A New Paradigm for Treating Adult-Onset Growth Hormone Deficiency

Richard F. Walker, Ph.D., R.Ph.
Executive Director, SARA
A progressive decline in physiological functions occurs after reproductive competence is reached and life progresses into the third and fourth decades.

Rates of decline reflect differential responses to the magnitude of a specific challenge, i.e., compliance is compromised with aging.

Brain/Adenohypophyseal Relationships

- Neurosecretory cells of the hypothalamus
- Portal vessels
- Hypothalamic hormones
- Endocrine cells of the anterior pituitary
- Pituitary hormones

Hormones and their targets:
- Growth hormone (GH)
  - Bones
- Prolactin (PRL)
  - Mammary glands
- Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
  - Testes or ovaries
- Thyroid-stimulating hormone (TSH)
  - Thyroid
- ACTH
  - Adrenal cortex
- MSH
  - Melanocytes
- Endorphins
  - Pain receptors in the brain

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Brain Initiates GH Secretory Cascade

1. Neural pathways impinge on hypothalamic neurosecretory cells
2. GHRH/Ghrelin/SRIF modulate GH secretion
Regulation of hGH production and secretion is under strict temporal, quantitative and qualitative feedback control.
Primary Regulatory Factors in the hGH Neuroendocrine Axis

- **Growth hormone-releasing hormone** (GHRH) is a hypothalamic peptide that stimulates both the synthesis and secretion of growth hormone.
- **Somatostatin** (SS) is a peptide produced by several tissues in the body, including the hypothalamus. Somatostatin inhibits growth hormone release in response to GHRH and to other stimulatory factors such as low blood glucose concentration.
- **Ghrelin** is a peptide hormone secreted from the stomach. Ghrelin binds to receptors on somatotrophs and potently stimulates secretion of growth hormone.
Signals from target tissues superimpose upon primary controllers in brain and pituitary.
The timing of interdependent physiological events becomes disturbed with advancing age. These changes result in suboptimal performance, loss of function and intrinsic disease. Reduced hormone production is one of the earliest signs of age related change and is followed by functional disturbances and ultimately by intrinsic disease.

Low levels or deficiency of a hormone can have dramatic effects on the body’s structure and functions, especially when more than one hormone is deficient as in multiple pituitary hormone deficiency (MPHD).
SOMATOPAUSE

Aging results in reduced production and secretion of growth hormone relative to that which occurs in youth. This is the first gross sign of neuroendocrine senescence that begins during the mid- to late thirties.
## IGF-I

500282B

<table>
<thead>
<tr>
<th>TERM</th>
<th>PRE-TERM*</th>
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<tbody>
<tr>
<td>RANGE (NG/ML)</td>
<td>RANGE (NG/ML)</td>
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<tr>
<td>MALE</td>
<td>FEMALE</td>
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<table>
<thead>
<tr>
<th>ADULTS:</th>
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<tbody>
<tr>
<td>21 - 30 Years:</td>
<td>155 - 432</td>
</tr>
<tr>
<td>31 - 40 Years:</td>
<td>132 - 333</td>
</tr>
<tr>
<td>41 - 50 Years:</td>
<td>121 - 237</td>
</tr>
<tr>
<td>51 - 60 Years:</td>
<td>68 - 245</td>
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<tr>
<td>61 - 70 Years:</td>
<td>60 - 220</td>
</tr>
<tr>
<td>71 - 80 Years:</td>
<td>36 - 215</td>
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## Lactic Acid (Lactate) Dehydrogenase (LDH)

500642

Reference Ranges

94 - 250 U/L

## Leptin

500237

Reference Ranges

<table>
<thead>
<tr>
<th>MALE</th>
<th>FEMALE</th>
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<tr>
<td>RANGE (ng/mL)</td>
<td>RANGE (ng/mL)</td>
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</table>

<table>
<thead>
<tr>
<th>ADULTS (BMI+22):</th>
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<tbody>
<tr>
<td>0.7 - 5.3</td>
<td>3.3 - 18.3</td>
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## Insulin, Free and Total

500226

Reference Ranges

NON-DIABETIC:

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<th>PUBERTAL CHILDREN AND ADULTS:</th>
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<td>0.17 uU/mL</td>
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## Iron

500648

Reference Ranges

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<tr>
<th>MALE:</th>
<th>FEMALE:</th>
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<tbody>
<tr>
<td>45 - 160 ug/dL</td>
<td>30 - 160 ug/dL</td>
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</table>
Normal Changes in the Growth Hormone Axis with Aging

• The rate of GH secretion from the anterior pituitary is highest around puberty, and declines progressively thereafter. This age-related decline in GH secretion involves a number of changes in the GH axis, including decreased serum levels of insulin-like growth factor-1 (IGF-1) and decreased secretion of growth hormone-releasing hormone from the hypothalamus. The cause of the normal age-related decrease in GH secretion is not well understood, but is thought to result, in part, from increased secretion of somatostatin, the GH-inhibiting hormone.

