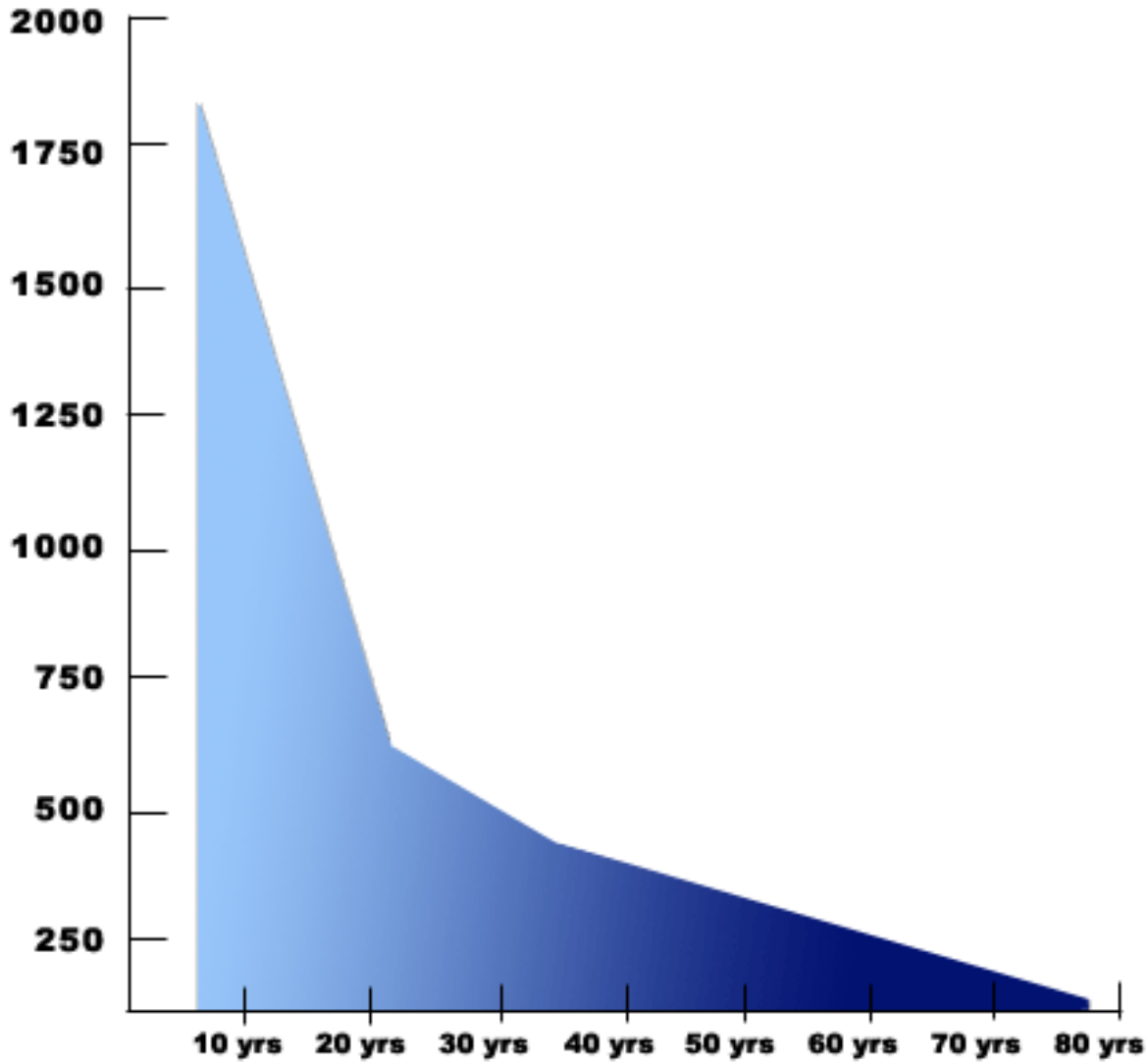
Sermorelin

A Unique Approach to GHRT for Age-Management Medicine

RF Walker, Ph.D., R.Ph.

One of the most significant effects of aging resulting from loss of temporal order and internal stability is neuroendocrine tissue degeneration with reduced production and secretion of hormones relative to that which occurs in youth!

DECLINE IN GROWTH HORMONE WITH AGE



Reduced Longevity in Untreated Subjects with Isolated GH Deficiency

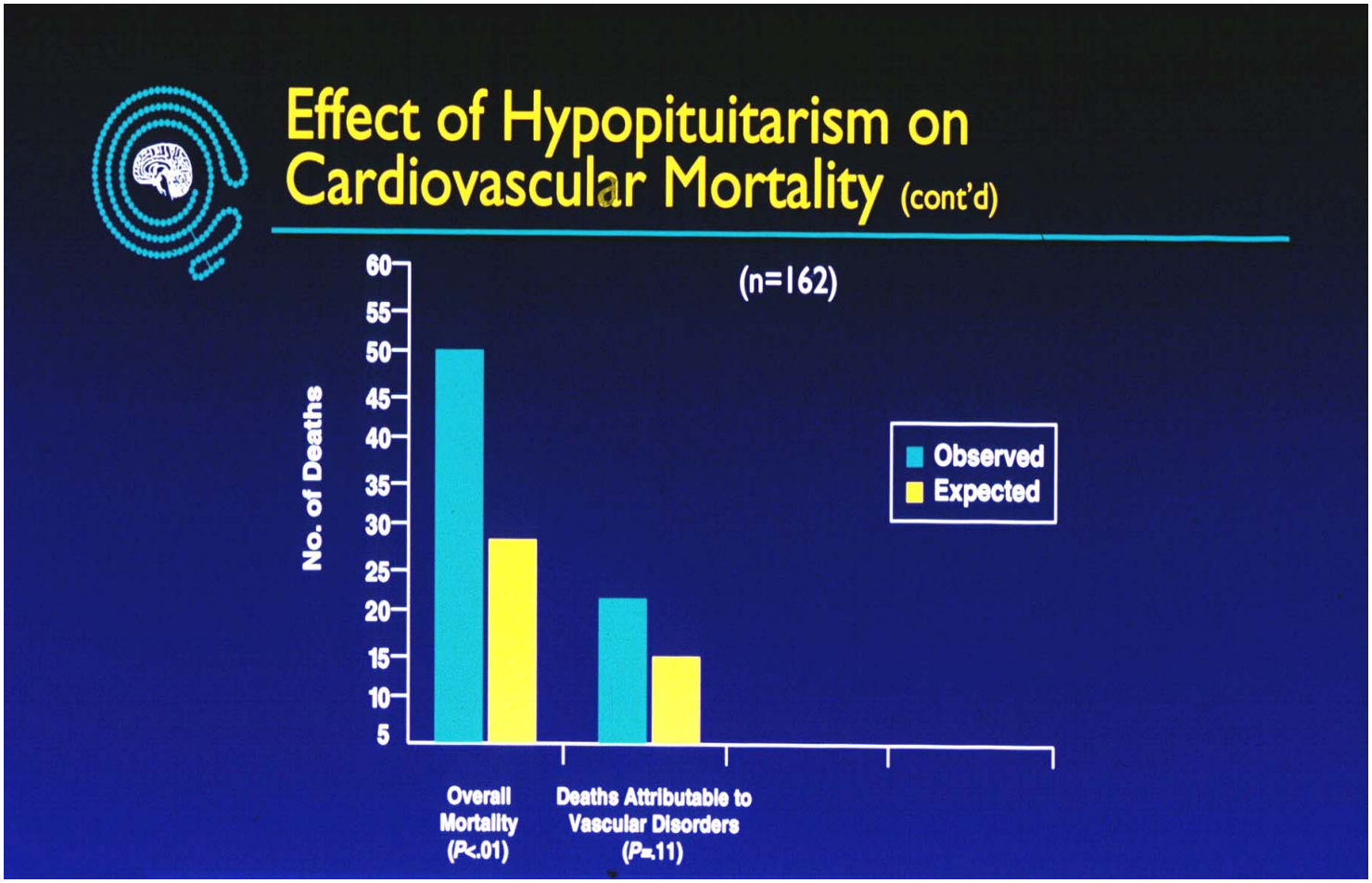
TABLE 1. Life span

		Life span (yr) mean (median, range)	
Affected males (IGHD type 1A)	n:5	57.4 (56, 41–77)	$P < 0.0001$
Unaffected healthy brothers	n:11	70.9 (75, 40–87)	
Unaffected healthy males (same population)	n:100	70.2 (74, 23–91)	ns
Affected females (IGHD type 1A)	n:6	47.4 (46, 29–63)	$P < 0.0001$
Unaffected healthy sisters	n:14	74.2 (80, 22–89)	
Unaffected healthy females (same population)	n:100	75.3 (79, 21–90)	ns

ns, Not significant.

