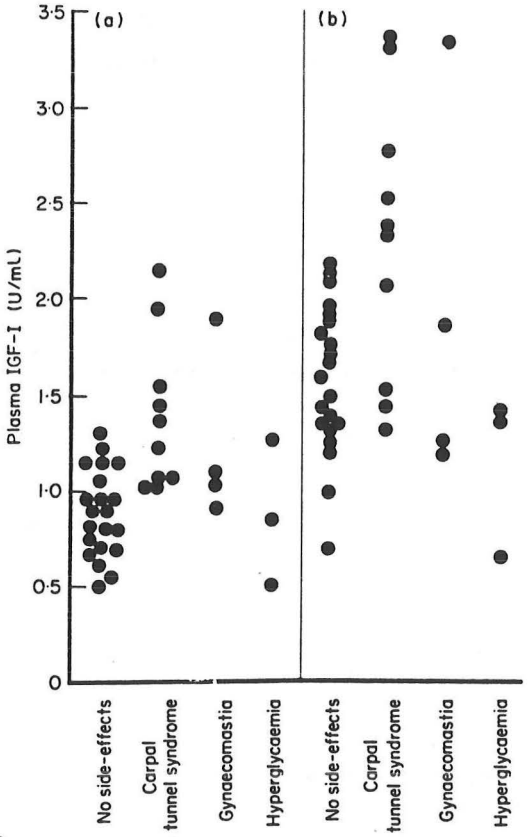


Fig. 9a, Mean and b, peak plasma IGF-I levels (units/ml) during hGH treatment in subgroups of group 1.

Several of the complications are predictable based on symptoms observed in acromegalic patients. These include carpal tunnel syndrome and increases in fasting blood glucose measurements. Fluid retention, although not a prominent feature of acromegaly, has clearly been associated with recombinant growth hormone administration. An unusual side effect noted in this patient population is that of gynecomastia. This side effect has not been reported in patients with acromegaly, although increased rates of breast cancer were noted by Nabarro et al (99) in his female patients with acromegaly.

Inspection of the data in these series suggests that the side effects observed may be minimized by carefully controlling the range targeted by the growth hormone administration regimen. In particular, Cohn et al (27) have suggested that the growth hormone dose be adjusted to bring the IGH-I level to 0.5-1.0 units/ml. These same authors have also proposed that patients be excluded from such regimens on the basis of positive

screening for hyperglycemia and subclinical carpal tunnel syndrome. Similar types of complications were observed in elderly female patients (47, 87).

Are There Alternative Approaches That Avoid the Toxicities Associated with Injections of rGH?

As implied in the above discussion, the complications associated with injections of growth hormone are likely due to the dose and pattern of administration. This constitutes an inherent weakness pertaining to treatment using injections of growth hormone. For this reason, several alternatives have been explored to attempt to avoid a non-physiologic pattern of growth hormone presentation and/or to maintain some level of feedback inhibition in the growth hormone axis.

GHRH Administration

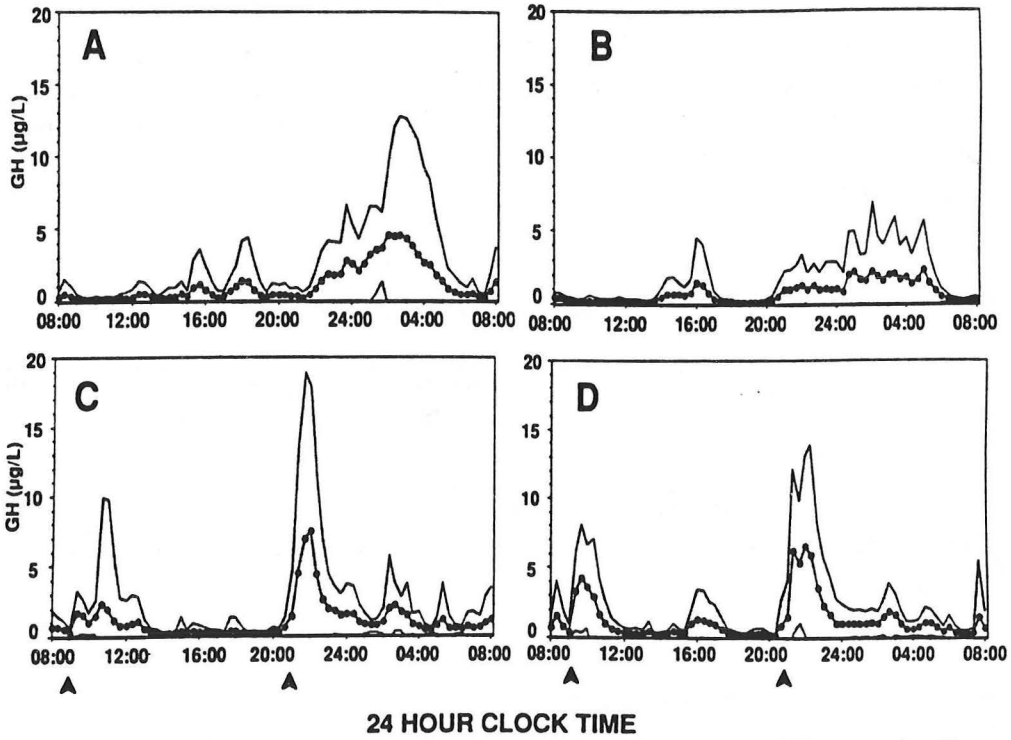


FIG. 10 Serum GH values (mean ± SD) at 20-min intervals during a 24-h period in young (A) and old (B) men at baseline and in old men during low (C) and high (D) dose GHRH treatment. *Arrowheads* in C and D indicate the time of sc GHRH injections.

