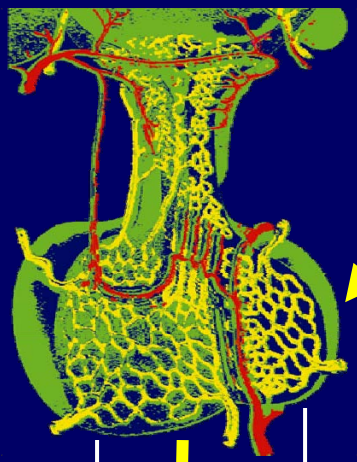
Pituitary

March 8, 2010

Hypothalamic-Pituitary Axes

Hypothalamic Factors
Releasing/Inhibiting



Anterior
Pituitary
Hormones

ACTH PRL GH
LH FSH TSH

Circulating
Hormones

Posterior
Pituitary
Hormones

ADH, oxytocin

Target
Gland and
Tissue
Effects

CAUSES OF PITUITARY DISEASE

Tumors and Other Mass Lesions

Pituitary Tumors (most common)

- Hormone Secreting
- Non-hormone secreting

Non-Pituitary Lesions

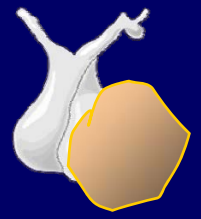
- Cell Rest Tumors
  - Craniopharyngioma, Rathke's Cleft Cysts, Chordoma
- Meningioma
- Metastatic Tumors
- Lymphoma
- Granulomatous, Infectious and Inflammatory
  - Sarcoid, Tuberculosis
  - Abscess
  - Lymphocytic Hypophysitis

Other causes

- Vascular Lesions: Aneurysm
- Pituitary Apoplexy- pituitary hemorrhage
- Infarction of pituitary- Sheehan syndrome
- Head Trauma
- Genetic diseases - pit-1 mutation
- Empty sella syndrome

- Hypothalamic Disease
  - Mass lesions – eg. craniopharyngiomas, germ cell tumors
  - Radiation - for CNS and nasopharyngeal malignancies
  - Infiltrative lesions - sarcoidosis, Langerhans cell histiocytosis, tuberculosis

Pituitary Tumors



Nearly All Benign

Can be: Non-secreting

Hormone Secreting

Prolactin
Growth Hormone
ACTH- Cushing's
TSH, LH, FSH

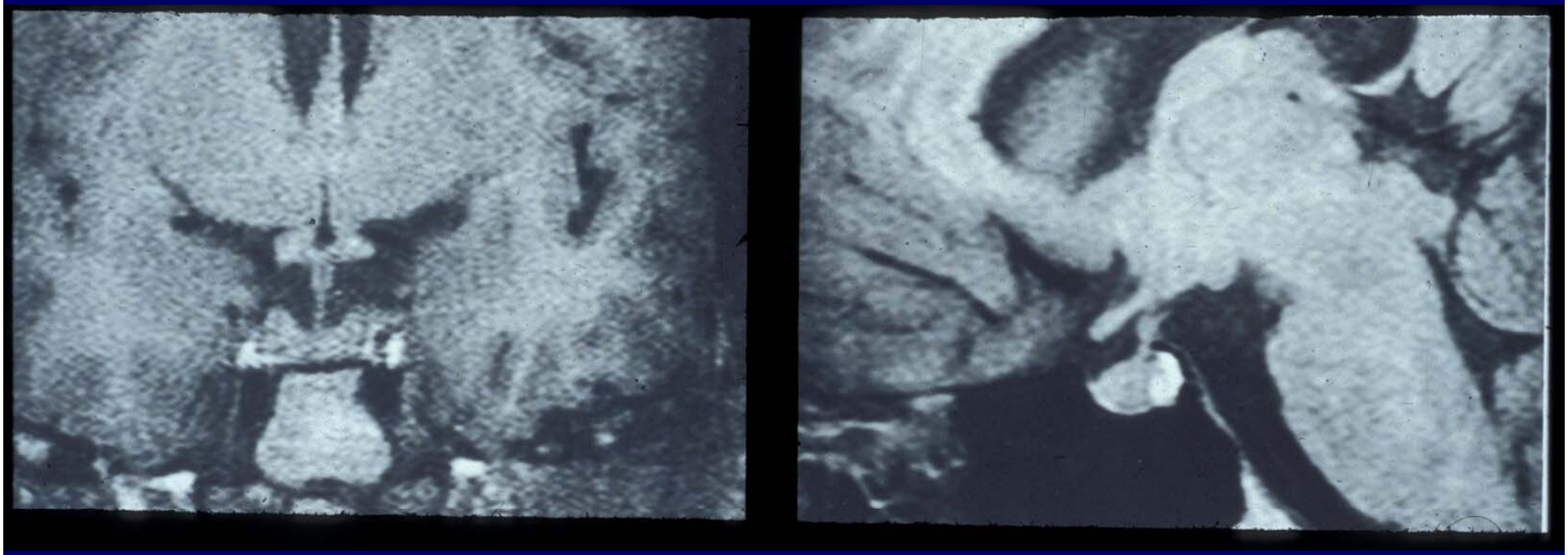
Cause Disease:

