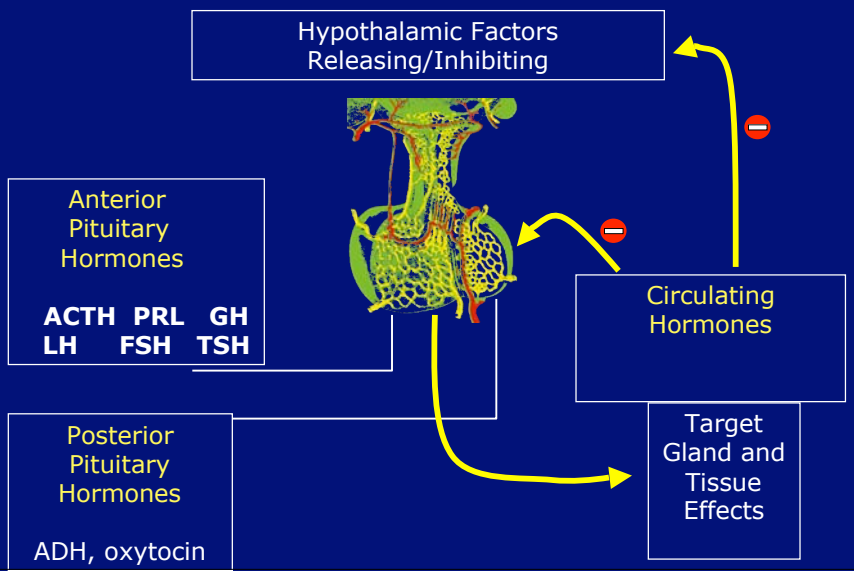
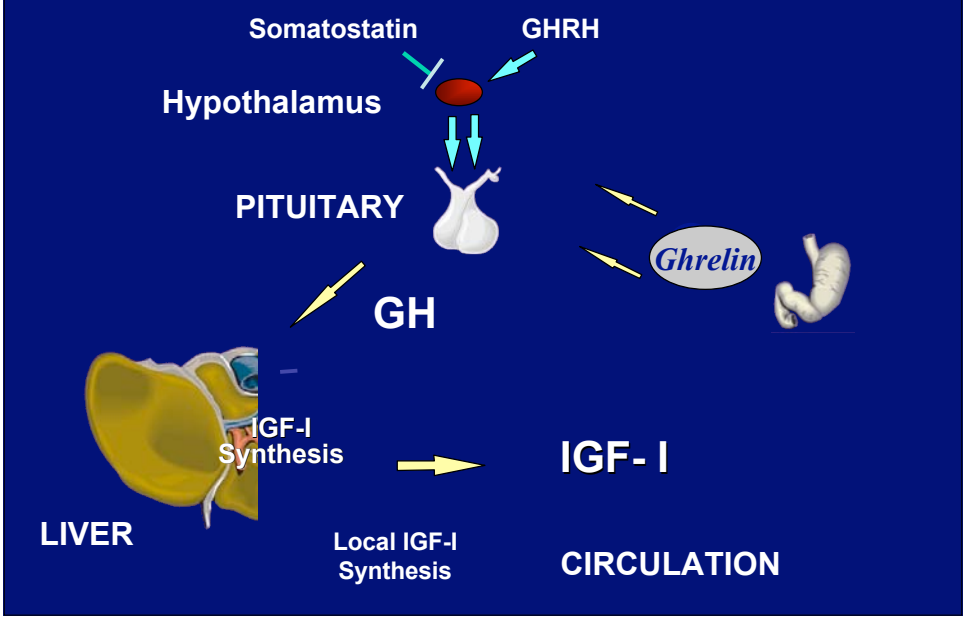
Pituitary