- Genetic deletion encompassing GH-1 gene causes isolated GHD
- Subjects were never treated for GHD. They provide an opportunity to compare life span and cause of death directly with unaffected siblings as well as the normal population
- Life span significantly shortened in GHD subjects indicating GHRT is crucially important for sustaining life and health during aging

Besson et al. J Clin Endocrinol Metab 88:3664-3667, 2003



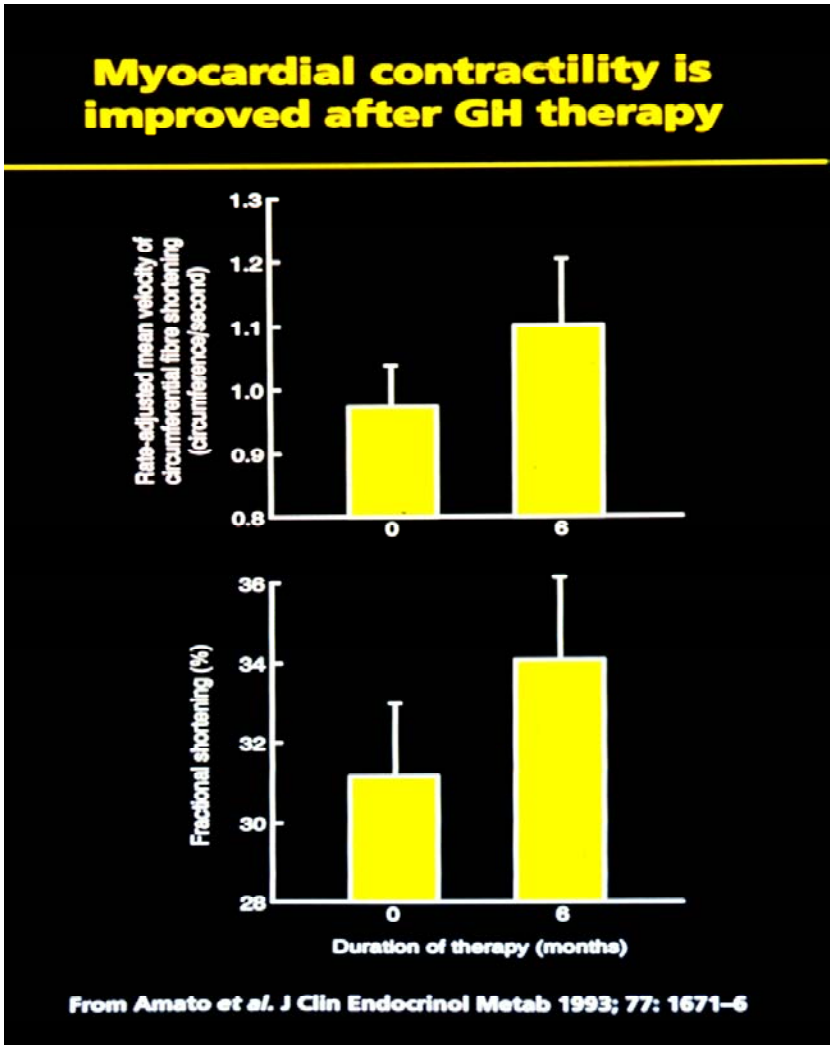
Overall number of deaths in 162 patients with partial or complete hypopituitarism (observed deaths) was greater than age and sex matched controls (expected deaths)

(adapted from Bates, AS et al. J. Clin Endo Metab 81:1171;1996)

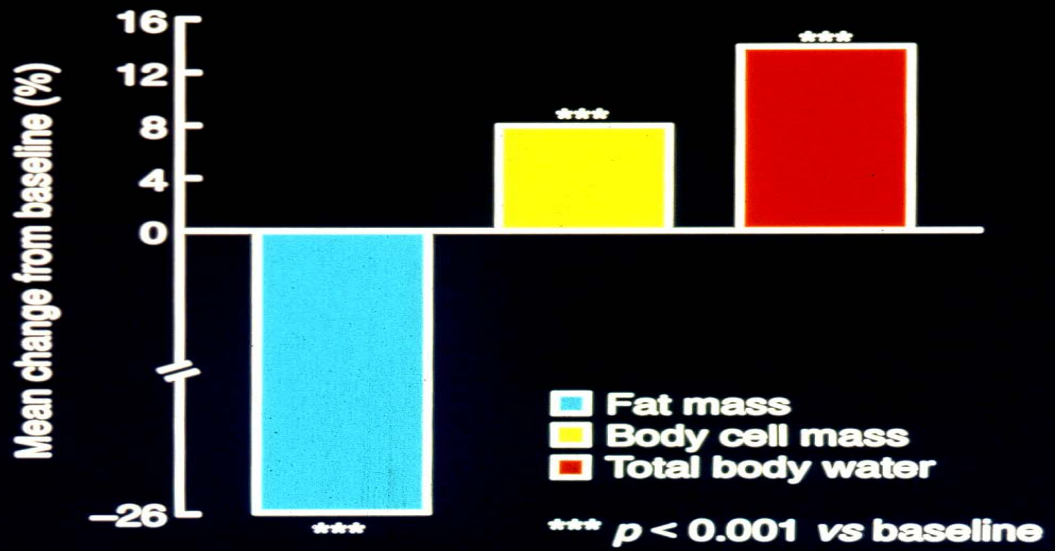
EFFECTS OF SIX MONTHS GH THERAPY ON MYOCARDIAL CONTRACTILITY

- Mean velocity of circumferential fiber shortening increased (shortening/second)
- Fractional shortening increased (%)

(Amato et al. JCEM 77:1671-76; 1993)