Problems related to: Excess hormone

Pressure of tumor on: optic nerves, other surrounding

Or normal pituitary - pituitary insufficiency

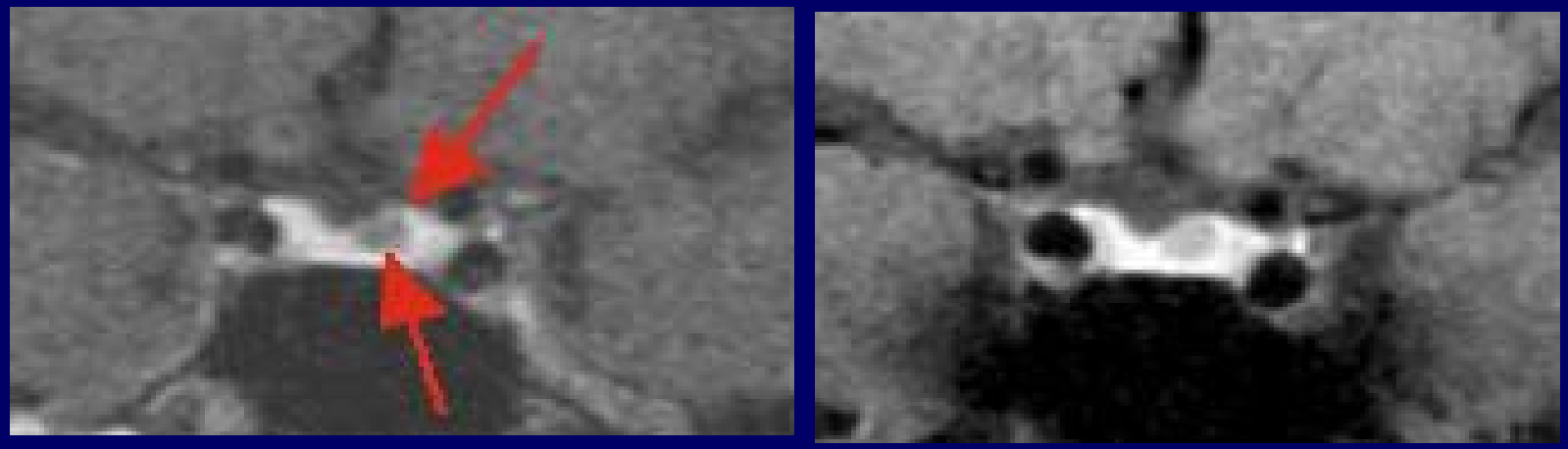
MRI: Normal Pituitary Gland

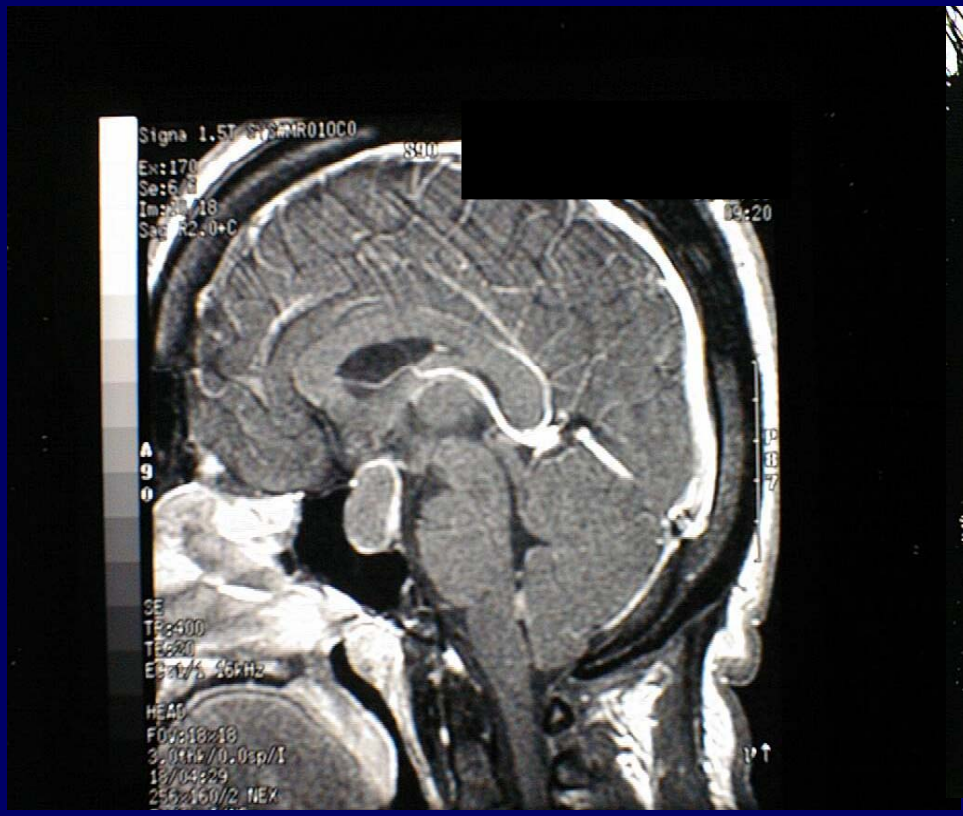


Coronal

Sagittal

MRI: Pituitary Gland Microadenoma

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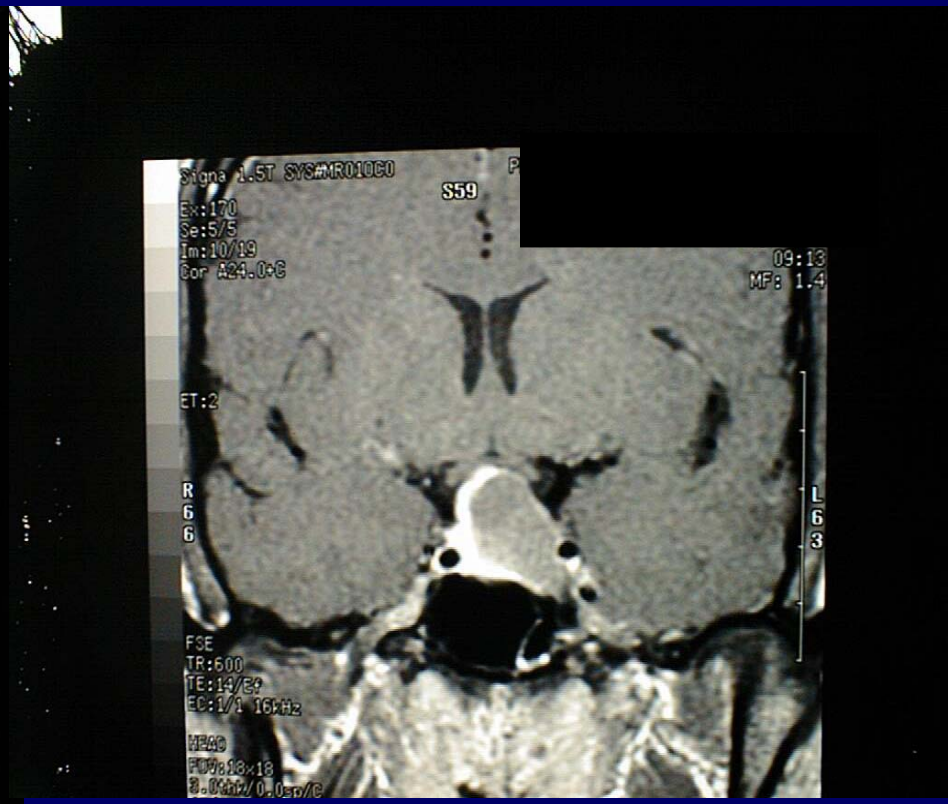