February 11, 2008

Hypothalamic-Pituitary Axes



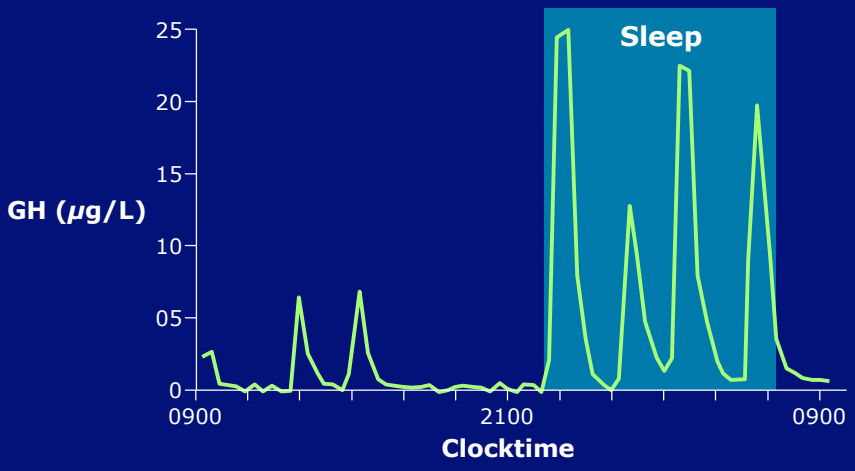
The GH/IGF-I Axis



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 µg/m^2/day**
  - **Men: 350 µg/m^2/day**

Pulsatile Pattern of GH Secretion in a Healthy Adult



From: "Acromegaly" by Alan G. Harris, M.D.

