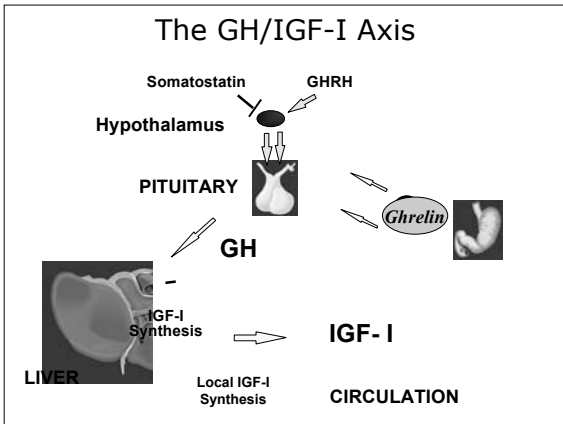
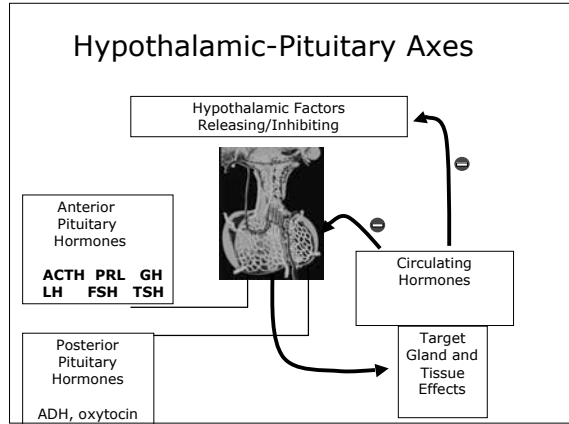
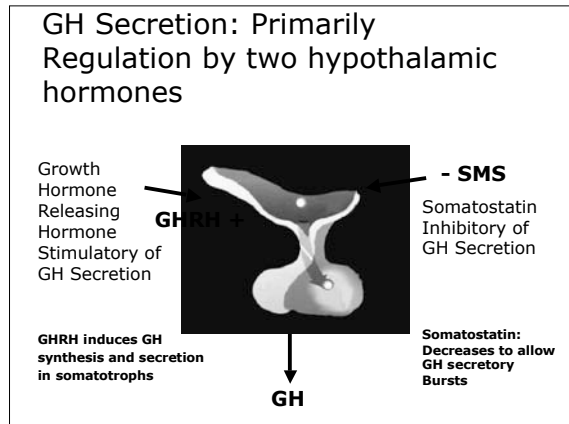
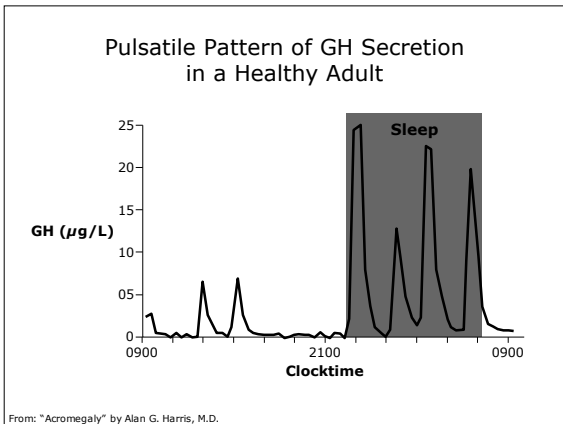


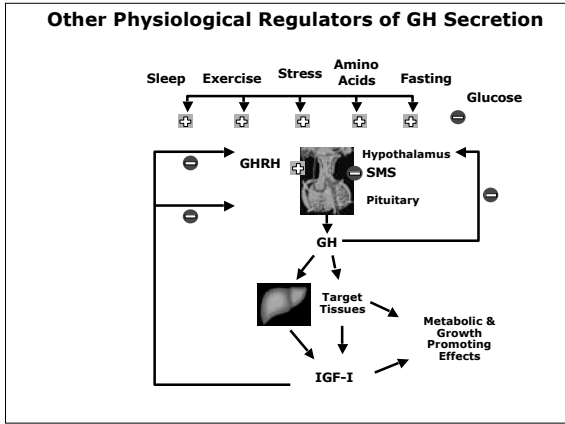
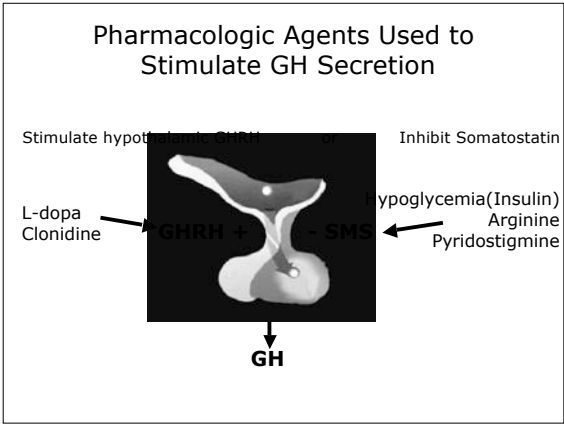
Pituitary