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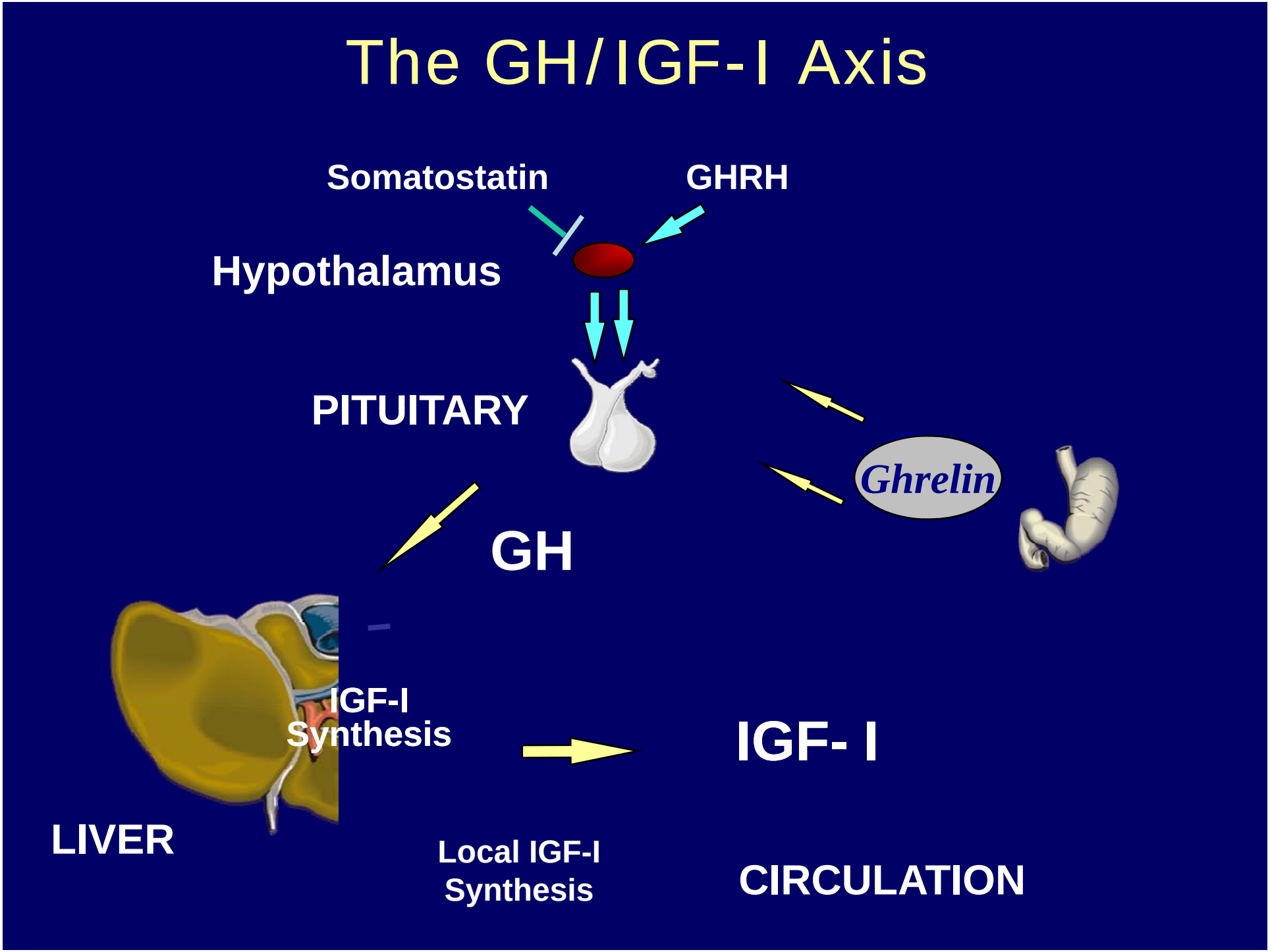
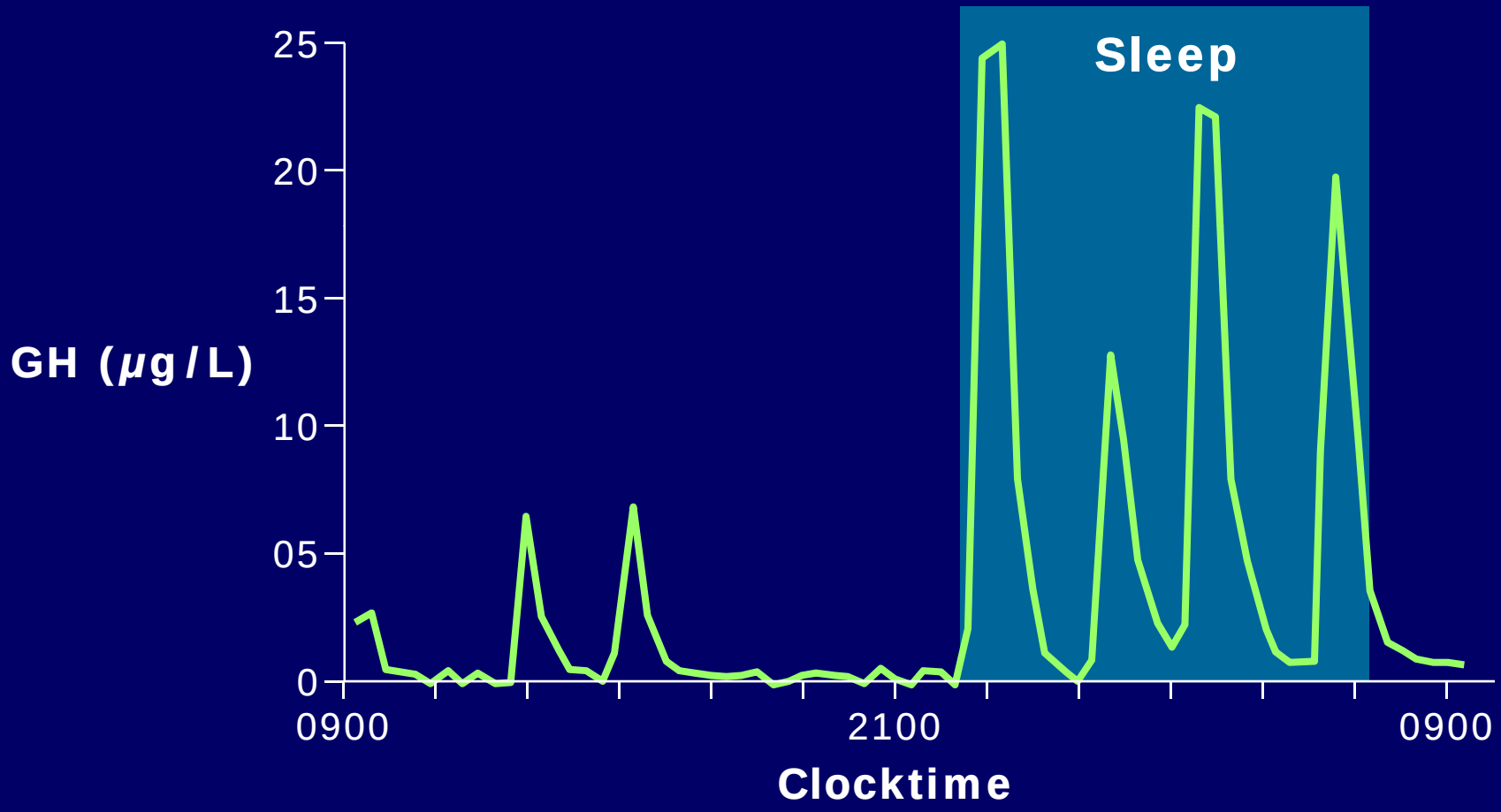
Evaluation of the Patient for Pituitary Disease

- 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

The GH/IGF-I Axis



Pulsatile Pattern of GH Secretion in a Healthy Adult

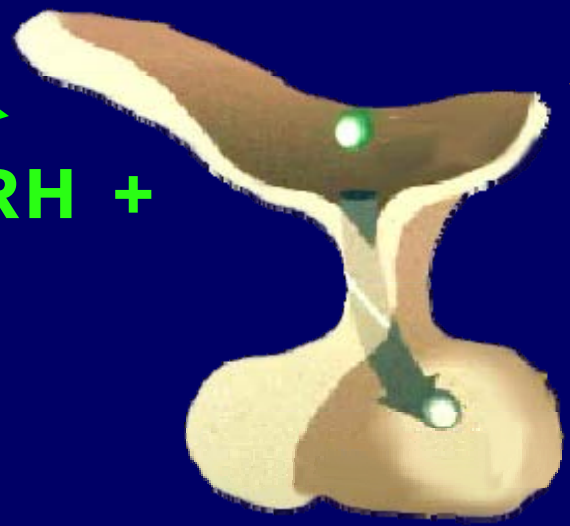


From: “Acromegaly” by Alan G. Harris, M.D.