GH Secretion: Primarily Regulation by two hypothalamic hormones

Growth Hormone Releasing Hormone
Stimulatory of GH Secretion

GHRH +

- SMS

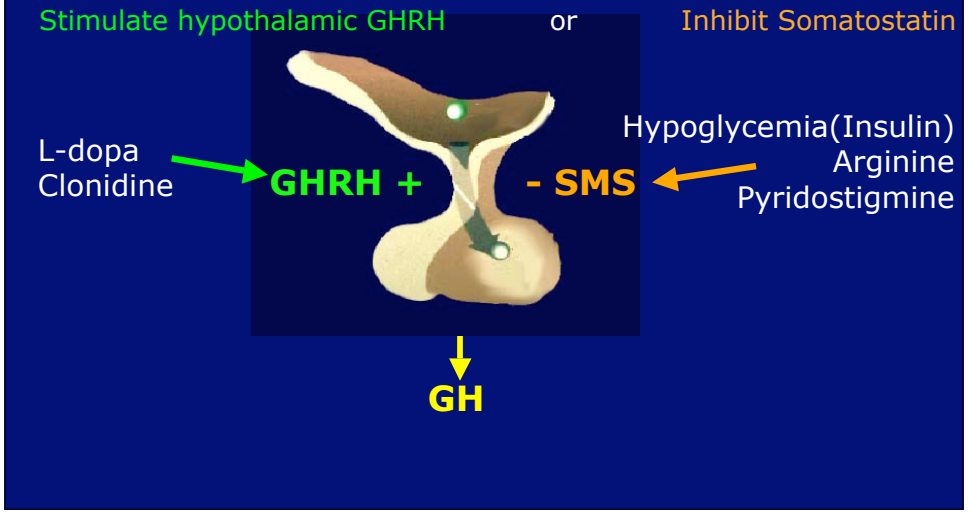
Somatostatin
Inhibitory of GH Secretion

GHRH induces GH synthesis and secretion in somatotrophs

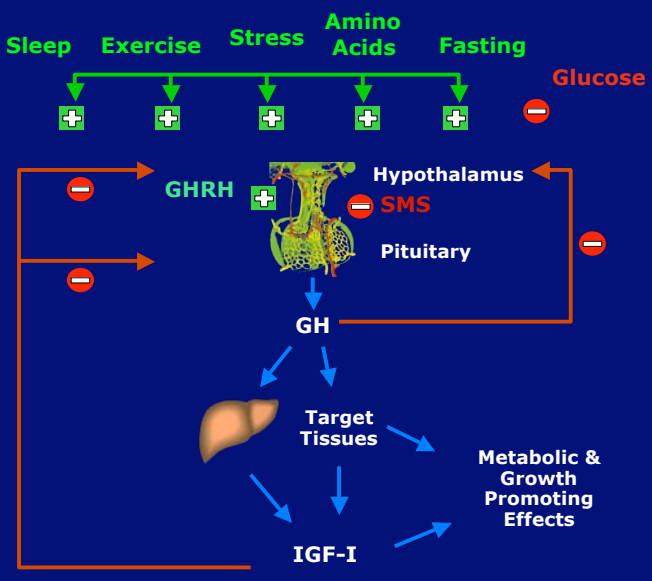
GH

Somatostatin: Decreases to allow GH secretory Bursts

Pharmacologic Agents Used to Stimulate GH Secretion



Other Physiological Regulators of GH Secretion



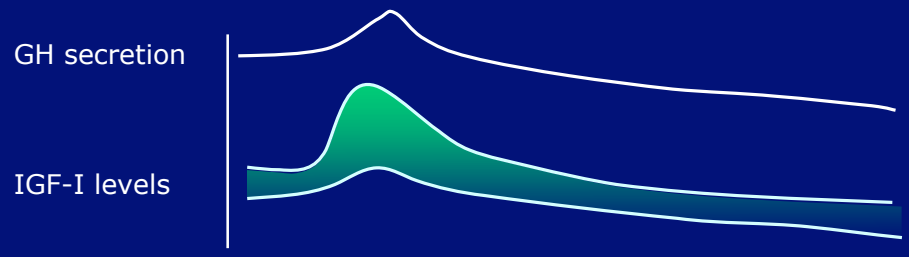
Insulin-like growth factor I (IGF-I)

- **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**

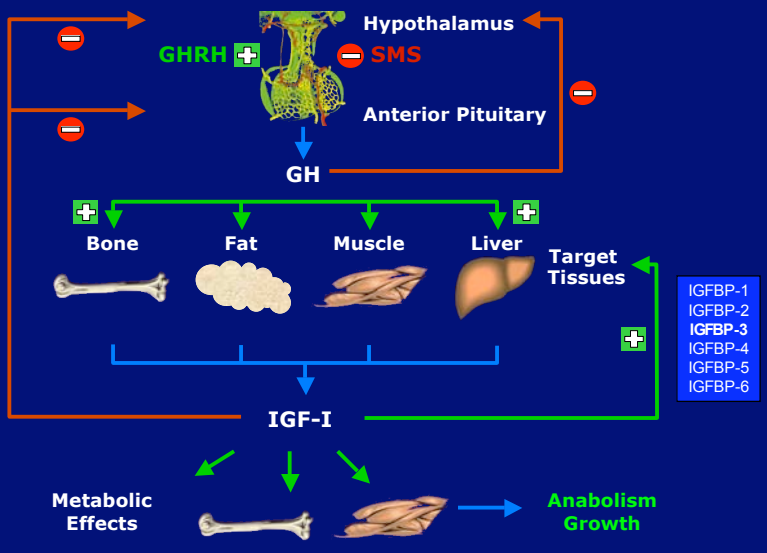
GH Secretion & IGF-I Levels Across Lifespan



Prepubertal Pubertal Adult <35 yr Adult >35 yr

- GH secretion declines with age
- Serum IGF-I levels also decline with age.

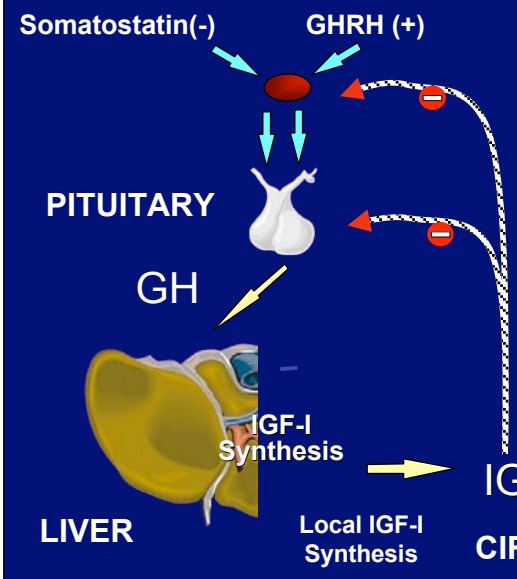
GH & IGF-I Actions



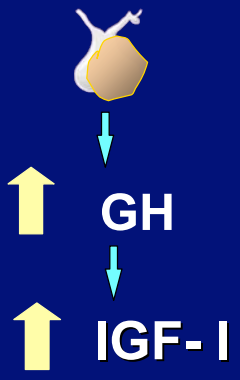
Disorders of GH Secretion

- **GH Excess**:
  GH overproduction by a GH Secreting pituitary tumor - ACROMEGALY
- **GH Deficiency**:
  Childhood onset
  Adult onset