The first report of this type was published in 1989 by Iovino et al (76). These authors observed that treatment with an intravenous bolus of GHRH (1-40) for a 12-day period resulted in an increase in plasma growth hormone. These observations were extended by Corpas et al (34) who examined the effects of injections of GHRH (1-29) to a group of old and young men. This study demonstrated significant increases of indices of 24-hour mean growth hormone secretion and IGF-I in the old men. This was due to large growth hormone peaks occurring shortly following injection of GHRH. A number of investigations have further refined this approach using continuous administration of GHRH, using either short-term (50, 134) or long-term (35) administration. These studies demonstrated that using this approach that pulsatility of growth hormone release was maintained. Although some differences are apparent in the results of the different studies, particularly during the daytime hours when growth hormone secretion is typically lowest. Despite these differences, it is apparent that this methodology is an alternative one that does permit growth hormone levels to be increased. This approach, however, requires parenteral administration.

Growth Hormone Secretagogues

It is in this arena that the most interesting biology exists and where potential therapeutic compounds may lie. Recall that investigators had originally discovered that GHRP - a synthetic hexapeptide - could act to effect substantial growth hormone release (97). As reviewed above, there is considerable evidence to suggest that this compound acts through a receptor different than that of the GHRH-R, acts via distinct second messenger pathways (22), and can act synergistically with GHRH to effect growth hormone release.

TABLE XI Integrated serum GH concentrations (IGHC) and serum IGF-I before (Pre) and 24 h after (Post) administration of placebo, L, or GHRH.

	Placebo	L (0.2 mg/kg)	L (0.75 mg/kg)	GHRH (1 μg/kg)
IGHC (min/μg·L)	124 ± 17	887 ± 128[a]	1937 ± 283[a]	487 ± 83[a,b]
IGF-I (μg/L)				
Pre	142 ± 12	143 ± 11	136 ± 11	146 ± 13
Post	159 ± 13	161 ± 16	163 ± 13	169 ± 16

Values are the mean ± SE. Significance was determined by analysis of variance with Duncan's multiple comparison test.
[a] $P < 0.05$ *vs.* placebo.
[b] $P < 0.05$ *vs.* L (0.75 mg/kg).

Table XII Peak or integrated (AUC) serum cortisol and PRL concentrations

	Placebo	L (0.2 mg/kg)	L (0.75 mg/kg)	GHRH (1 μg/kg)
Cortisol				
Peak (μg/dL)	9.9 ± 0.98	13.0 ± 1.0[a,b]	15.4 ± 1.3[a,b]	8.9 ± 0.96
AUC (min/μg·dL)	854 ± 38	1167 ± 40[a]	1387 ± 50[a,b]	860 ± 45
PRL				
Peak (μg/L)	4.5 ± 0.47	10.2 ± 0.76[a,b]	17.1 ± 1.7[a,b]	5.8 ± 0.96
AUC (min/μg·L)	553 ± 26	894 ± 32[a]	1375 ± 65[a,b]	685 ± 38

Values are the mean ± SE. Significance was determined by analysis of variance with Duncan's multiple comparison test.
[a] $P < 0.05$ *vs.* saline.
[b] $P < 0.05$ *vs.* GHRH.

These observations have been exploited by a number of groups, particularly that of Smith and co-workers at Merck Sharp & Dohme Research Laboratories. These investigators used the chemical structure of GHRP to devise non-peptidyl analogues that have similar activity to GHRP-6 (67, 125, 126). The most interesting features of this compound are 1) that it is active in a variety of species including man and 2) it, like GHRP, acts through sites distinct from that of the GHRH-R. Recently the first studies of the lead Merck compound (L-692,429) was reported by Aloi et al (1). These studies demonstrated that intravenous administration of L resulted in large amount of growth hormone, in fact, in many cases larger than the amounts released in response to GHRH. This was a highly selective response, with only small changes in cortisol or prolactin being discernible. The compound was well tolerated and was without significant side effects. This compound is orally active and is already the subject of a large number of clinical investigations. Of note, this approach leaves intact many of the normal feedback regulatory loops.

Summary

A large body of work has been published in the last five years relating to the changes that occur in the growth hormone axis in normal aging humans. At this juncture, it seems clear that reduced levels of growth hormone are secreted as age advances and that this decline is due to central mechanisms and due to increased levels of adipose tissue in older men and women. It is evident as well that growth hormone administration to growth hormone deficient children, growth hormone deficient adults, or elderly subjects results in increased lean body mass and decrease in adipose tissue. A few reports have suggested that these changes have resulted in increased muscle strength or exercise tolerance. It is not at all certain that these changes will be observed when studies are conducted in larger groups of the general population.