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

Stimulate hypothalamic GHRH or Inhibit Somatostatin

L-dopa
Clonidine

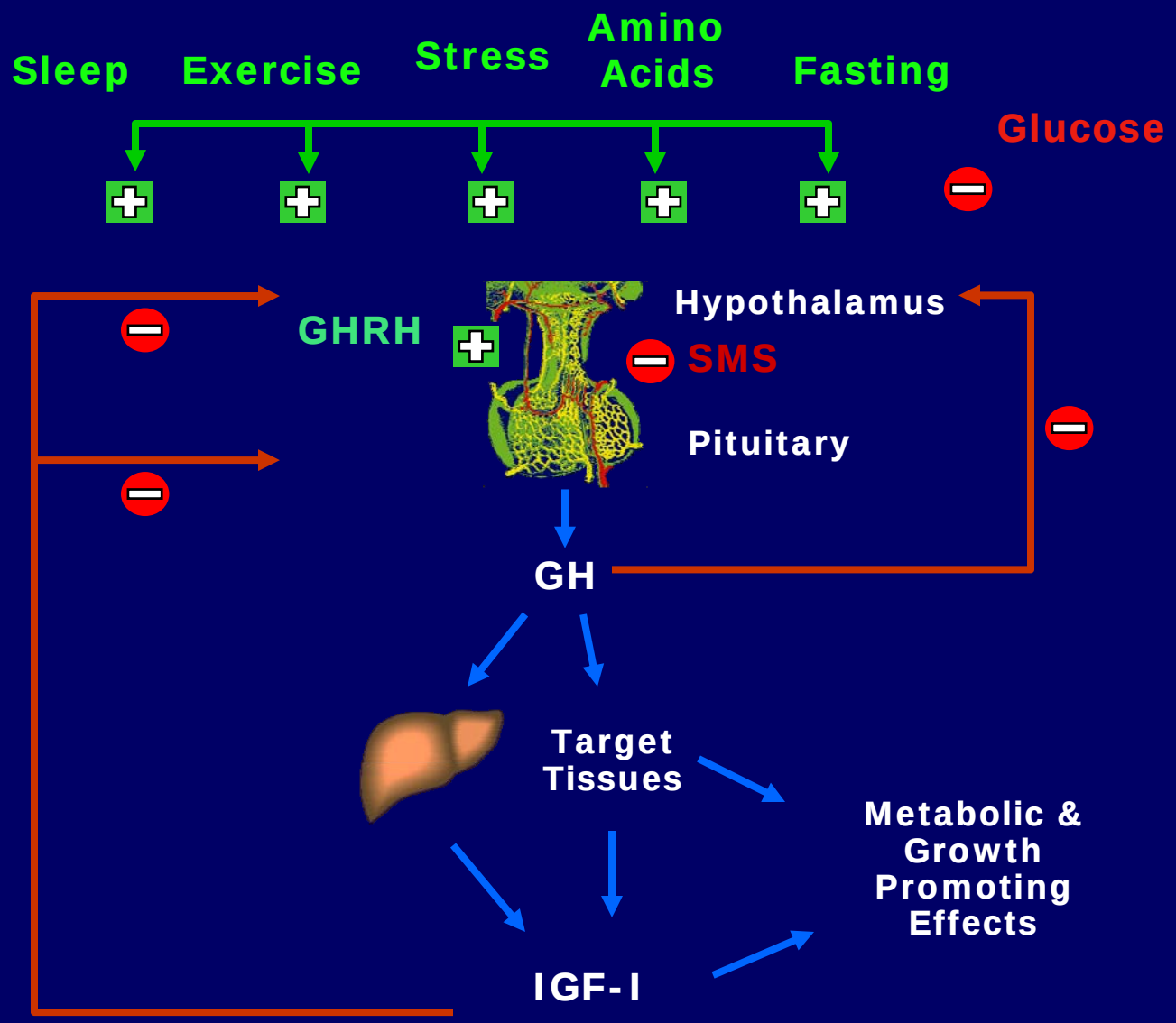
GHRH +

- SMS

Hypoglycemia(Insulin)
Arginine
Pyridostigmine

GH

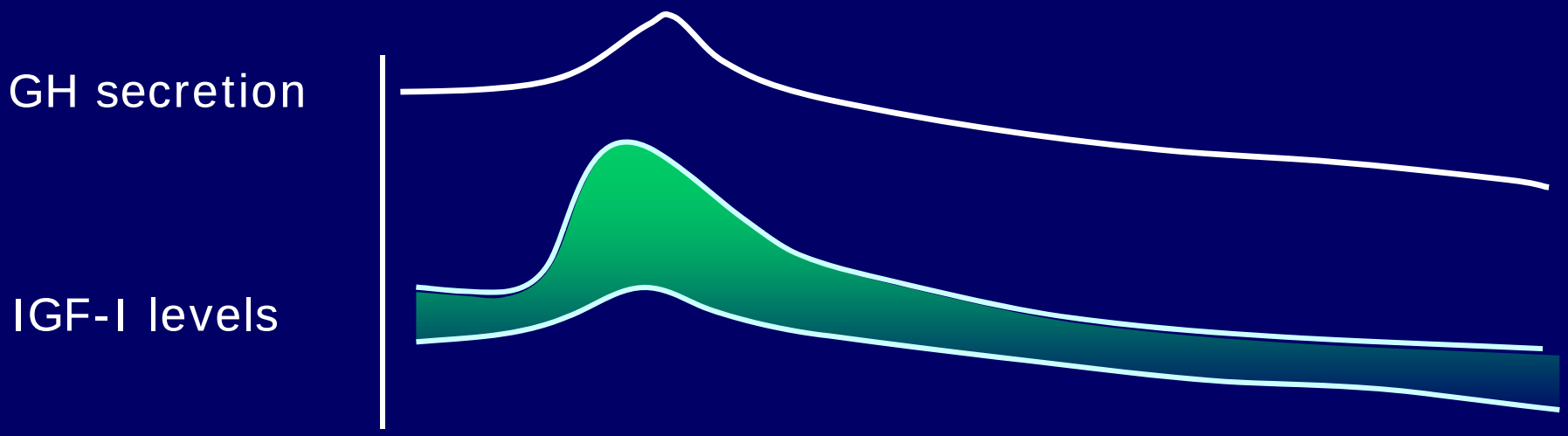
Other Physiological Regulators of GH Secretion