GH/IGF-I Axis



Acromegaly



Biochemical Diagnosis of Acromegaly

Growth Hormone

Random GH Levels

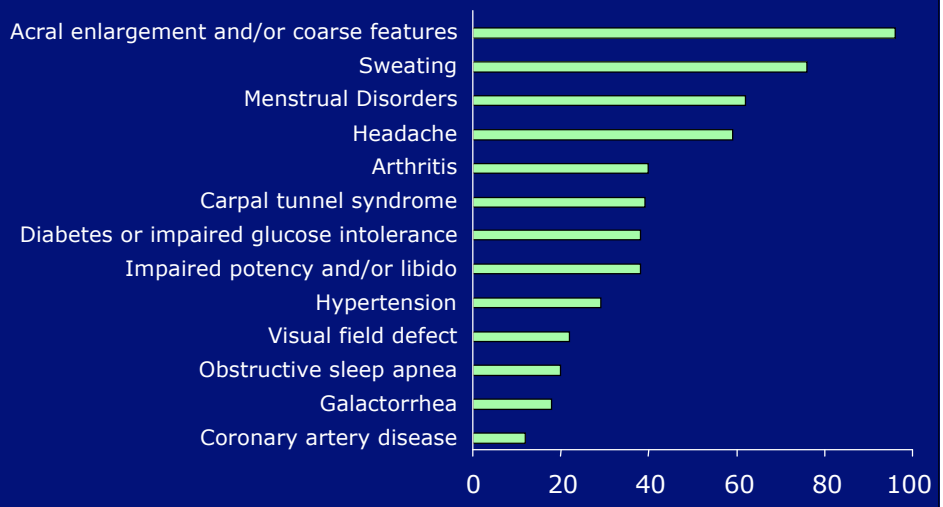
GH Suppression after Oral Glucose:

Failure of GH to Fall < 1 µg/L

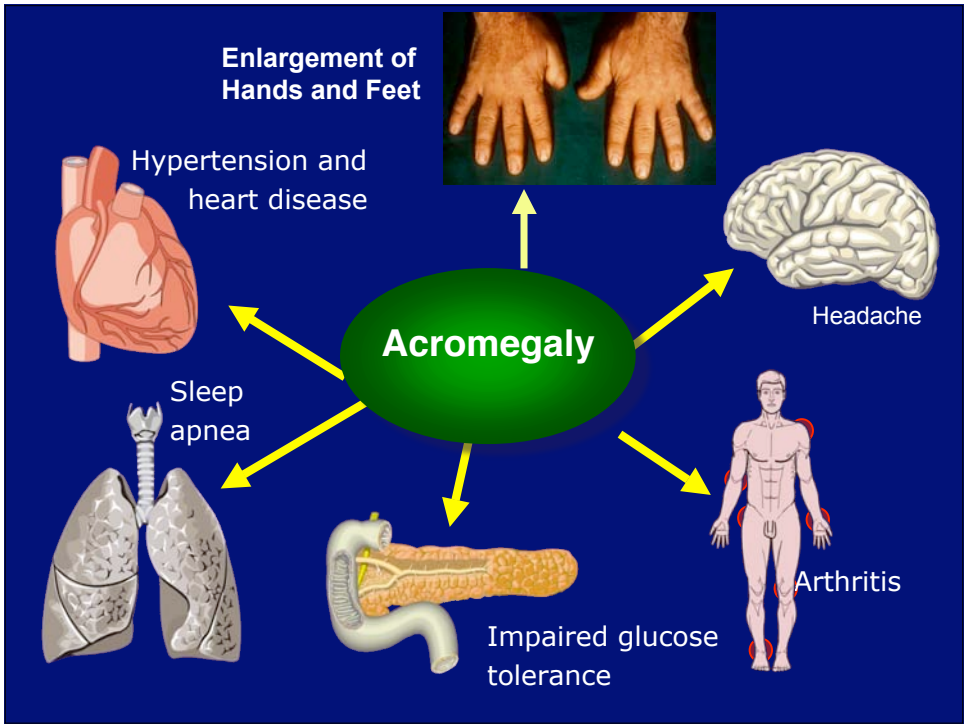
Serum IGF-I Level:

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)

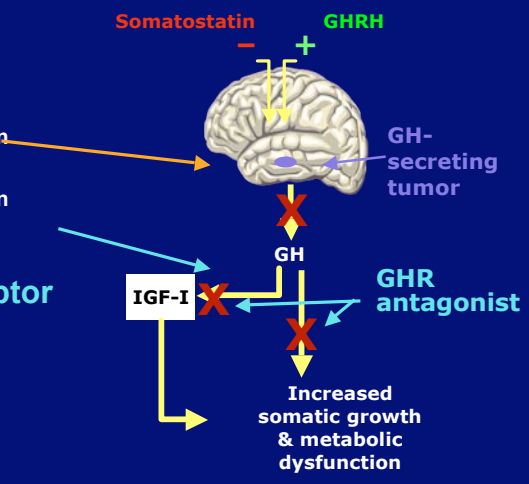
- Directly inhibit GH secretion

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

ala gly cys lys asn phe phe trp lys thr cys ser thr phe

Somatostatin-14

Amino acids common to native hormone & analog.

Analogs: Clinical Use

D nal cys tyr D trp lys Thr cys val

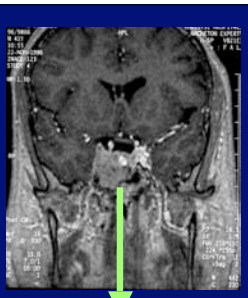
Lanreotide

D phe cys phe D trp lys Thr ol cys thr

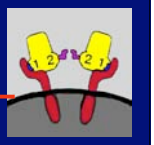
Octreotide

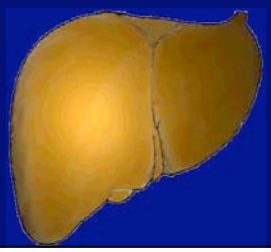
Pegvisomant

- 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



GH





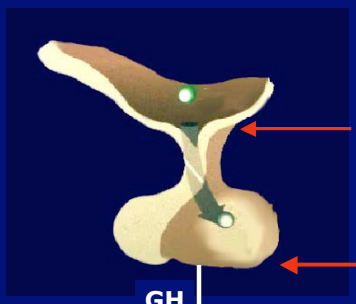
IGF-I Levels Fall

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

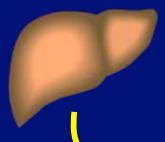
Etiologies of Clinical Syndromes of Growth Hormone Deficiency



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

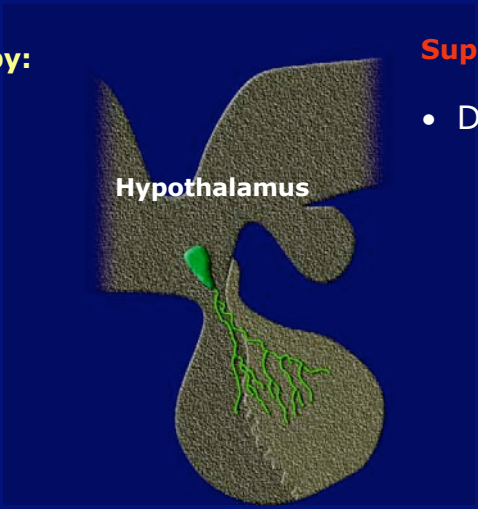
Therapy of GH Deficiency:

- 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



Suppressed 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
  - Methydopa
  - 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/hirsuitism
- 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 ocassionally 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