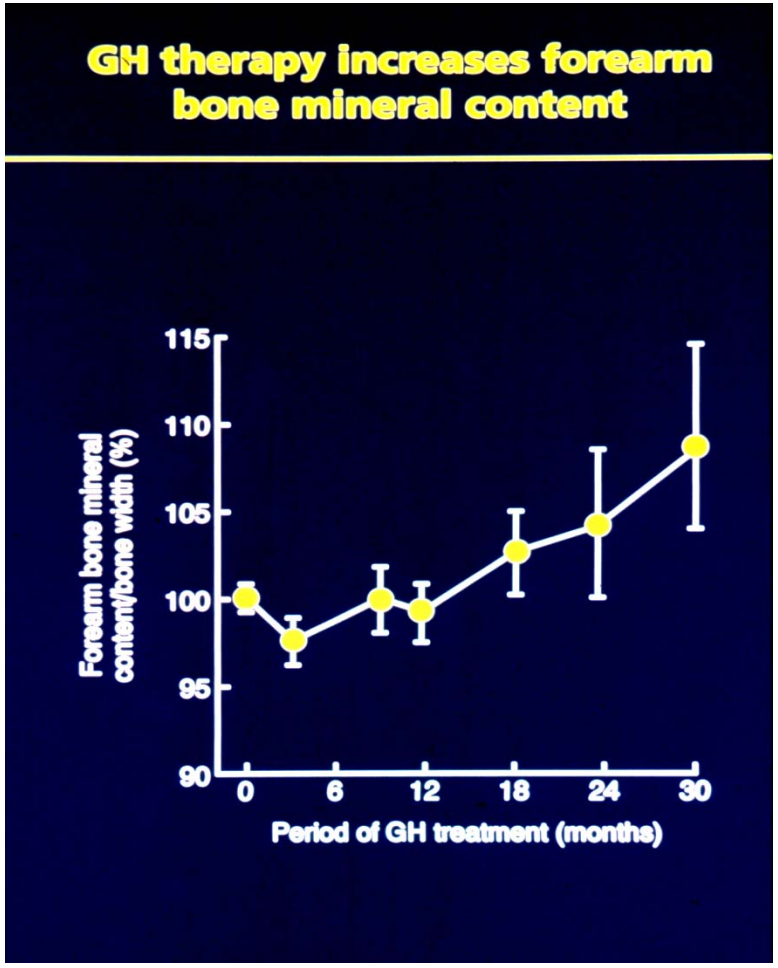


Effect of GH therapy for 18 months on body composition

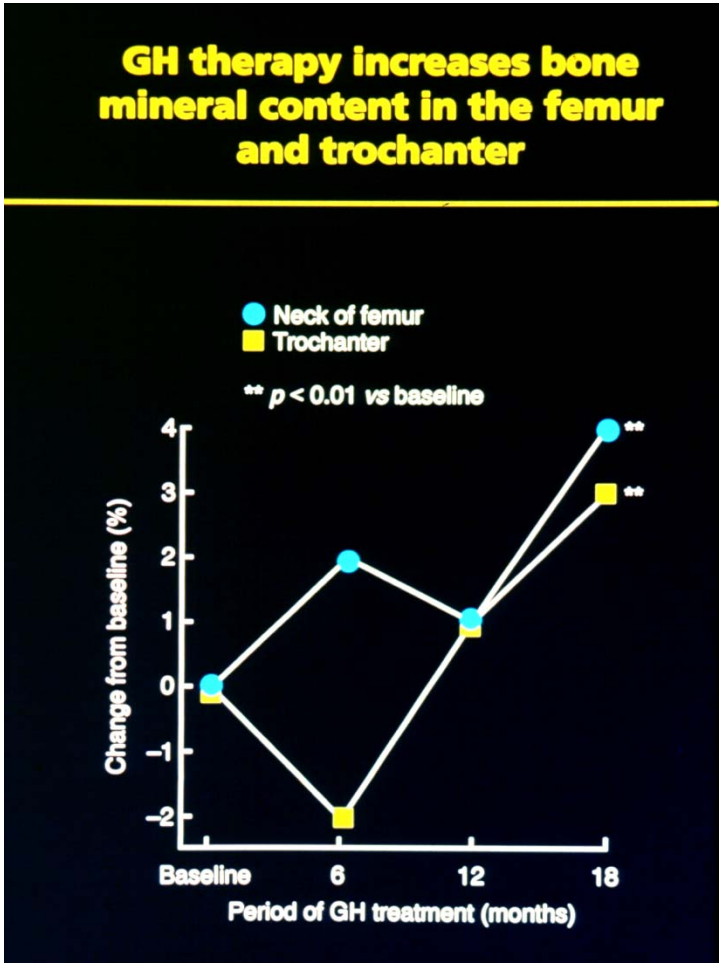


From Johannsson *et al.* Endocrinol Metab 1994; 1 (Suppl A): Abstract 27

Effect of GH on Bone



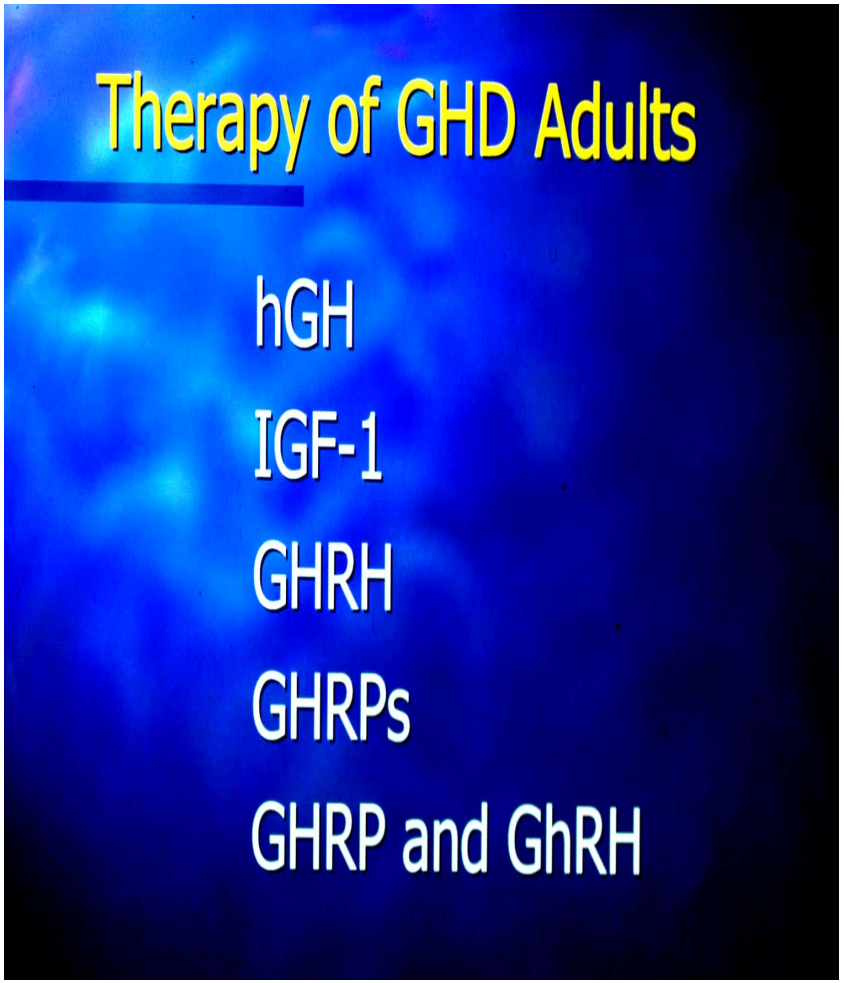
Vandeweghe et al. Clin Endo 39:409-415, 1993



Rosen et al. Endo Metab 1, Suppl A:55-66, 1994

Compounds for GH Replacement

- Hepatic site of action
- Immediate tissue availability
- Requires functional pituitary gland
- Inhibits SRIF and/or stimulates GHRH
- Synergistic actions



Types of GHS

- Non-specific (certain amino acids, clonidine, l-dopa, insulin)
- Receptor Specific (GHRH analogs; sermorelin; works through cAMP)
- Receptor Specific (Ghrelin analogs; GHRP's; works through phosphoinsoitide, protein kinase C)

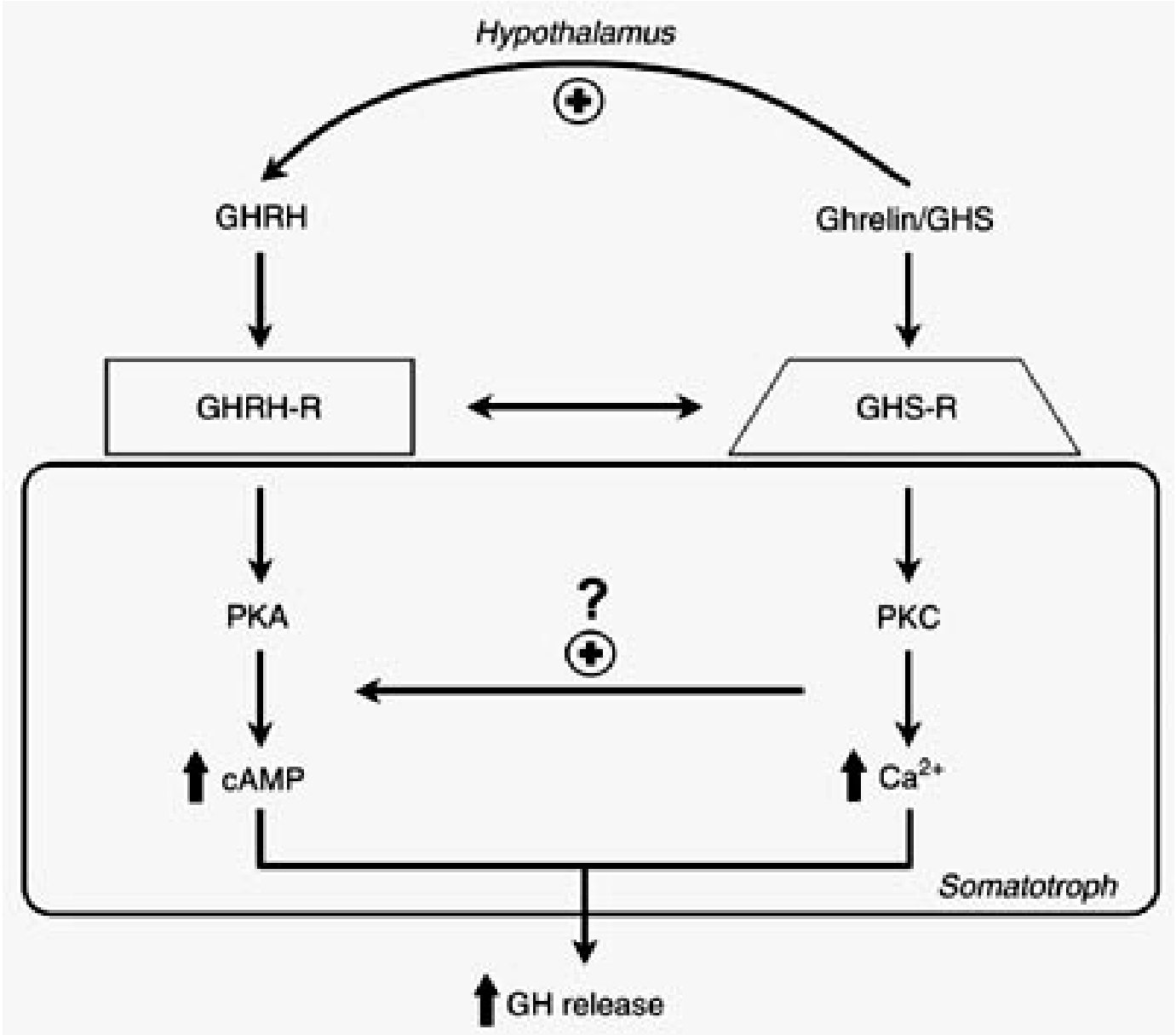
The structure of Sermorelin consists of the first 29 amino acids of GHRH