February 11, 2008



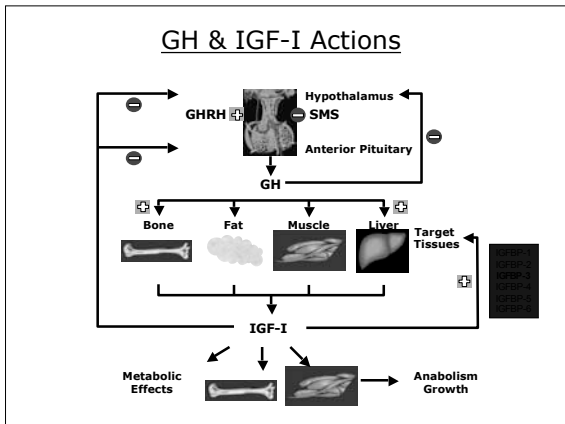
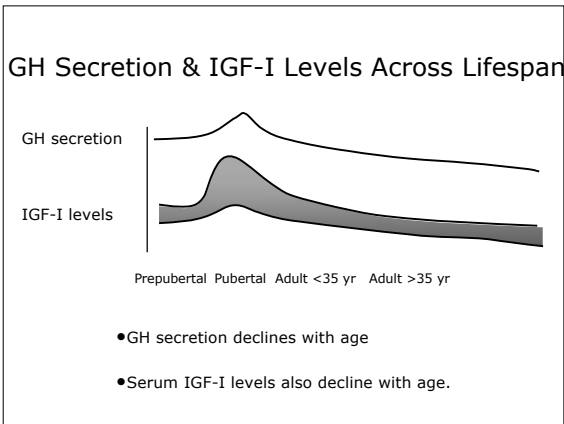
- ## Growth Hormone
- Synthesized in the anterior lobe of the pituitary gland in somatotroph cells
 - ~75% of GH in the pituitary and in circulation is 191 amino acid single chain peptide, 2 intra-molecular disulfide bonds
Weight; 22kD
 - Amount of GH secreted:
Women: 500 $\mu\text{g}/\text{m}^2/\text{day}$
Men: 350 $\mu\text{g}/\text{m}^2/\text{day}$





- ### Insulin-like growth factor I (IGF-I)
- **70 amino acid polypeptide**
 - **Produced predominantly in the liver**
 - **Endocrine and autocrine/paracrine actions**
 - Mediates major anabolic and growth-promoting effects of GH
 - Insulin-like effect, independent of GH
 - **Does not mediate the lipolytic effects of GH**

- ### Major Determinants of Circulating IGF-I Levels
- **Growth Hormone**
Increases IGF-I production in liver, major source of circulating IGF-I
 - **Nutritional Status**
 - **Age**
 - **Genetic Factors**
 - **Binding proteins**
 - **Increased levels in pregnancy and puberty**



Disorders of GH Secretion



- **GH Excess:**

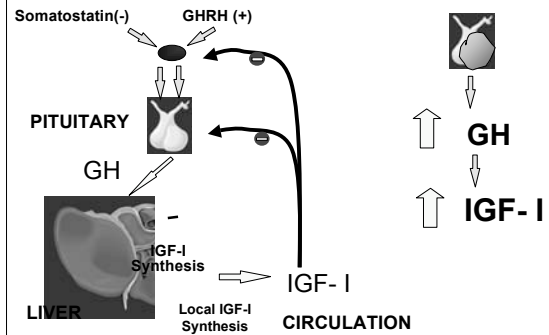
GH overproduction by a GH secreting pituitary tumor - ACROMEGALY



- **GH Deficiency:**

Childhood onset
Adult onset

GH/IGF-I Axis



Biochemical Diagnosis of Acromegaly



Growth Hormone

Random GH Levels

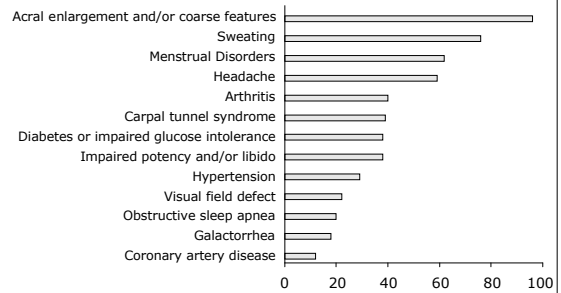
GH Suppression after Oral Glucose:

Failure of GH to Fall < 1 µg/L

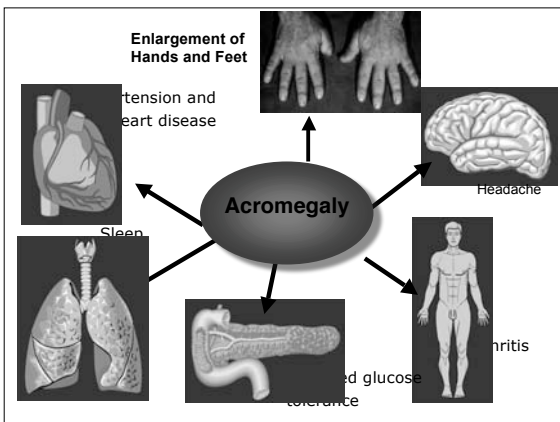
Serum IGF-I Level:

Elevated above age-adjusted normal range

Prevalence of Clinical Features at Diagnosis



Clemmons DR, et al. *J Clin Endocrinol Metab.* 2003;88:4759-4767.



Current Therapies for Acromegaly



- **Primary therapy**

- Transsphenoidal surgery
- Medical therapy

- **Adjunctive therapy**

- Medical therapy
 - Dopamine agonists
 - Somatostatin analogs
 - GH receptor antagonist
- Radiotherapy (+ Interim medical therapy)

Role of Surgery for Acromegaly



First Line Therapy in Nearly All patients:

- Potential for cure
- Leads to immediate decline in GH level
- Reduces tumor size and relieves mass effect
- Surgical complication rate is low

Targets of the GH/IGF-I Pathway for Medical Therapy of GH Producing Pituitary Tumor

Somatostatin Analogs (SA)

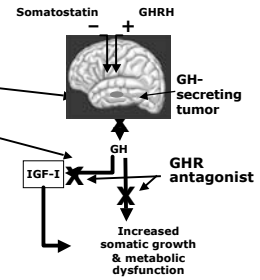
- Directly inhibit GH secretion

Dopamine Agonists (DA)

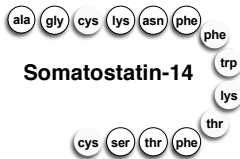
- Directly inhibit GH secretion

Growth Hormone Receptor (GHR) Antagonist (pegvisomant)

- Blocks the GH receptor, negating effects of GH in periphery
- Directly inhibits IGF-I secretion

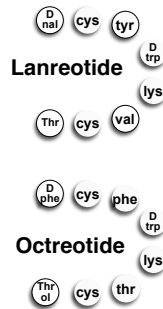


Somatostatin



Amino acids common to native hormone & analog.

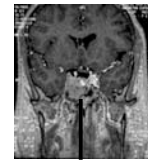
Analogs: Clinical Use



Pegvisomant

- GH molecule that has been mutated to function as a receptor antagonist
- GH Receptors are blocked.
- GH does not fall, but GH actions are blocked.
- IGF-I levels fall and clinical symptoms of acromegaly improve

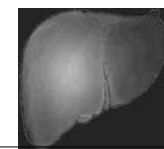
IGF-I Levels Fall



GH



Functional GHR Dimerization Is Prevented

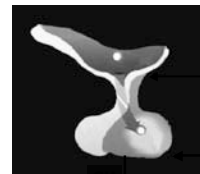


Goals of Therapy



- Biochemical control
 - GH suppression
 - IGF-I normalization
- Relieve signs and symptoms
- Reduce tumor size & mass effect
- Preserve pituitary function
- Minimal side effects

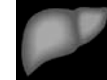
Etiologies of Clinical Syndromes of Growth Hormone Deficiency



Hypothalamic Disease: GHRH Deficiency

Pituitary Disease: Failure to Secrete GH

Liver & Other Tissue



Failure to generate IGF-I peripherally

- Deficiencies of GH or IGF-I receptors in liver; IGF-I not produced; GH resistance, GH not low.