REFERENCES

1. Aloi JA, Gertz BJ, Hartman ML, Huhn WC, Pezzoli SS, Wittreich JM, Krupa DA, Thorner MO: Neuroendocrine responses to a novel growth hormone secretagogue, L-692,429, in healthy older subjects. J Clin Endocrinol Metab 79:943-949, 1994

2. Aloia JF, Roginsky MS, Jowsey J, Dombrowski CS, Shukla KK, Cohn SH: Skeletal metabolism and body composition in acromegaly. J Clin Endocrinol Metab 35:543, 1972

3. Alster DK, Bowers CY, Jaffe CA, Ho PJ, Barkan AL: The growth hormone (GH) response to GH-releasing peptide (His-dTrp-Ala-Trp-dPhe-Lys-NH2), GH-releasing hormone, and thyrotropin-releasing hormone in acromegaly. J Clin Endocrinol Metab 77:842-845, 1993

4. Arce V, Cella SG, Loche S, Ghigo E, Devesa J, Müller EE: Synergistic effect of growth hormone-releasing hormone (GHRH) and clonidine in stimulating GH release in young and old dogs. Brain Res 537:359-362, 1990

5. Argetsinger LS, Campbell GS, Yang X, Witthuhn BA, Silvennoinen O, Ihle JN, Carter-Su C: Identification of JAK2 as a growth hormone receptor-associated tyrosine kinase. Cell 74:237-244, 1993

6. Arimura A: Regulation of growth hormone secretion. In The Pituitary Gland. Edited by H Imura, New York, Raven Press, 1994, pp 217-259

7. Bando H, Zhang C, Takada Y, Yamasaki R, Saito S: Impaired secretion of growth hormone-releasing hormone, growth hormone and IGF-I in elderly men. Acta Endocrinol (Copenh) 124:31-36, 1991

8. Bellantoni MF, Harman SM, Cho DE, Blackman MR: Effects of progestin-opposed transdermal estrogen administration on growth hormone and insulin-like growth factor-I in postmenopausal women of different ages. J Clin Endocrinol Metab 72:172-178, 1991

9. Bengtsson B-A, Brummer R-JM, Eden S, Bosaeus I: Body composition in acromegaly. Clin Endocrinol 30:121-130, 1989

10. Bercu BB, Weideman CA, Walker RF: Sex differences in growth hormone (GH) secretion by rats administered GH-releasing hexapeptide. Endocrinology 129:2592-2598, 1991

11. Bercu BB, Yang S-W, Masuda R, Hu C-S, Walker RF: Effects of coadministered growth hormone (GH)-releasing hormone and GH-releasing hexapeptide on maladaptive aspects of obesity in Zucker rats. Endocrinology 131:2800-2804, 1992

12. Bercu BB, Yang S-W, Masuda R, Walker RF: Role of selected endogenous peptides in growth hormone-releasing hexapeptide activity: Analysis of growth hormone-releasing hormone, thyroid hormone-releasing hormone, and gonadotropin-releasing hormone. Endocrinology 130:2579-2586, 1992

13. Borst SE, Millard WJ, Lowenthal DT: Growth hormone, exercise, and aging: The future of therapy for the frail elderly. J Am Geriatr Soc 42:528-535, 1994

14. Bowers CY, Alster DK, Frentz JM: The growth hormone-releasing activity of a synthetic hexapeptide in normal men and short statured children after oral administration. J Clin Endocrinol Metab 74:292-298, 1992

15. Bowers CY, Reynolds GA, Durham D, Barrera CM, Pezzoli SS, Thorner MO: Growth hormone (GH)-releasing peptide stimulates GH release in normal men and acts synergistically with GH-releasing hormone. J Clin Endocrinol Metab 70:975-982, 1990

16. Bowers CY, Sartor AO, Reynolds GA, Badger TM: On the actions of the growth hormone-releasing hexapeptide, GHRP. Endocrinology 128:2027-2035, 1991

17. Carlson HE, Gillin JC, Gorden P, Snyder F: Absence of sleep-related growth hormone peaks in aged normal subjects and in acromegaly. J Clin Endocrinol Metab 34:1102-1105, 1972

18. Casanueva FF: Physiology of growth hormone secretion and action. Endocrinol Metab Clin North Am 21:483, 1992

19. Ceda GP, Ceresini G, Denti L, Magnani D, Marchini L, Valenti G, Hoffman AR: Effects of cytidine 5'-diphosphocholine administration on basal and growth hormone-releasing hormone-induced growth hormone secretion in elderly subjects. Acta Endocrinol (Copenh) 124:516-520, 1991

20. Cella SG, Arce VM, Pieretti F, Locatelli V, Settembrini BP, Müller EE: Combined administration of growth-hormone-releasing hormone and clonidine restores defective growth hormone secretion in old dogs. Neuroendocrinology 57:432-438, 1993

21. Cheek DB, Wyllie RG: Postnatal cellular growth: Hormonal considerations. In Fetal and Postnatal Cellular Growth: Hormones and Nutrition. Edited by DB Cheek, New York, John Wiley & Sons, 1975, pp 415-435

22. Cheng K, Chan WW-S, Butler B, Barreto A,Jr., Smith RG: Evidence for a role of protein kinase-C in His-d-Trp-Ala-Trp-d-Phe-Lys-NH2-induced growth hormone release from rat primary pituitary cells. Endocrinology 129:3337-3342, 1991

23. Christensen H, Andreassen TT, Oxlund H: Increased mechanical strength of left colon in old rats treated with growth hormone. Gerontology 38:245-251, 1992