GROWTH HORMONE RELEASING HORMONE

Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-
Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-
Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH2

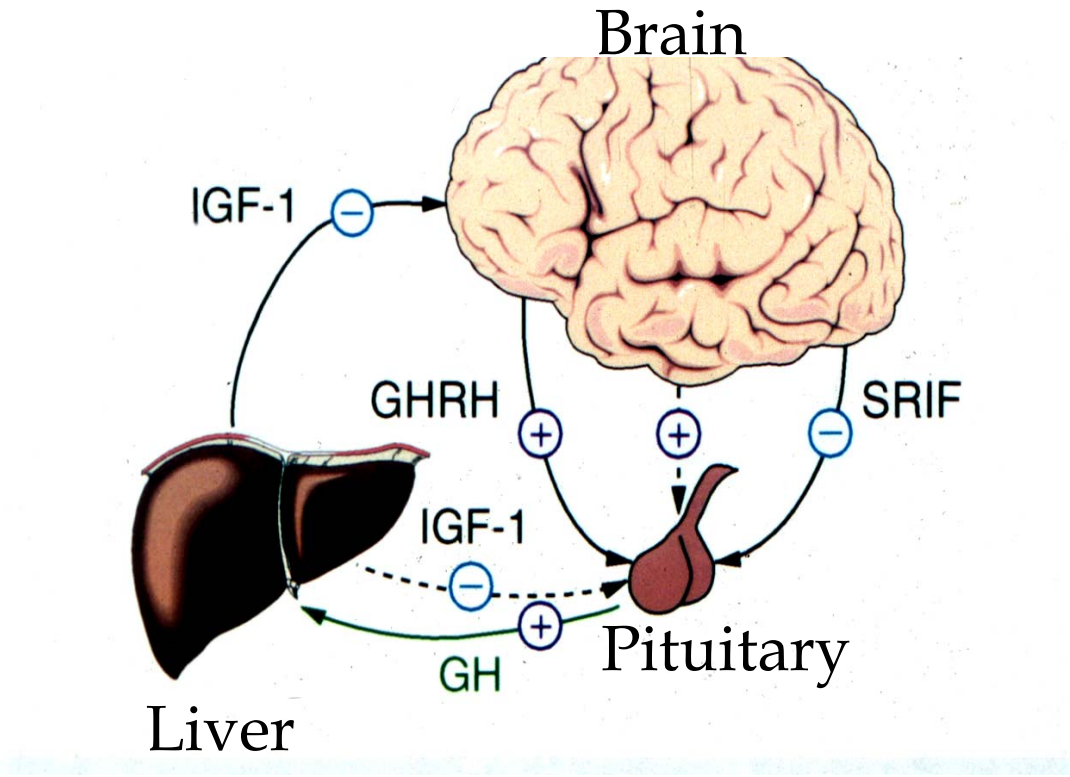
SERMORELIN

Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-
Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH2



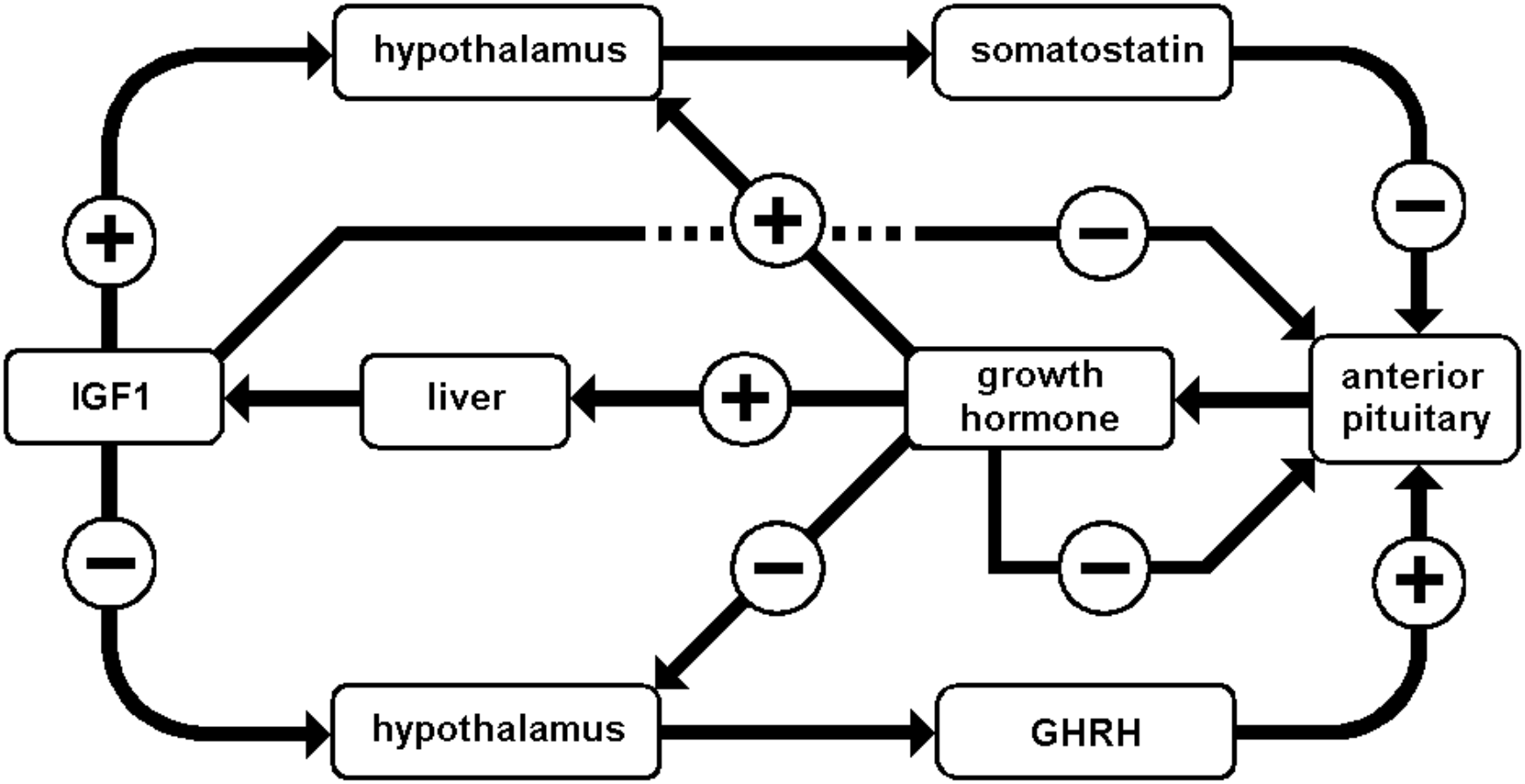
M.J. Lengyel. Novel mechanisms of growth hormone regulation: growth hormone - releasing peptides and ghrelin. Braz J Med Biol Res 2006; 39: 1003-1011

Sermorelin versus recombinant hGH Sites of Action



GHRH (sermorelin) activity is physiologically modulated by feedback while recombinant human growth hormone activity is not!

rhGH suppresses pituitary function and thus, may accelerate neuroendocrine senescence