• Normal aging is accompanied by a number of catabolic effects, including a decrease in lean mass, increase in fat mass, and decrease in bone density. Associated with these physiologic changes is a clinical picture often referred to as the somatopause: frailty, muscle atrophy, relative obesity, increased frequency of fractures and disordered sleep.

• These clinical signs of aging are, without doubt, the manifestation of a very complex set of changes which involve, at least in part, the GH-axis. Naturally, this has spurred considerable interest in administering supplemental GH as a "treatment" for aging in humans, and the availability of recombinant human GH has made such studies feasible.
Hypothesis

Replacement therapy intended to restore optimal concentrations of growth hormone may improve or sustain good youthful anatomy, physiology and thereby, good health and vitality during aging.
But what hormone should be used in GH replacement therapy?
Compounds for GH Replacement

- Hepatic site of action
- Immediate tissue availability
- Requires functional pituitary gland
- Inhibits SRIF and/or stimulates GHRH
- Synergistic actions
Effective GHRT can be achieved by using recombinant hGH or recombinant IGF-1

• **Direct effects** are the result of growth hormone binding its receptor on target cells. Fat cells (adipocytes), for example, have growth hormone receptors, and growth hormone stimulates them to break down triglyceride and suppresses their ability to take up and accumulate circulating lipids.

• **Indirect effects** are mediated primarily by a **insulin-like growth factor-I (IGF-I)**, a hormone that is secreted from the liver and other tissues in response to growth hormone. A majority of the growth promoting effects of growth hormone is actually due to IGF-I acting on its target cells.
However, Single Dose Mean Growth Hormone Concentrations are Pharmacologic
And Serum hGH Profiles are Abnormal

- Serum GH remains above peak physiological levels for hours
- GH isoform ratios are not stable
- Non-physiological tissue exposure to GH

Also, rhGH suppresses pituitary function and thus, may accelerate neuroendocrine senescence.
GH Neurohormone Relationships

- GHRH stimulates GH production and secretion
- SRIF inhibits GH production, release & activity
- GHRP stimulates GHRH and GH secretion & inhibits SRIF activity

Smith et al. Science, 1998
Considerations for Replacement Therapies

**Efficacy and Safety Concerns**

- Naturally occurring rhythms (practical considerations)
- Interactions with other hormones and essential substances
- Health state of the patient
- Individual dosage requirements
- Biomarkers for evaluation of outcomes
Age-related defects in GH production and secretion seem to involve higher centers.
Age-Related Decline in Episodes of Spontaneous GH Secretion

Sonntag et al., 2001 JAAM 4:311
Growth Hormone Secretion Patterns

- Ultradian rhythm in GH secretion absent
- Low amplitude in partial GHD
- Attenuated in GHND
- High amplitude and obvious in normal, control subjects
Short and Long Term Effects of GHRH Infusion on GH Release

- Episodic GH release occurs at start of infusion
- Dose-dependent pulses of GH are related to infusion
- GH pulses stop with saline infusion

Chapman et al. JCEM 81:2874, 1996
GH Response to GHRH

Thorner et al. Lancet 1:24, 1983
Stimulated GH Secretion

- Highest mean peak of stimulated GH occurs in control subjects
- GH response blunted in GHND subjects
- Marginal or absent response in GHD
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