Major Determinants of Circulating IGF-I Levels

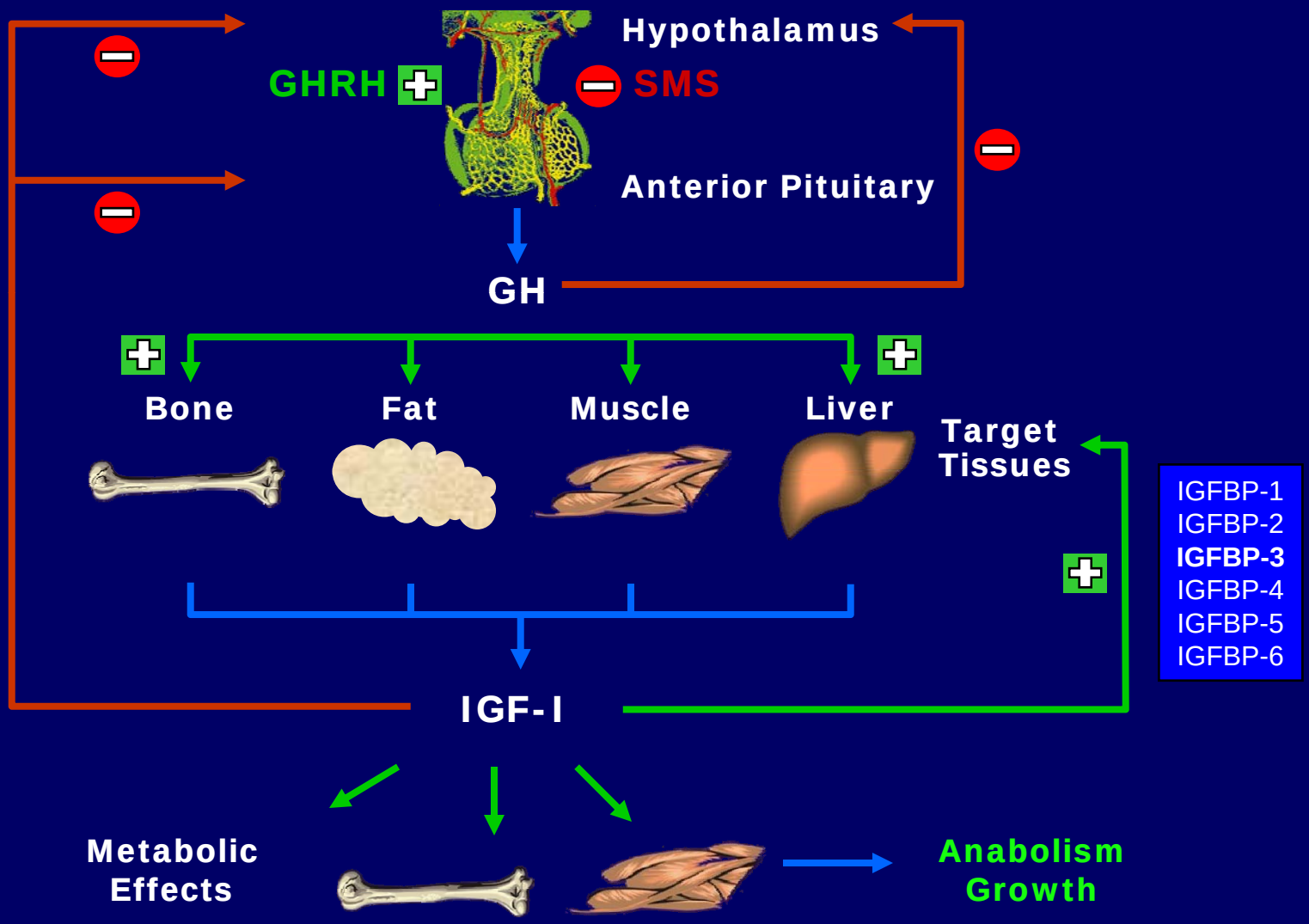
- **Growth Hormone**
  Increases IGF-I production in liver, major source of circulating IGF-I
- **Nutritional Status**
- **Age**
- **Genetic Factors**
- **Binding proteins**
- **Increased levels in pregnancy and puberty**

GH Secretion & IGF-I Levels Across Lifespan

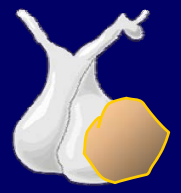


- GH secretion declines with age
- Serum IGF-I levels also decline with age.

GH & IGF-I Actions



Disorders of GH Secretion



- **GH Excess**:

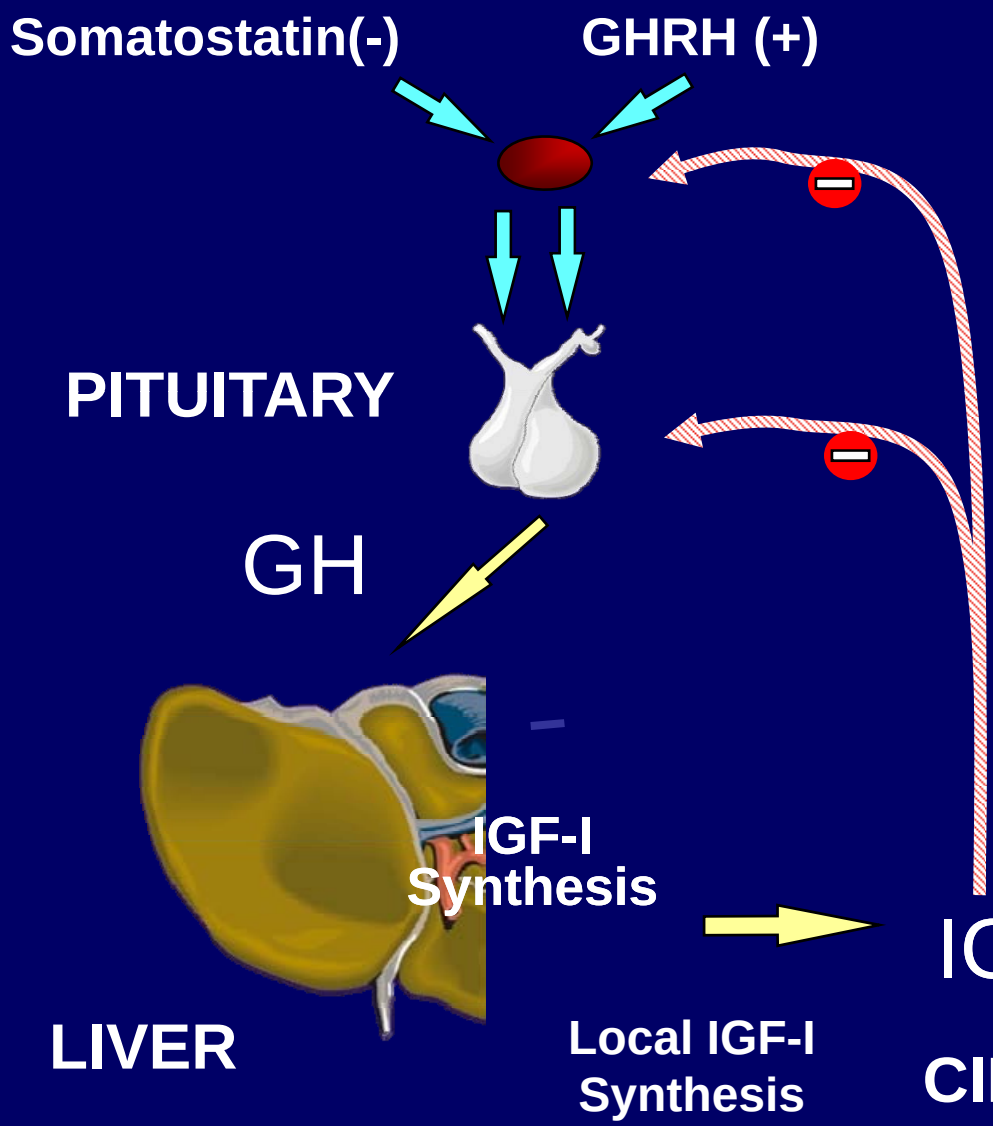
  GH overproduction by a GH Secreting pituitary tumor - ACROMEGALY