Exogenous ***Growth Hormone*** Suppresses Pituitary GRF Receptor mRNA

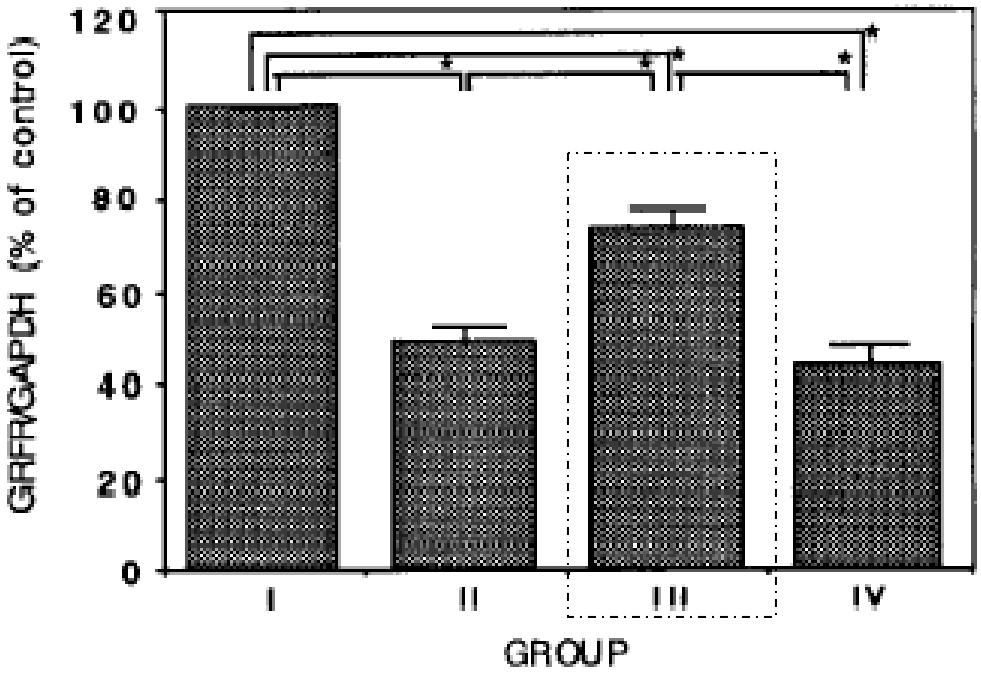
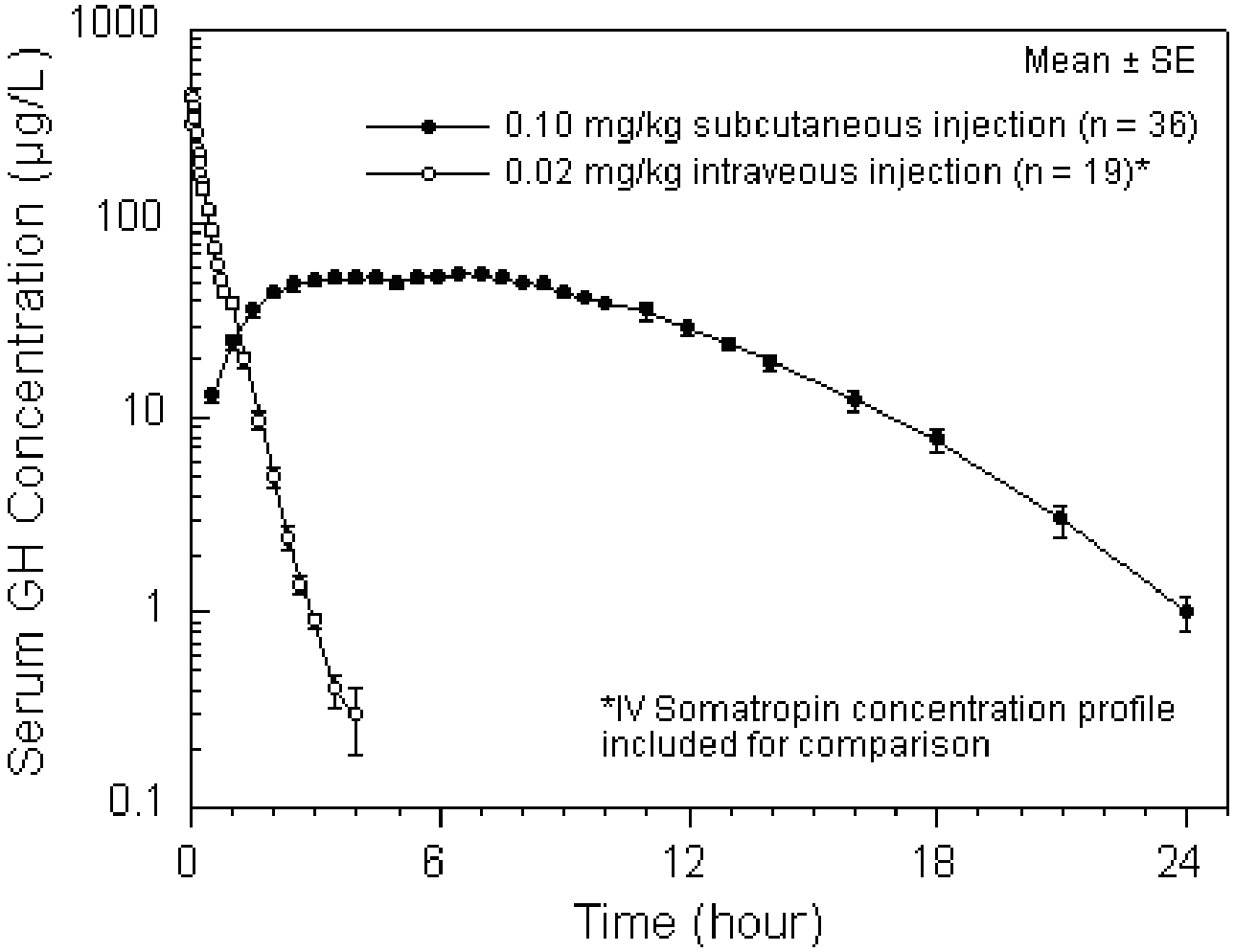


Figure 2. The changes in GRF receptor/GAPDH ratio by treatment with GRF antibody and/or GH. GRFR/GAPDH ratios were expressed as % (mean ± SD of four independent experiments) of group I. Treatments to each group were; group I: normal rabbit serum (control group), group II: GRF-ab, Group III: normal rabbit serum & GH, group IV: GRF-ab & GH. *P<0.01, analyzed by ANOVA.

GAPDG - Glyceraldehyde 3-phosphate dehydrogenase

Horikawa et al. Endocrinology 137(6) 1996:2642-2645

Single Dose Mean Growth Hormone Concentrations are Pharmacologic



Effect of Daily Injections of GHS on Episodic GH Release in Young and Old Men

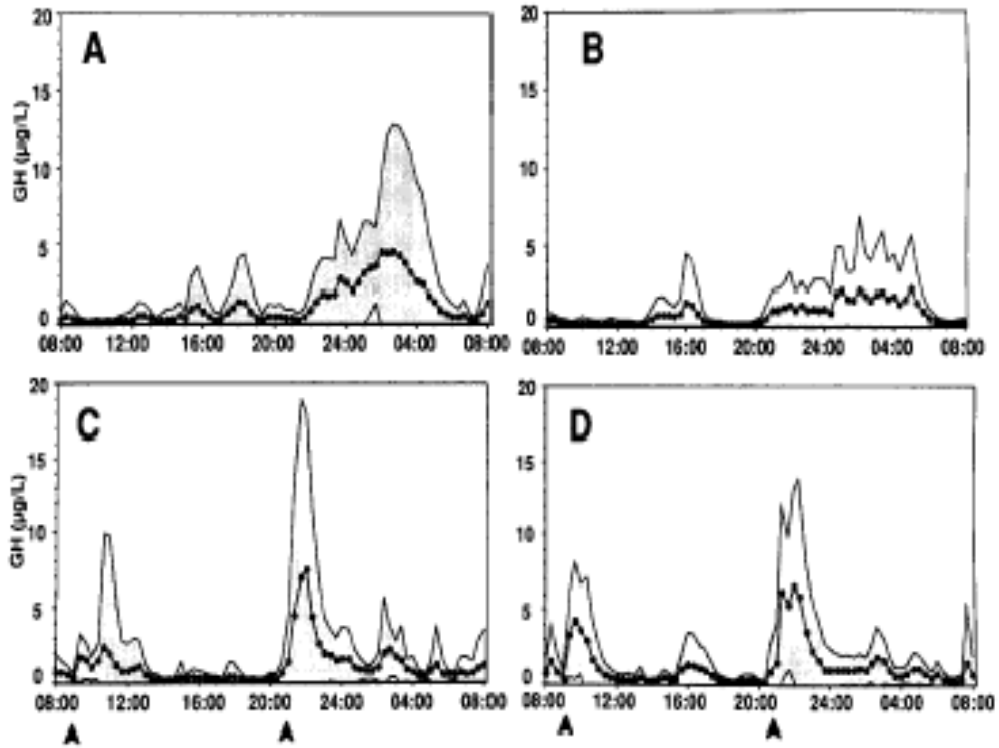


FIG. 1. Serum GH values (mean ± SD) at 20-min intervals during a 24-h period in young (A) and old (B) men at baseline and in old men during low (C) and high (D) dose GHRH treatment. *Arrowheads* in C and D indicate the time of sc GHRH injections.