IGF-I

Etiologies of Adult Onset of GH Deficiency

Cause	N=1034	Percent
Pituitary tumor		53.9
Craniopharyngioma		12.3
Idiopathic		10.2
CNS tumor		4.4
Empty sella syndrome		4.2
Sheehan's syndrome		3.1
Head trauma		2.4
Hypophysitis		1.6
Surgery other than for pituitary treatment		1.5
Granulomatous diseases		1.3
Irradiation other than for pituitary treatment		1.1
Other		4.0

Abs R, et al. *Clin Endocrinol (Oxf)* 1999;50:703-713.

Clinical Consequences of Adult Onset GH Deficiency

- Increased cholesterol and increased levels of some cardiovascular risk markers eg. CRP.
- Abnormal body composition; increased central body fat.
- Decreased bone density
- Decreased quality of life

Therapy of GH Deficiency:

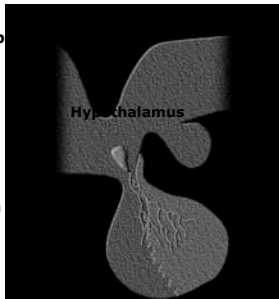
- Requires daily subcutaneous injections of human growth hormone. (Some newer formulations may be longer acting)
- Effect in GH deficient adults; Modest improvements in the effects of GH deficiency listed above.

Regulation of Prolactin Secretion



Stimulated by:

- Sleep
- Food
- Stress
- Pregnancy
- Nursing
- Breast stimulation



Inhibited by:

- Dopamine
- Under Tonic Inhibition

Hyperprolactinemia



- **Defined as excess serum prolactin:**
Prolactin >20 µg/L in men or >25 µg/L in women
- **Most common endocrine disorder of the hypothalamic-pituitary axis**
- **Prevalence: 0.4% in unselected normal adult population**
 - Many different etiologies
 - Prolactinomas are the most frequent cause of hyperprolactinemia

Pathological Causes of Hyperprolactinemia



Pituitary/Hypothalamic Disorders

- Prolactinoma
- Acromegaly
- Other sellar masses
- Infiltrative disorders
- Hypothalamic and pituitary stalk disease or damage

Other Causes

- Primary hypothyroidism
- Seizures
- Polycystic ovary disease
- Neurogenic causes (chest wall trauma or surgery, herpes zoster)
- Renal insufficiency
- Cirrhosis
- Medications

Pharmacologic Causes of Hyperprolactinemia



- Antihypertensives
 - Verapamil
 - Methyldopa
 - Reserpine
- GI Medications
 - Chlorpromazine
 - Metoclopramide
 - Domperidone
 - H2 blockers?
- Antipsychotics
 - Phenothiazines
 - Butyrophenones
 - Atypicals
- Antidepressants
 - Tricyclics
 - MAO inhibitors
 - SSRIs
- Other
 - Cocaine
 - Opiates
 - Protease Inhibitors?

Clinical Manifestations of Hyperprolactinemia



Hyperprolactinemia: Suppresses gonadotropins
- leads to varying degrees of gonadal dysfunction.

Women

- Oligo-amenorrhea
- Infertility
- Galactorrhea
- Estrogen deficiency
- Acne/hirsutism
- Osteopenia

Men

- Decreased libido
- Erectile dysfunction
- Gynecomastia
- Galactorrhea
- Infertility
- Osteopenia

Treatment of Hyperprolactinemia



- **Dopamine agonist therapy** is primary treatment for almost all patients
- Surgery and radiation therapy occasionally used
- Careful follow-up without treatment is an option for patients if they
 - do not have a macroadenoma
 - are asymptomatic
 - have normal gonadal function
 - are not seeking fertility

Dopamine Agonists used to treat Hyperprolactinemia/Prolactinomas



- Bromocriptine
- Cabergoline

Hyperprolactinemia: Treatment Goals



- Restore gonadal function
 - Improvement in sexual dysfunction
 - Fertility
- Resolve galactorrhea (if bothersome)
- Reduce/stabilize tumor size
 - Reverse mass effects
 - Preserve/restore pituitary function
- Normalize PRL level

Pituitary Tumors



Nearly All Benign

Can be: Non-secreting

Hormone Secreting

Prolactin

Growth Hormone

ACTH- Cushing's

TSH, LH, FSH

Cause Disease:

Problems related to: Excess hormone

Pressure of tumor on: optic nerves, other surrounding

Or normal pituitary - pituitary insufficiency

Evaluation of the Patient for Pituitary Disease



- History and Physical examination
- Laboratory: Pituitary hormone overproduction and hypopituitarism
 - Prolactin
 - Free T4, TSH
 - Cortisol, ACTH
 - GH, IGF-I
 - LH, FSH, testosterone
 - Pregnancy test
- MRI
- Visual fields