- **GH Deficiency**:

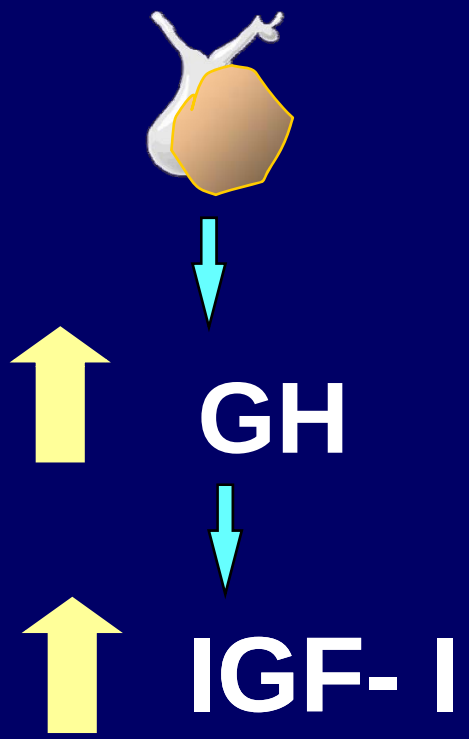
  Childhood onset

  Adult onset

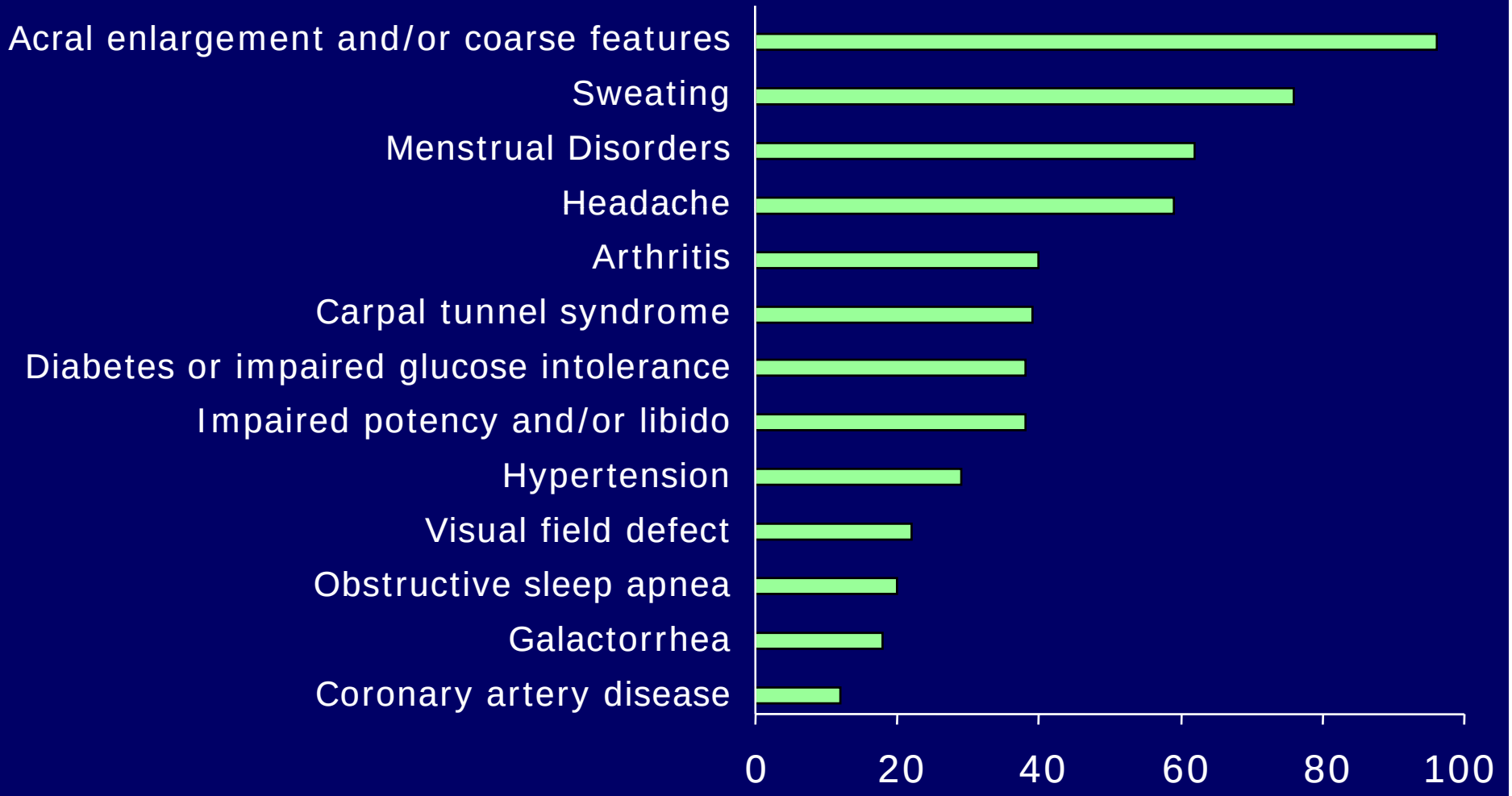
GH/IGF-I Axis



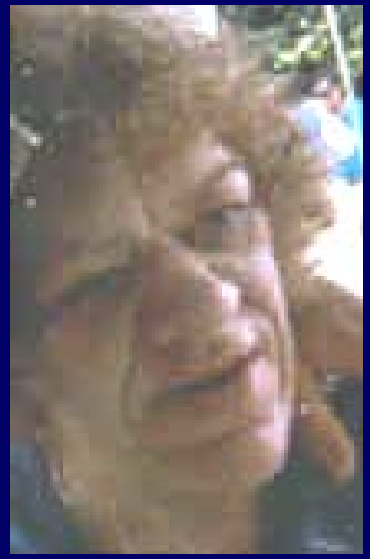
Acromegaly



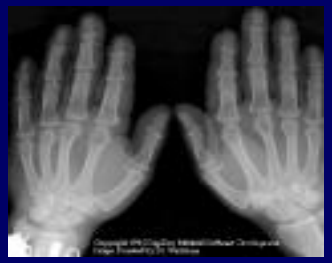
Prevalence of Clinical Features at Diagnosis