Low Dose = 500ug sc bid x 14 days
High Dose = 1mg sc bid x 14 days

Corpas et al. J Clin Endo Metab 75, 1992:530-535

Effect of GRF on Approximate Entropy (Relative Randomness) of GH Release Patterns in Postmenopausal Women

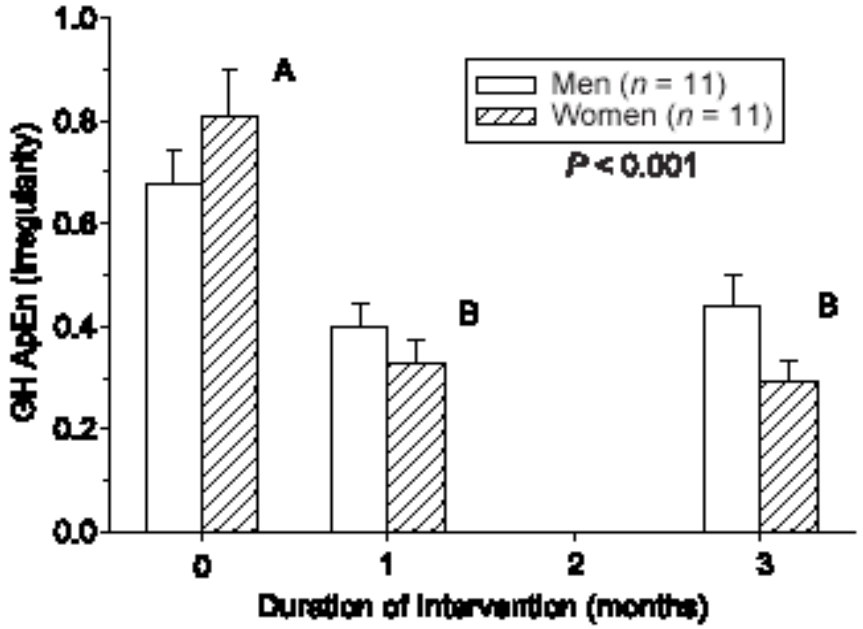


Figure 5 GHRH administration lowers approximate entropy (ApEn), a quantitative measure of irregularity (relative randomness) of GH release patterns. A lower ApEn indicates enhanced orderliness, which denotes stronger feedback inputs. In other respects, data are presented as described in the legend of Fig. 4.

Veldhius et al. Eur J Endo 153, 2005:669-677

Acute and Integrated GH AUC in Response to GRF Administration

1. Significantly more hGH released in response to GRF than placebo injection
2. More hGH occurs throughout the day in serum of subjects treated with GRF
3. Longer treatment increases response to GRF
4. Women are more responsive than men

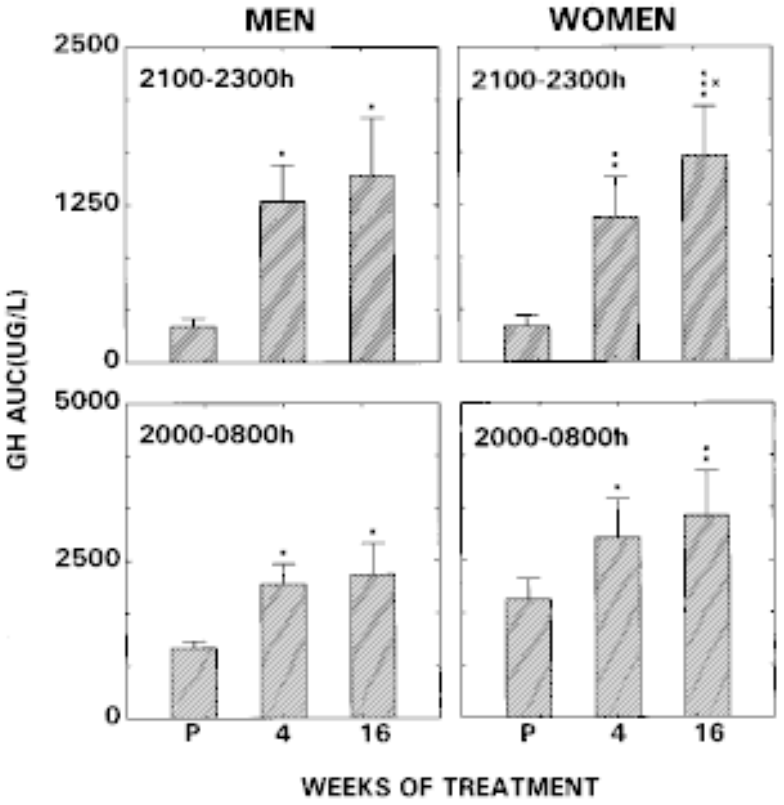


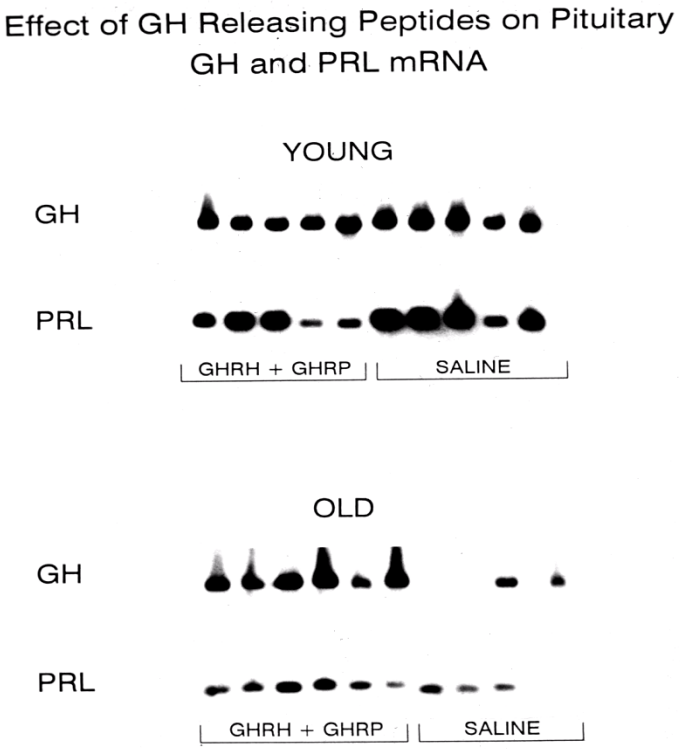
FIG. 2. GH AUC in acute response (2100–2300 h; *top*) and integrated 12-h values (2000–0800 h) in response to placebo (p) and GHRH analog treatments in men and women. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ (*vs.* placebo). X, $P < 0.01$ (*vs.* 4 weeks in women).

Khorram et al. J Clin Endo Metabol 82(5) 1997:1472-1479

GH SECRETAGOGUES REJUVENATE PITUITARY GLAND

- GH and PRL mRNA are concentrated in young pituitary glands
- GH mRNA is practically absent in old pituitary glands
- GH secretagogues restore pituitary mRNA to youthful levels

(Walker et al. Endocrine 2:633-38, 1994)



Effect of Two Daily Injections of GHS on Serum IGF-1 Concentrations in Older Men

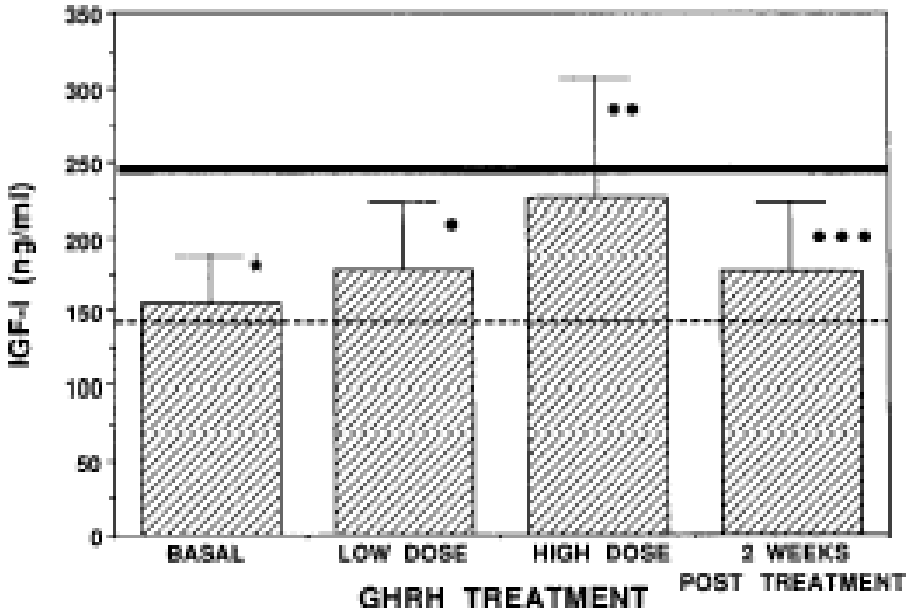


FIG. 2. Serum IGF-1 levels (mean ± SD) in old men at baseline, during low and high dose GHRH treatment, and 2 weeks after discontinuing GHRH treatment are compared with mean (*solid line*) and 2 SD below the mean (*dotted line*) values for young men at baseline. *, $P < 0.0001$ (*vs.* young basal). ●, $P < 0.05$; ●●, $P < 0.005$; ●●●, $P < 0.01$ (*vs.* old basal).