24. Christiansen JS, Jorgensen JO, Pedersen SA, Müller J, Jorgensen J, Moller J, Heickendorf L, Skakkebaek NE: GH-replacement therapy in adults. Horm Res 36(Suppl.1):66-72, 1991

25. Clemmons DR, Smith-Banks A, Underwood LE: Reversal of diet-induced catabolism by infusion of recombinant insulin-like growth factor-I in humans. J Clin Endocrinol Metab 75:234-238, 1992

26. Cohen P, Ocrant I, Fielder PJ, Neely EK, Gargosky SE, Deal CI, Ceda GP, Youngman O, Pham H, Lamson G, Giudice LC, Rosenfeld RG: Insulin-like growth factors (IGFs): Implications for aging. Psychoneuroendocrinology 17:335-342, 1992

27. Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D: Carpal tunnel syndrome and gynaecomastia during growth hormone treatment of elderly men with low circulating IGF-I concentrations. Clin Endocrinol 39:417-425, 1993

28. Coiro V, Volpi R, Bertoni P, Ginzi G, Marcato A, Caiazza A, Colla R, Giacalone G, Rossi G, Chiodera P: Effect of potentiation of cholinergic tone by pyridostigmine on the GH response to GHRH in elderly men. Gerontology 38:217-222, 1992

29. Collipp PJ, Curti V, Thomas J, Sharma RK, Maddaiah VT, Cohn SH: Body compositiion changes in children receiving human growth hormone. Metabolism 22:589, 1973

30. Colonna VdG, Fidone F, Cocchi D, Müller EE: Feedback effects of growth hormone on growth hormone-releasing hormone and somatostatin are not evident in aged rats. Neurobiol Aging 14:503-507, 1993

31. Copeland KC, Nair KS: Recombinant human insulin-like growth factor-I increases forearm blood flow. J Clin Endocrinol Metab 79:230-232, 1994

32. Cordido F, Penalva A, Dieguez C, Casanueva FF: Massive growth hormone (GH) discharge in obese subjects after the combined administration of GH-releasing hormone and GHRP-6: Evidence for a marked somatotroph secretory capability in obesity. J Clin Endocrinol Metab 76:819-823, 1993

33. Corpas E, Harman SM, Blackman MR: Human growth hormone and human aging. Endocr Rev 14:20, 1993

34. Corpas E, Harman SM, Pineyro MA, Roberson R, Blackman MR: Growth hormone (GH)-releasing hormone-(1-29) twice daily reverses the decreased GH and insulin-like growth factor-I levels in old men. J Clin Endocrinol Metab 75:530-535, 1992

35. Corpas E, Harman SM, Pineyro MA, Roberson R, Blackman MR: Continuous subcutaneous infusions of growth hormone (GH) releasing hormone 1-44 for 14 days increase GH and insulin-like growth factor-I levels in old men. J Clin Endocrinol Metab 76:134-138, 1993

36. Cuneo RC, Salomon F, McGauley GA, Sönksen PH: The growth hormone deficiency syndrome in adults. Clin Endocrinol 37:387-397, 1992

37. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sönksen PH: Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. J Appl Physiol 70:695-700, 1991

38. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sönksen PH: Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. J Appl Physiol 70:688-694, 1991

39. Cuttler L, Collins BJ, Marone PA, Szabo M: The effect of isobutylmethylxanthine, forskolin, and cholera toxin on growth hormone release from pituitary cell cultures of perinatal and mature rats. Endocr Res 19(1):33-46, 1993

40. Daughaday WH, Rotwein P: Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. Endocr Rev 10:68, 1989

41. Deslauriers N, Gaudreau P, Abribat T, Renier G, Petitclerc D, Brazeau P: Dynamics of growth hormone responsiveness to growth hormone releasing factor in aging rats: Peripheral and central influences. Neuroendocrinology 53:439-446, 1991

42. Dysken MW, Skare SS, Burke MS, Mach JR,Jr., Galka T, Billington CJ: Intrasubject reproducibility of growth hormone-releasing hormone-stimulated growth hormone in older women, older men, and younger men. Biol Psychiatry 33:610-617, 1993

43. Ebeling PR, Jones JD, O'Fallon WM, Janes CH, Riggs BL: Short-term effects of recombinant human insulin-like growth factor I on bone turnover in normal women. J Clin Endocrinol Metab 77:1384-1387, 1993

44. Bowers CY: Editorial: A new dimension on the induced release of growth hormone in obese subjects. J Clin Endocrinol Metab 76:817, 1993

45. Ellis KJ, Eastman JD: Human Body Composition: In Vivo Methods, Models, and Assessment. New York, Plenum Press, 1993

46. Ferguson JK, Donald RA, Weston TS, Espiner EA: Skin thickness in patients with acromegaly and Cushing's syndrome and response to treatment. Clin Endocrinol 18:347-353, 1983

47. Finkelstein JW, Roffwarg HP, Boyar RM, Kream J, Hellman L: Age-related change in the twenty-four hour spontaneous secretion of growth hormone. J Clin Endocrinol Metab 35:665-670, 1972

48. Florini JR, Prinz PN, Vitiello MV, Hintz RL: Somatomedin-C levels in healthy young and old men: Relationship to peak and 24-hour integrated levels of growth hormone. J Gerontol 40:2-7, 1985