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

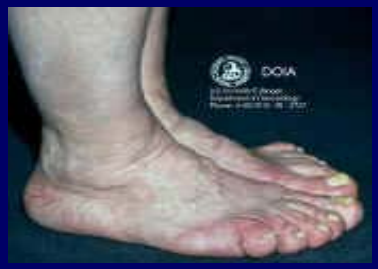


Clinical Features: Extremities

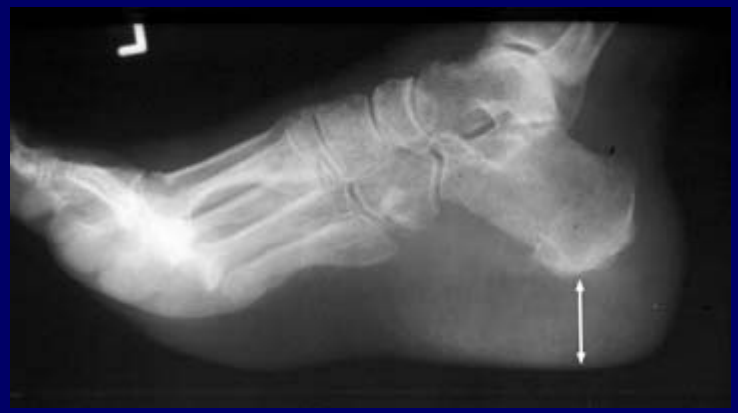


Tufting of the terminal phalanges

Enlarged hands



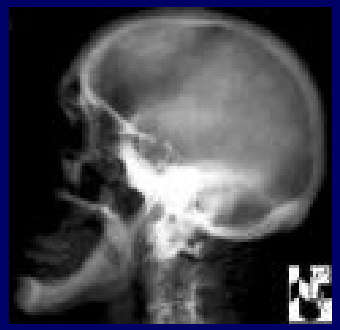
Enlarged Feet



Increased heel pad thickness

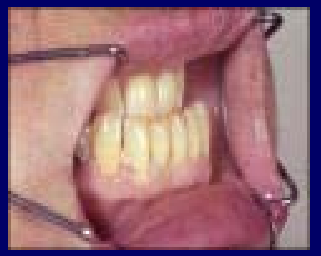
Clinical Features: Maxillofacial

Characteristic facies: enlarged nose, chin and mandible

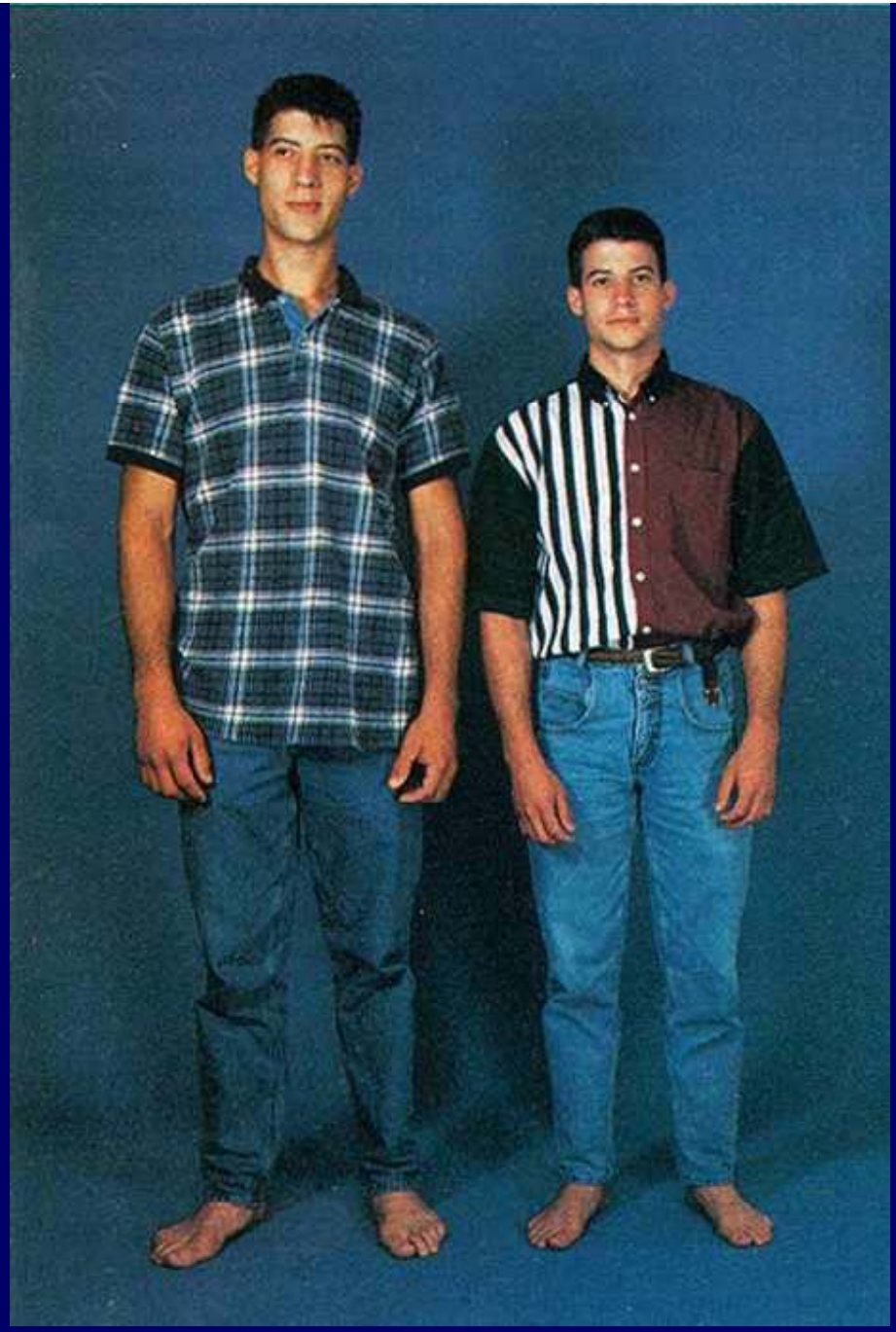


Prognathism, TMJ

Macroglossia

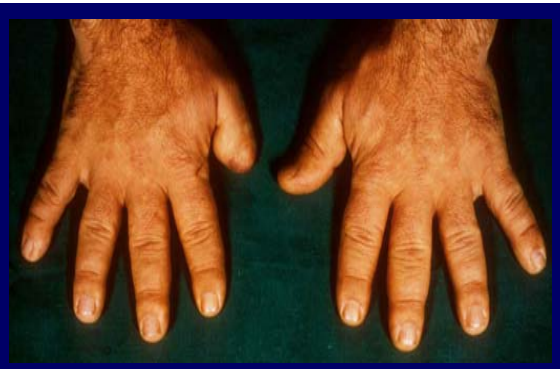


Spreading of Teeth or Malocclusion

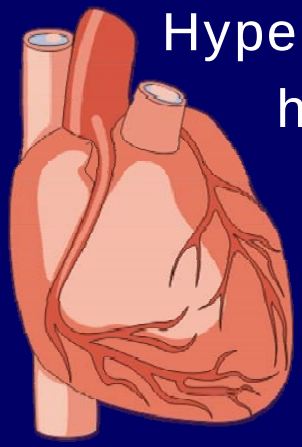


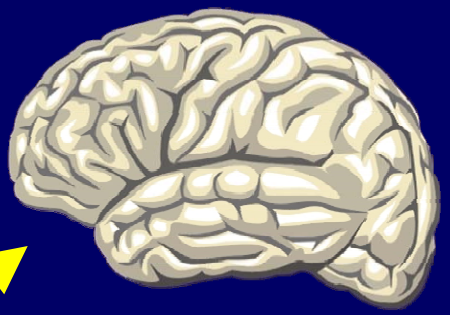
Gagel et al, N Engl J Med 1999;340(7):524