Low Dose = 500ug sc bid x 14 days
High Dose = 1mg sc bid x 14 days

Corpas et al. J Clin Endo Metab 75, 1992:530-535

Individual IGF-1 Responses to 14 Days GRF Administration in Older Men

Not all individuals respond with increased IGF-1. The reason for the lack of effect in some individuals is unclear but can be attributed to multiple potential causes ranging from poor GH secretion to hepatic insensitivity to stimulation

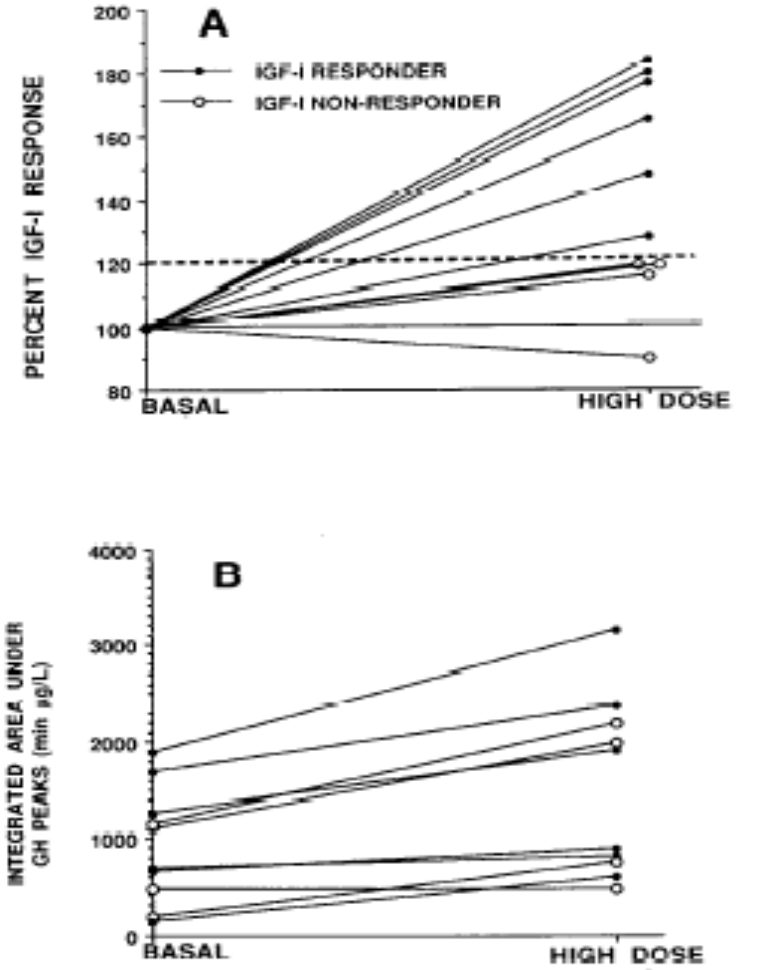


FIG. 3. A, The percent changes in plasma IGF-I for each subject from baseline to high dose GHRH. ●, IGF-I responders; ○, nonresponders. The *horizontal dotted line* indicates the minimum detectable IGF-I response. B, Corresponding changes in the integrated areas under the GH response peaks for IGF-I responders and nonresponders.

Corpas et al. J Clin Endo Metab 75, 1992:530-535

Effect of GHS Administration on Body Composition of Menopausal Women

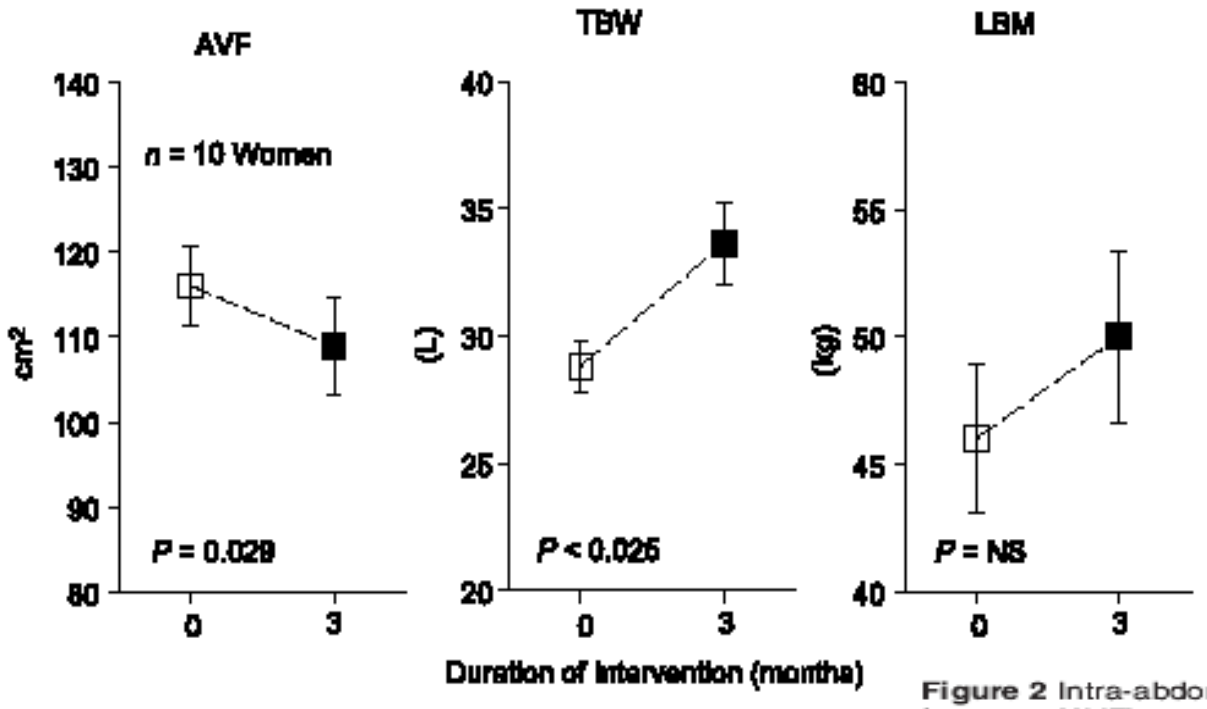


Figure 2 Intra-abdominal visceral fat mass (AVF), total body water (TBW) and lean body mass (LBM) in ten postmenopausal women assessed at baseline and after 3 months of rhGHRH administration. Data are presented as described in the legend of Fig. 1, except that statistical values apply to the indicated paired outcomes.

Dosage = 1mg sc qd x 90 days

Veldhius et al. Eur J Endo 153, 2005:669-677

Effect of Twice Daily GHS Injections on Physical Performance in Postmenopausal Women

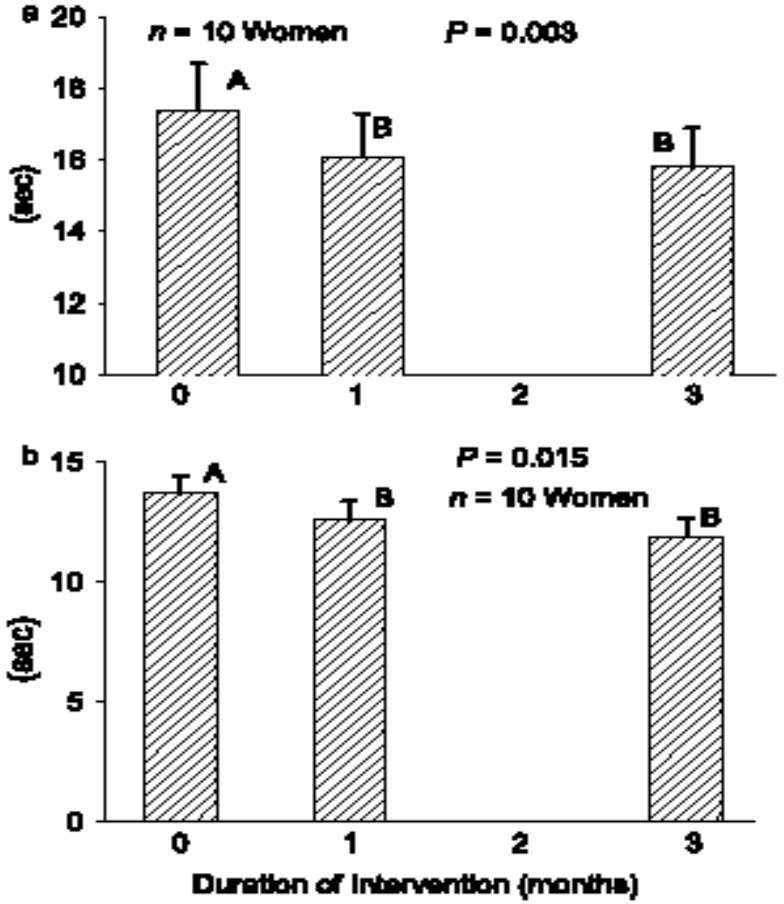


Figure 3 Time required to ascend two flights of stairs (a) or walk 30 m (b) assessed at baseline (time zero) and after 1 and 3 months of GHRH administration in ten postmenopausal individuals. The data format is that given in Fig. 1.