49. Fryburg DA, Louard RJ, Gerow KE, Gelfand RA, Barrett EJ: Growth hormone stimulates skeletal muscle protein synthesis and antagonizes insulin's antiproteolytic action in humans. Diabetes 41:424-429, 1992

50. Gelato MC, Oldfield E, Loriaux DL, Merriam GR: Pulsatile growth hormone secretion in patients with acromegaly and normal men: The effects of growth hormone-releasing hormone infusion. J Clin Endocrinol Metab 71:585-590, 1990

51. Gertner JM: Effects of growth hormone on body fat in adults. Horm Res 40:10-15, 1993

52. Ghigo E, Goffi S, Arvat E, Imperiale E, Boffano GM, Valetto MR, Mazza E, Santi I, Magliona A, Boghen MF, Boccuzzi G, Camanni F: A neuroendocrinological approach to evidence an impairment of central cholinergic function in aging. J Endocrinol Invest 15:665-670, 1992

53. Ghigo E, Goffi S, Arvat E, Nicolosi M, Procopio M, Bellone J, Imperiale E, Mazza E, Baracchi G, Camanni F: Pyridostigmine partially restores the GH responsiveness to GHRH in normal aging. Acta Endocrinol (Copenh) 123:169-174, 1990

54. Ghigo E, Goffi S, Nicolosi M, Ervat E, Valente F, Mazza E, Ghigo MC, Camanni F: Growth hormone (GH) responsiveness to combined administration of arginine and GH-releasing hormone does not vary with age in man. J Clin Endocrinol Metab 71:1481-1485, 1990

55. Giustina A, Bodini C, Doga M, Schettino M, Pizzocolo G, Giustina G: Galanin decreases circulating growth hormone levels in acromegaly. J Clin Endocrinol Metab 74:1296-1300, 1992

56. Giustina A, Bossoni S, Cimino A, Pizzocolo G, Romanelli G, Wehrenberg WB: Impaired growth hormone (GH) response to pyridostigmine in type 1 diabetic patients with exaggerated GH-releasing hormone-stimulated GH secretion. J Clin Endocrinol Metab 71:1486-1490, 1990

57. Giustina A, Bussi AR, Conti C, Doga M, Legati F, Macca C, Zuccato F, Wehrenberg WB: Comparative effect of galanin and pyridostigmine on the growth hormone response to growth hormone-releasing hormone in normal aged subjects. Horm Res 37:165-170, 1992

58. Giustina A, Licini M, Bussi AR, Girelli A, Pizzocolo G, Schettino M, Negro-Vilar A: Effects of sex and age on the growth hormone response to galanin in healthy human subjects. J Clin Endocrinol Metab 76:1369-1372, 1993

59. Goodman HG, Grumbach MM, Kaplan SL: Growth and growth hormone. II. A comparison of isolated growth-hormone deficiency and multiple pituitary-hormone deficiencies in 35 patients with idiopathic hypopituitary dwarfism. N Engl J Med 278:57-68, 1968

60. Goya RG, Gagnerault M-C, Leite de Moraes MC, Savino W, Dardenne M: In vivo effects of growth hormone on thymus function in aging mice. Brain Behav Immun 6:341-354, 1992

61. Greenspan SL, Sparrow D, Rowe JW: Dopaminergic regulation of gonadotropin and thyrotropin hormone secretion is altered with age. Horm Res 36:41-46, 1991

62. Hanew K, Utsumi A, Sugawara A, Shimizu Y, Abe K: Enhanced GH responses to combined administration of GHRP and GHRH in patients with acromegaly. J Clin Endocrinol Metab 78:509-512, 1994

63. Hartman ML, Veldhuis JD, Thorner MO: Normal control of growth hormone secretion. Horm Res 40:37-47, 1993

64. Hattori N, Kurahachi H, Ikekubo K, Ishihara T, Moridera K, Hino M, Saiki Y, Imura H: Effects of sex and age on serum GH binding protein levels in normal adults. Clin Endocrinol 35:294-297, 1991

65. Heinrichs C, Vis HL, Bergmann P, Wilton P, Bourguignon JP: Effects of 17 months treatment using recombinant insulin-like growth factor-I in two children with growth hormone insensitivity (Laron) syndrome. Clin Endocrinol 38:647-651, 1993

66. Henneman PH, Forbes AP, Moldawer M, Dempsey EF, Carroll EL: Effects of human growth hormone in man. J Clin Invest 39:1223-1238, 1960

67. Hickey G, Jacks T, Judith F, Taylor J, Schoen WR, Krupa D, Cunningham P, Clark J, Smith RG: Efficacy and specificity of L-692,429, a novel nonpeptidyl growth hormone secretagogue, in beagles. Endocrinology 134:695-701, 1994

68. Ho KKY, Hoffman DM: Aging and growth hormone. Horm Res 40:80-86, 1993

69. Hoffman AR, Lieberman SA, Ceda GP: Growth hormone therapy in the elderly: Implications for the aging brain. Psychoneuroendocrinology 17:327-333, 1992

70. Holl RW, Snehotta R, Siegler B, Scherbaum W, Heinze E: Binding protein for human growth hormone: Effects of age and weight. Horm Res 35:190-197, 1991

71. Holloway L, Butterfield G, Hintz RL, Gesundheit N, Marcus R: Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. J Clin Endocrinol Metab 79:470-479, 1994