NORWELL, MA -- April 27, 1998 – Serono Laboratories, Inc. has launched Geref(R) (sermorelin acetate for injection), the first growth hormone releasing hormone for the treatment of idiopathic growth hormone deficiency (GHD) in children and Geref(R) Diagnostic (sermorelin acetate for injection), a complementary product for the diagnosis of growth disorders in the United States.
GHD results from either an abnormally low level of pituitary human growth hormone (hGH) or from a biochemical malfunction whereby growth hormone releasing hormone (GHRH) fails to trigger the release of hGH from the anterior pituitary. In the latter case, children with GHD may have endogenous hGH reserves which remain untapped.
As a growth hormone releasing hormone, Geref triggers the release of available reserves so that they can be used by the body. Traditionally, GHD has been treated by substituting natural hGH with a recombinant human growth hormone (r-hGH) product.
"It is widely believed that treatment should begin early for a child to reach his or her full growth potential, and there are some data to support the initiation of treatment before age five," said Michael Thorner, M.D., a leading expert on growth and chairman of the department of medicine at the University of Virginia Health Sciences Center.
Geref(R) (sermorelin acetate for injection) has demonstrated a favourable safety profile. The most common adverse reactions include local injection reactions (occurring in about one patient in six) characterised by pain, swelling or redness. During clinical trials, only three of 350 patients discontinued therapy due to injection reactions. Other treatment-related adverse events with occurrence rates of less than one percent include: headache, flushing, dysphagia, dizziness, hyperactivity, somnolence and urticaria.
A large portion of patients developed anti-GRF antibodies at least once during treatment with Geref. However, the significance of the antibodies is not clear. The presence of these antibodies does not appear to affect growth or be related to a specific adverse reaction profile and no generalised allergic reactions to Geref have been reported.
Adverse reactions reported with the use of Geref(R) Diagnostic (sermorelin acetate for injection), in decreasing order of frequency are: transient warmth and/or flushing of the face, injection site pain, redness and/or swelling at injection site, nausea, headache and vomiting. Approximately one in four patients given repeated doses of Geref Diagnostic has developed antibodies -- the clinical significance of these antibodies is unknown.
Receptors for GRF, coupled to G proteins which activate adenylyl cyclase stimulate somatotroph cell growth, growth hormone gene transcription and growth hormone secretion.

**Growth hormone-releasing hormone (GRH or GHRH)**

**Chemistry:**
- 37-, 40- and 44-amino acid single polypeptide chains
- Related to GI peptides- secretin, gastrin, VIP, GIP

**Preparation used clinically:**
- sermorelin acetate- first 29 (N-terminal) amino acids
  Activity is equivalent to full length forms

**Action and mechanism of action:**

- G protein-coupled receptor binding
- cAMP production
- GH synthesis and secretion

**Half-life:** 50 minutes
Sermorelin activity is physiologically modulated by feedback while recombinant human growth hormone activity is not!
## Comparison of rGH and GRF

<table>
<thead>
<tr>
<th></th>
<th>rGH</th>
<th>GRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>Recombinant gene technology</td>
<td>Chemical synthesis</td>
</tr>
<tr>
<td>Source</td>
<td>E-coli or Mouse cell</td>
<td>N/A</td>
</tr>
<tr>
<td>Viral potential</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Target tissue</td>
<td>Liver</td>
<td>Pituitary</td>
</tr>
<tr>
<td>Time for Tissue exposure</td>
<td>Instantaneous (GH injected directly; exogenous)</td>
<td>Delayed (GH secreted from pituitary after injection; endogenous)</td>
</tr>
<tr>
<td>Duration of Tissue Exposure</td>
<td>Long (square wave)</td>
<td>Short (episodic release)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>More rapid and pronounced; clinical effects more dramatic</td>
<td>Less rapid and pronounced; less clinical effect</td>
</tr>
<tr>
<td>Type</td>
<td>Pharmacological</td>
<td>Physiological</td>
</tr>
<tr>
<td>Effect on Pituitary</td>
<td>Shuts down endogenous production and secretion</td>
<td>Stimulates production and secretion</td>
</tr>
<tr>
<td>Toxicity Potential</td>
<td>Greater, but dose dependent; little at doses in protocol</td>
<td>Very little if any</td>
</tr>
<tr>
<td>Ancillary Effects</td>
<td>Direct on bone; may have benefit in relieving joint pain</td>
<td>May facilitate natural sleep</td>
</tr>
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</table>
Dose Ranging Study
Background and Hypothesis

Because the aging pituitary remains responsive to stimulation by growth hormone (GH) secretagogues, Sermorelin (GRF 1-29NH₂) can be used instead of GH itself to increase GH secretion in aging. The factors contributing to the age-related decline in GH secretion are largely extrapituitary, and with repeated or continuous administration GHS's can significantly increase GH secretion and elevate levels of insulin-like growth factor-I (IGF-I) to the young adult normal range. Treatment with sermorelin has both theoretical and practical advantages over rhGH - preserving feedback regulation by IGF-I to buffer against overdosing and yielding a more physiologic pulsatile pattern of GH secretion.
Research Objective

• The purpose of the clinical investigation was to determine whether a relatively low dosage of sermorelin (GRF 1-29-NH2; the truncated, bioactive form of GHRH 1-44) is effective in stimulating pituitary function in middle aged men. Since this was a pilot study, the only measures of efficacy were responses to a provocative test using sermorelin (GEREF diagnostic) at the onset of the study, and every month for 3 months thereafter, as well as serum concentrations of insulin like growth factor-1 (IGF-1) during the same time intervals.
**Procedure**