Veldhius et al. Eur J Endo 153, 2005:669-677

Clinical Findings

Normal BW Patient

Male; Caucasian; Russian/Polish-American; MD/PhD; 66 years old; BMI 25.8

Treatment: Sermorelin

History: No hGH or testosterone prior

Time line:

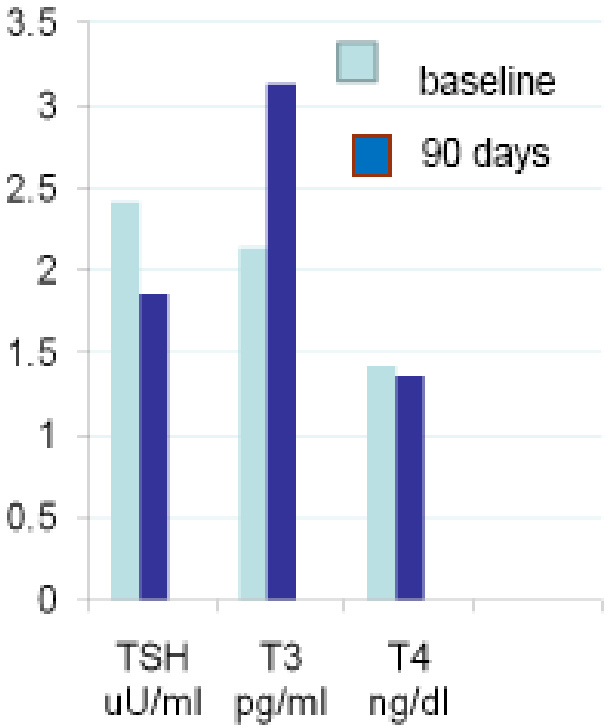
	Baseline	45 d	90 d	units	range
1. IGF-1	185.00	204	252	ng/ml	[75 - 250]
2. Total Testosterone	154.00 -->		296.70	ng/dl	[170 - 850]
3. Free Testosterone	11.20 -->		11.60	pg/ml	[9.00 - 31.00]
4. Estradiol			21	pg/ml	[5 - 30]

Effects of *Sermorelin sl* on Thyroid Function after 90 Consecutive Days

Thyroid Function* Euthyroid

Elderly Subject

- 65 year old male
- Pituitary feedback improved
- Hepatic conversion to bioactive T_3 increased
- Physiological T3/T4 ratios improved

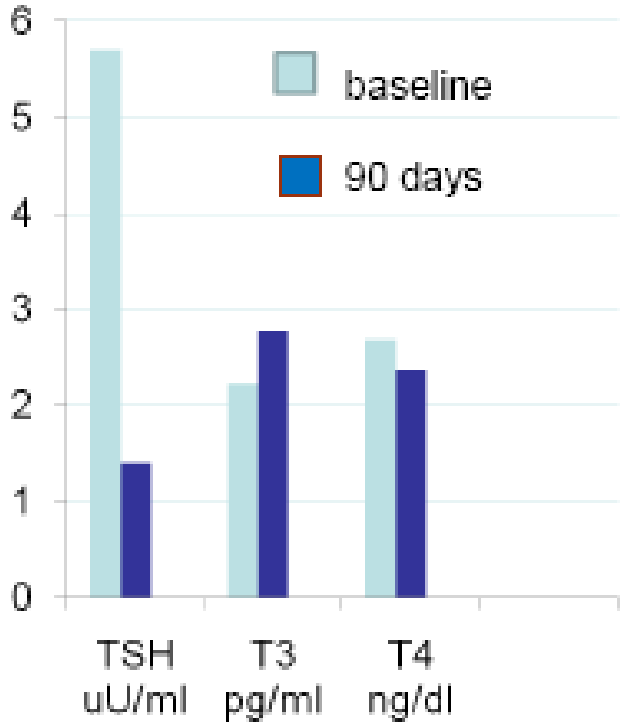


Effects of *Sermorelin sl* on Thyroid Function after 90 Consecutive Days

Thyroid Function*

Hypothyroid Subject

- 54 year old female
- Synthroid – 100 µg/d
- Pituitary feedback improved
- Hepatic conversion to bioactive T_3 increased
- Physiological T3/T4 ratios restored



*Sermorelin sl**

A receptor specific, potent,
non-injectable hGH secretagogue!

*novel sublingual dosage form

United States Patent [19]

Lu et al.

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[54] **COMPOSITIONS AND METHOD FOR THE SUBLINGUAL OR BUCCAL ADMINISTRATION THERAPEUTIC AGENTS**

[75] Inventors: **Mou-Ying F. Lu**, Lake Bluff; **Thomas L. Reiland**, Gages Lake, both of Ill.

[73] Assignee: **Abbott Laboratories**, Abbott Park, Ill.

[*] Notice: The portion of the term of this patent subsequent to Feb. 8, 2011, has been disclaimed.

[21] Appl. No.: **193,374**

[22] Filed: **Feb. 7, 1994**

United States Patent [19]
Lu et al.

[11] **Patent Number: 5,487,898**
[45] **Date of Patent: * Jan. 30, 1996**

TECHNICAL FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions and a method of using such compositions. More particularly, the present invention concerns pharmaceutical compositions useful for the sublingual or buccal administration of oligopeptides of twenty aminoacyl residues or less and to a method of using such compositions.

The composition of *Sermorelin sl* includes the therapeutic agent dissolved in a carrier composed of a solvent, an optional cosolvent, an optional hydrogel, and oral mucosal membrane transport enhancing agents.

Composition of *Sermorelin sl*

- **Peptide:** Sermorelin
- **Solvent**: an alcohol such as ethanol, isopropanol, stearyl alcohol, propylene glycol, polyethelene glycol (MW < 650 daltons)
- **Co-solvent**: water or a pharmaceutically acceptable oil such as mineral oil, olive oil, sunflower oil, corn oil, peanut oil, etc.
- **Hydrogels**: (*viscosity)* hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethylcellulose, polyacrylic acid, poly(methyl methacrylic acid), etc.
- **Oral mucosal membrane transport enhancing agent**: *(bioavailability)* peppermint oil, spearmint oil, menthol, pepper oil, eucalyptus oil, cinnamon oil, fennel oil, ginger oil, dill oil, etc.
- **Aromatic or aliphatic mono or dicarboxylic acids**: (*bioavailability*) acetic, cictric, lactic, oleic, linoleic, lauric, palmitic, benzoic, salicylic acid, etc.
- **Buffers**: phosphate, chloride, lactate, etc.

Summary

- Functional failure of the growth hormone neuroendocrine axis is one of the earliest maladaptive changes of aging.
- Progressive loss of neuroendocrine function increases risk for intrinsic diseases especially of the cardiovascular system and shortens life span
- Normal patterns of pituitary production and secretion of endogenous growth hormone are blunted during aging
- Administration of recombinant hGH opposes age changes in body composition but accelerates degenerative changes in pituitary and feedback control of the neuroendocrine system.
- Tissue exposure to hGH released by the pituitary under the influence of GHS is episodic not “square wave” preventing tachphylaxis by mimicking normal physiology

Summary

- Sermorelin's effects are regulated at the level of the pituitary gland by negative feedback and by release of somatostatin so that overdoses of hGH are difficult if not impossible to achieve,
- *Sermorelin* restores youthful physiological pituitary function and because it sustains normal feedback relationships is relatively free of side effects.
- By stimulating the pituitary it preserves more of the growth hormone neuroendocrine axis that is the first to fail during aging.
- Pituitary recrudescence resulting from GHS opposes the cascade of hypophyseal hormone failure that occurs during aging
- Clinical benefits of *Sermorelin* are equal to or better than those of recombinant hGH

Conclusions

- Increased responses to provocative testing and/or elevated concentrations of serum IGF-1 indicate that Sermorelin is suitable for practical application in acquired (age-associated) growth hormone insufficiency.
- Sermorelin is orally bioavailable and is currently available in sublingual dosage form. This non-injectable dosage form should improve patient compliance.
- Unlike hGH, sermorelin affects a more primary source of age-failure in the GH neuroendocrine axis, has more physiological activity, a better safety profile and its use in anti-aging medicine is not prohibited (as is hGH).
- Sermorelin is more effective alternative to recombinant growth hormone for better preserving health and vitality of normal individuals during aging.