72. Horber FF, Haymond MW: Human growth hormone prevents the protein catabolic side effects of prednisone in humans. J Clin Invest 86:265-272, 1990

73. Houben H, Denef C, Vranckx C: Stimulation of growth hormone and prolactin release from rat pituitary cell aggregates by bombesin- and ranatensin-like peptides is potentiated by estradiol, 5α-dihydrotestosterone, and dexamethasone. Endocrinology 126:2257-2266, 1990

74. Huhn WC, Hartman ML, Pezzoli SS, Thorner MO: Twenty-four-hour growth hormone (GH)-releasing peptide (GHRP) infusion enhances pulsatile GH secretion and specifically attenuates the response to a subsequent GHRP bolus. J Clin Endocrinol Metab 76:1202-1208, 1993

75. Imura H: The Pituitary Gland. New York, Raven Press, 1994

76. Iovino M, Monteleone P, Steardo L: Repetitive growth hormone-releasing hormone administration restores the attenuated growth hormone (GH) response to GH-releasing hormone testing in normal aging. J Clin Endocrinol Metab 69:910, 1989

77. Iranmanesh A, Lizarralde G, Veldhuis JD: Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab 73:1081-1088, 1991

78. Iranmanesh A, Veldhuis JD: Clinical pathophysiology of the somatotropic (GH) axis in adults. Endocrinol Metab Clin North Am 21:783, 1992

79. Jaffe CA, Ho PJ, Demott-Friberg R, Bowers CY, Barkan AL: Effects of a prolonged growth hormone (GH)-releasing peptide infusion on pulsatile GH secretion in normal men. J Clin Endocrinol Metab 77:1641-1647, 1993

80. Jorgensen JOL, Christiansen JS: Growth hormone therapy. Lancet 341:1247, 1993

81. Jorgensen JOL, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS: Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet 1:1221, 1989

82. Kaiser FE, Silver AJ, Morley JE: The effect of recombinant human growth hormone on malnourished older individuals. J Am Geriatr Soc 39:235-240, 1991

83. Kaufman J-M, Taelman P, Vermeulen A, Vandeweghe M: Bone mineral status in growth hormone-deficient males with isolated and multiple pituitary deficiencies of childhood onset. J Clin Endocrinol Metab 74:118-123, 1992

84. Kelly PA, Djiane J, Postel-Vinay M-C, Edery M: The prolactin/growth hormone receptor family. Endocr Rev 12:235-251, 1991

85. Khansari DN, Gustad T: Effects of long-term, low-dose growth hormone therapy on immune function and life expectancy of mice. Mech Ageing Dev 57:87-100, 1991

86. Kupfer SR, Underwood LE, Baxter RC, Clemmons DR: Enhancement of the anabolic effects of growth hormone and insulin-like growth factor I by use of both agents simultaneously. J Clin Invest 91:391-396, 1993

87. Lamberts SWJ, Valk NK, Binnerts A: The use of growth hormone in adults: a changing scene. Clin Endocrinol 37:111-115, 1992

88. Laron Z, Klinger B: Body fat in Laron syndrome patients: Effect of insulin-like growth factor I treatment. Horm Res 40:16-22, 1993

89. Laron Z, Klinger B, Jensen LT, Erster B: Biochemical and hormonal changes induced by one week of administration of rIGF-I to patients with Laron type dwarfism. Clin Endocrinol 35:145-150, 1991

90. Malozowski S, Hao EH, Ren SG, Marin G, Liu L, Southers JL, Merriam GR: Growth hormone (GH) responses to the hexapeptide GH-releasing peptide and GH-releasing hormone (GHRH) in the cynomolgus macaque: Evidence for non-GHRH-mediated responses. J Clin Endocrinol Metab 73:314-317, 1991

91. Martinoli MG, Ouellet J, Rheaume E, Pelletier G: Growth hormone and somatostatin gene expression in adult and aging rats as measured by quantitative in situ hybridization. Neuroendocrinology 54:607-615, 1991

92. Mauras N, Horber FF, Haymond MW: Low dose recombinant human insulin-like

growth factor-I fails to affect protein anabolism but inhibits islet cell secretion in humans. J Clin Endocrinol Metab 75:1192-1197, 1992

93. Meacham LR, Brown MR, Murphy TL, Keret R, Silbergeld A, Laron Z, Parks JS: Characterization of a noncontiguous gene deletion of the growth hormone receptor in Laron's syndrome. J Clin Endocrinol Metab 77:1379-1383, 1993

94. Merimee TJ, Russell B, Quinn S: Growth hormone-binding proteins of human serum: Developmental patterns in normal man. J Clin Endocrinol Metab 75:852-854, 1992

95. Miell JP, Taylor AM, Jones J, Buchanan CR, Rennie J, Sherwood R, Leicester R, Ross RJM: Administration of human recombinant insulin-like growth factor-I to patients following major gastrointestinal surgery. Clin Endocrinol 37:542-551, 1992

96. Moller J, Jorgensen JOL, Lauersen T, Frystyk J, Naeraa RW, Orskov H, Christiansen JS: Growth hormone dose regimens in adult GH deficiency: Effects on biochemical growth markers and metabolic parameters. Clin Endocrinol 39:403-408, 1993