- **Provocative Test:** Indwelling iv catheter with heparin block was inserted. 1cc blood samples were drawn for baseline measures of serum growth hormone concentrations. Thereafter, Geref (sermorelin) was administered by intravenous push at time 0. A slow infusion (30 minutes) of arginine (0.5 gm/kg body weight not to exceed 25 gm) was started at time 0. Blood samples were drawn from the venous catheter at times 10, 20, 25, 30, 40, 60 and 90 minutes. Heparinized blood samples were used to measure plasma hGH concentrations.

- **IGF-1 measurements:** Concentrations of IGF-1 were measured in the pooled plasma samples from each provocative test, i.e. those taken at onset of the study and on months 1, 2 and 3 thereafter.

- **Sermorelin administration:** Each subject self administered (sc injection once daily approximately at bedtime) 200 ug sermorelin for 90 consecutive days.
Test Material
Growth Hormone Releasing Factor 1-29 NH₂

- **Sermorelin** acetate is the acetate salt of an amidated synthetic 29-amino acid peptide (GRF 1-29 NH₂) that corresponds to the amino-terminal segment of the naturally occurring human growth hormone-releasing hormone (GHRH or GRF) consisting of 44 amino acid residues. The structural formula for sermorelin acetate is:

The free base of sermorelin has the empirical formula C₁₄₉ H₂₄₆ N₄₄ O₄₂ S and a molecular weight of 3,358 daltons.

- **Amino Acid Sequence**

  SERMORELIN

Outcomes

• Increased IGF-1 measures following each month of sermorelin treatment indicated that endogenous hGH production and secretion increased and that the secretagogue has physiological efficacy at the dosage administered.

• Increased peak responses to the provocative testing following each month of treatment with sermorelin indicated positive feedback to the secretagogue and suggested pituitary recrudescence as the result of treatment.
Serum IGF-1 values after sc Sermorelin administration for 30 consecutive days

<table>
<thead>
<tr>
<th>Patient ID/Age</th>
<th>Baseline (ng/ml)</th>
<th>Interim Analysis (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP/50</td>
<td>134</td>
<td>195</td>
</tr>
<tr>
<td>DP/52</td>
<td>126</td>
<td>220</td>
</tr>
<tr>
<td>JA/53</td>
<td>57.1</td>
<td>150</td>
</tr>
<tr>
<td>LM/56</td>
<td>113</td>
<td>126</td>
</tr>
<tr>
<td>RW/66</td>
<td>127</td>
<td>199</td>
</tr>
</tbody>
</table>
EFFECTS OF DAILY SERMORELIN ADMINISTRATION ON PITUITARY RESERVE

After 30 Days Treatment

Before Treatment

Serum Growth Hormone (ng/ml)

TIME (Minutes)

0 2 4 6 8 10 12 14

GHRH
Sermorelin Dosage Recommendations

- 3 mg MDV: 200 ug/day for men with BMI from 18.5 – 24.9
- 4.5 mg MDV: 300 ug/day for men with BMI between 25 and 29.9
- 6 mg MDV: 400 ug/day for women or for men with BMI between 25 and 29.9
- 7.5 mg MDV: 500ug/day for women or for men with BMI between 25 and 29.9
Benefits of Sermorelin

• It’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,
• Tissue exposure to hGH released by the pituitary under the influence of SERMORELIN is episodic not “square wave” preventing tachphylaxis by mimicking normal physiology
• 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 SERMORELIN blocks the cascade of hypophyseal hormone failure that occurs during aging
GHRT Liability Concerns
Human growth hormone produced by recombinant gene technology has been used extensively for anti-aging therapy during the past decade. Although effective in restoring certain youthful characteristics in aging subjects, hGH has certain medical and legal issues that sometimes restrict practitioners use of the product.
RECOGNIZED MEDICAL CONDITIONS FOR WHICH HGH USE HAS BEEN AUTHORIZED BY THE SECRETARY OF HEALTH AND HUMAN SERVICES

• Short stature of childhood
• Wasting syndrome of AIDS
• Growth hormone deficiency in adults
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 dose ranging studies indicate that 200 – 500 ug sc qd hs are appropriate for clinical use.

• 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).

• A more effective alternative to recombinant growth hormone is available to anti-aging practitioners to support their efforts in providing treatments that better preserve the health and vitality of their patients during aging.