97. Momany FA, Bowers CY, Reynolds GA, Chang D, Hong A, Newlander K: Design, synthesis, and biological activity of peptides which release growth hormone in vitro. Endocrinology 108:31, 1981

98. Morrison WB, Goff BL, Stewart-Brown B, Incefy GS, Arp LH, Roth JA: Orally administered clonidine as a secretagogue of growth hormone and as a thymotrophic agent in dogs of various ages. Am J Vet Res 51:65, 1990

99. Nabarro JDN: Acromegaly. Clin Endocrinol 26:481-512, 1987

100. Novak LP, Hayles AB, Cloutier MD: Effect of HGH on body composition of hypopituitary dwarfs. Mayo Clin Proc 47:241-246, 1972

101. Parra A, Argote RMa, Garcia G, Cervantes C, Alatorre S, Pérez-Pasten E: Body composition in hypopituitary dwarfs before and during human growth hormone therapy. Metabolism 28:851, 1979

102. Penalva A, Pombo M, Carballo A, Barreiro J, Casanueva FF, Dieguez C: Influence of sex, age and adrenergic pathways on the growth hormone response to GHRP-6. Clin Endocrinol 38:87-91, 1993

103. Perry HM,III, Morley JE, Coe RM(eds): Aging and Musculoskeletal Disorders: Concepts, Diagnosis, and Treatment. New York, Springer, 1993

104. Pontiroli AE, Ruga S, Maffi P, Scaglia L, Perfetti MG, Pozza G: Pituitary reserve after repeated administrations of releasing hormones in young and in elderly men: Reproducibility on different days. J Endocrinol Invest 15:559-566, 1992

105. Popovic V, Damjanovic S, Micic D, Petakov M, Dieguez C, Casanueva FF: Growth hormone (GH) secretion in active acromegaly after the combined administration of GH-releasing hormone and GH-releasing peptide-6. J Clin Endocrinol Metab 79:456-460, 1994

106. Prins GS, Cecim M, Birch L, Wagner TE, Bartke A: Growth response and androgen receptor expression in seminal vesicles from aging transgenic mice expressing human or bovine growth hormone genes. Endocrinology 131:2016-2023, 1992

107. Prysor-Jones RA, Jenkins JS: Effect of excessive secretion of growth hormone on tissues of the rat, with particular reference to the heart and skeletal muscle. J Endocrinol 85:75-82, 1980

108. Pyka G, Wiswell RA, Marcus R: Age-dependent effect of resistance exercise on growth hormone secretion in people. J Clin Endocrinol Metab 75:404-407, 1992

109. Raskind MA, Peskind ER, Veith RC, Wilkinson CW, Federighi D, Dorsa DM: Differential effects of aging on neuroendocrine responses to physostigmine in normal men. J Clin Endocrinol Metab 70:1420-1425, 1990

110. Rasmussen MH, Frystyk J, Andersen T, Breum L, Christiansen JS, Hilsted J: The impact of obesity, fat distribution, and energy restriction on insulin-like growth factor-1 (IGF-1), IGF-binding protein-3, insulin, and growth hormone. Metabolism 43:315-319, 1994

111. Renner U, Brockmeier S, Strasburger CJ, Lange M, Schopohl J, Müller OA, Werder KV, Stalla GK: Growth hormone (GH)-releasing peptide stimulation of GH release from human somatotroph adenoma cells: Interaction with GH-releasing hormone, thyrotropin-releasing hormone, and octreotide. J Clin Endocrinol Metab 78:1090-1096, 1994

112. Robinson BM, Friberg RD, Bowers CY, Barkan AL: Acute growth hormone (GH) response to GH-releasing hexapeptide in humans is independent of endogenous GH-releasing hormone. J Clin Endocrinol Metab 75:1121-1124, 1992

113. Rogol AD, Weltman JY, Evans WS, Veldhuis JD, Weltman AL: Long-term endurance training alters the hypothalamic-pituitary axes for gonadotropins and growth hormone. Endocrinol Metab Clin North Am 21:817, 1992

114. Rose SR, Municchi G, Barnes KM, Kamp GA, Uriarte MM, Ross JL, Cassorla F, Cutler GB,Jr.: Spontaneous growth hormone secretion increases during puberty in normal girls and boys. J Clin Endocrinol Metab 73:428-435, 1991

115. Rosen T, Eden S, Göran L, Wilhelmsen L, Bengtsson B-Å: Cardiovascular risk factors in adult patients with growth hormone deficiency. Acta Endocrinol (Copenh) 129:195-200, 1993

116. Rosen T, Hansson T, Granhed H, Szucs J, Bengtsson B-Å: Reduced bone mineral content in adult patients with growth hormone deficiency. Acta Endocrinol (Copenh) 129:201-106, 1993

117. Roubenoff R, Rall LC: Humoral mediation of changing body composition during aging and chronic inflammation. Nutr Rev 51:1-11, 1993

118. Rubin CD, Reed B, Sakhaee K, Pak CYC: Treating a patient with the Werner syndrome and osteoporosis using recombinant human insulin-like growth factor. Ann Intern Med 121:665-668, 1994

119. Rudman D, Feller AG, Cohn L, Shetty KR, Caindec N, Rudman IW: Growth hormone in elderly men. In Aging and Musculoskeletal Disorders: Concepts, Diagnosis, and Treatment. Edited by HM Perry,III, JE Morley, RM Coe, New York, Springer, 1993, pp 267-291

120. Rudman D, Feller AG, Cohn L, Shetty KR, Rudman IW, Draper MW: Effects of human growth hormone on body composition in elderly men. Horm Res 36(Suppl.1):73-81, 1991

121. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE: Effects of human growth hormone in men over 60 years old. N Engl J Med 323:1-6, 1990

122. Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP: Impaired growth hormone secretion in the adult population. J Clin Invest 67:1361-1369, 1981

123. Rudman D, Shetty KR: Unanswered questions concerning the treatment of hyposomatotropism and hypogonadism in elderly men. J Am Geriatr Soc 42:522-527, 1994

124. Salomon F, Cuneo RC, Hesp R, Sönksen PH: The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321:1797-1803, 1989

125. Schoen WR, Pisano JM, Prendergast K, Wyvratt MJ,Jr., Fisher MH, Cheng K, Chan WW-S, Butler B, Smith RG, Ball RG: A novel 3-substituted benzazepinone growth hormone secretagogue (L-692,429). J Med Chem 37:897-906, 1994

126. Smith RG, Cheng K, Schoen WR, Pong S-S, Hickey G, Jacks T, Butler B, Chan WW-S, Chaung L-YP, Judith F, Taylor J, Wyvratt MJ, Fisher MH: A nonpeptidyl growth hormone secretagogue. Science 260:1640, 1993

127. Sohmiya M, Kato Y: Renal clearance, metabolic clearance rate, and half-life of human growth hormone in young and aged subjects. J Clin Endocrinol Metab 75:1487-1490, 1992

128. Taaffe DR, Pruitt L, Reim J, Hintz RL, Butterfield G, Hoffman AR, Marcus R: Effect of recombinant human growth hormone on the muscle strength response to resistance exercise in elderly men. J Clin Endocrinol Metab 79 (in press):1994

129. Tanaka K, Inoue S, Shiraki J, Shishido T, Saito M, Numata K, Takamura Y: Age-related decrease in plasma growth hormone: Response to growth hormone-releasing hormone, arginine, and L-dopa in obesity. Metabolism 40:1257-1262, 1991

130. Tanner JM, Hughes PCR, Whitehouse RH: Comparative rapidity of response of height, limb muscle and limb fat to treatment with human growth hormone in patients with and without growth hormone deficiency. Acta Endocrinol (Copenh) 84:681-696, 1977

131. Thompson JL, Butterfield GE, Marcus R, Hintz RL, Van Loan M, Ghiron L, Hoffman AR: The effects of recombinant human insulin-like growth factor-I and growth hormone on body composition in elderly women. Submitted 1994

132. Ullman M, Ullman A, Sommerland H, Skottner A, Oldfors A: Effects of growth hormone on muscle regeneration and IGF-I concentration in old rats. Acta Physiol Scand 140:521-525, 1990

133. Usala A-L, Madigan T, Burguera B, Cefalu W, Sinha MK, Powell JG, Usala SJ: High dose intravenous, but not low dose subcutaneous, insulin-like growth factor-I therapy induces sustained insulin sensitivity in severely resistant type I diabetes mellitus. J Clin Endocrinol Metab 79:435-440, 1994

134. Vance ML, Kaiser DL, Martha PM,Jr., Furlanetto R, Rivier J, Vale W, Thorner MO: Lack of in vivo somatotroph desensitization or depletion after 14 days of continuous growth hormone (GH)-releasing hormone administration in normal men and a GH-deficient boy. J Clin Endocrinol Metab 68:22-28, 1989

135. Vanderschueren-Lodeweyckx M: The effect of simple obesity on growth and growth hormone. Horm Res 40:23-30, 1993

136. Vandeweghe M, Taelman P, Kaufman J-M: Short and long-term effects of growth hormone treatment on bone turnover and bone mineral content in adult growth hormone-deficient males. Clin Endocrinol 39:409-415, 1993

137. Wabitsch M, Heinze E: Body fat in GH-deficient children and the effect of treatment. Horm Res 40:5-9, 1993

138. Walker RF, Yang S-W, Bercu BB: Robust growth hormone (GH) secretion in aged female rats co-administered GH-releasing hexapeptide (GHRP-6) and GH-releasing hormone (GHRH). Life Sci 49:1499-1504, 1991

139. Ward HC, Halliday D, Sim AJW: Protein and energy metabolism with biosynthetic human growth hormone after gastrointestinal surgery. Ann Surg 206:56-61, 1987

140. Wheeler MD, Schutzengel RE, Barry S, Styne DM: Changes in basal and stimulated growth hormone secretion in the aging rhesus monkey: A comparison of chair restraint and tether and vest sampling. J Clin Endocrinol Metab 71:1501-1507, 1990

141. Yarasheski KE, Zachwieja JJ, Angelopoulos TJ, Bier DM: Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters. J Appl Physiol 74:3073-3076, 1993

142. Yasumura S, Harrison JE, McNeill KG, Woodhead AD, Dilmanian FA: In Vivo Body Composition Studies: Recent Advances. New York, Plenum Press, 1990

143. Zachwieja JJ, Bier DM, Yarasheski KE: Growth hormone administration in older adults: Effects on albumin synthesis. Am J Physiol (Endocrinol Metab 29) 266:E840-E844, 1994