Enlargement of Hands and Feet



Hypertension and heart disease

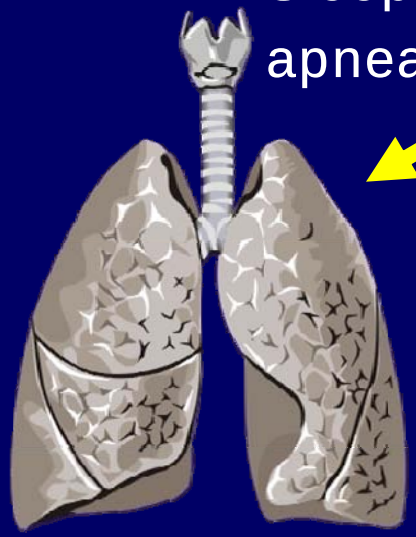


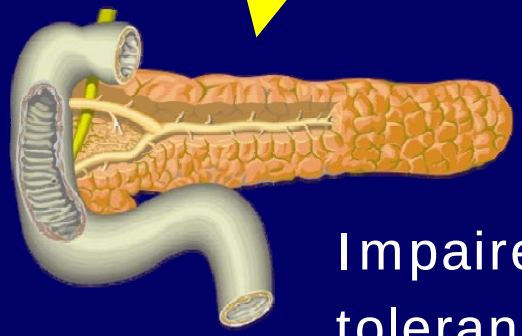


Headache

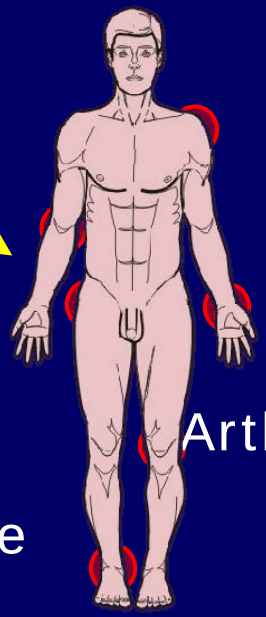
Acromegaly

Sleep apnea





Impaired glucose tolerance



Arthritis

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

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)

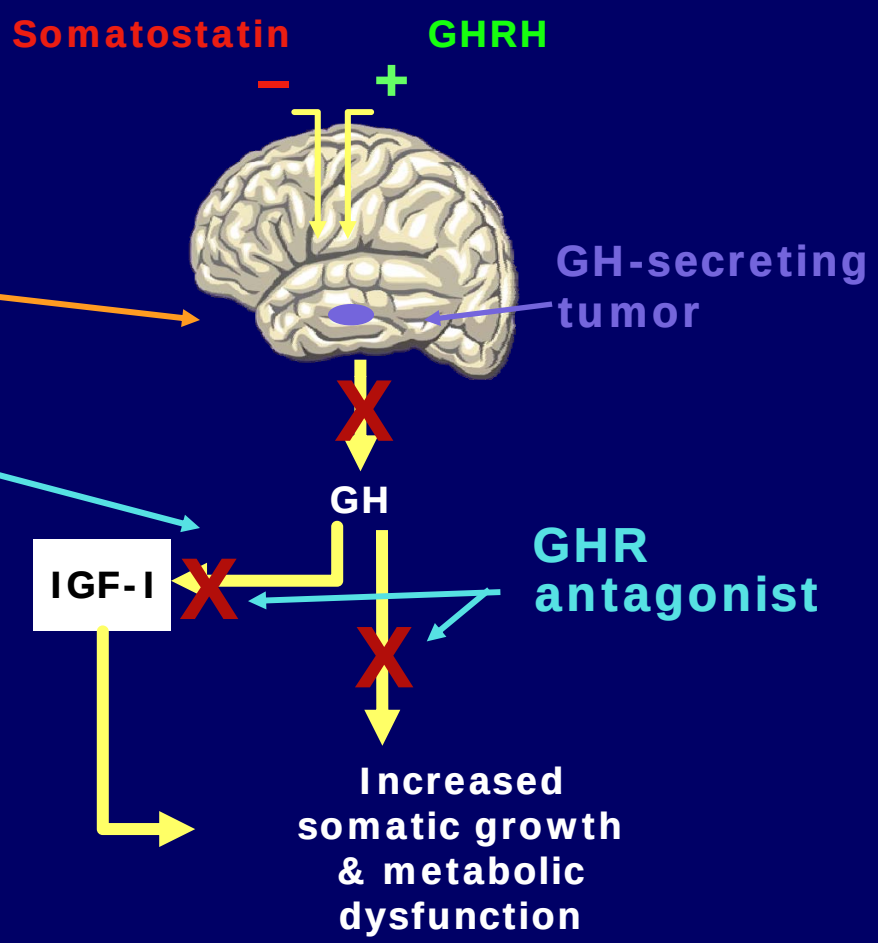
- Directly inhibit GH secretion

Dopamine Agonists (DA)

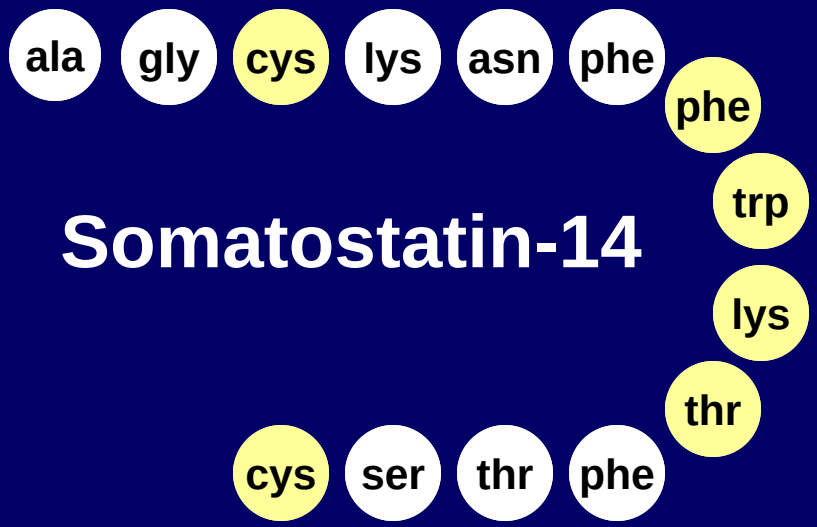
- Directly inhibit GH secretion

Growth Hormone Receptor (GHR) Antagonist (pegvisomant)

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

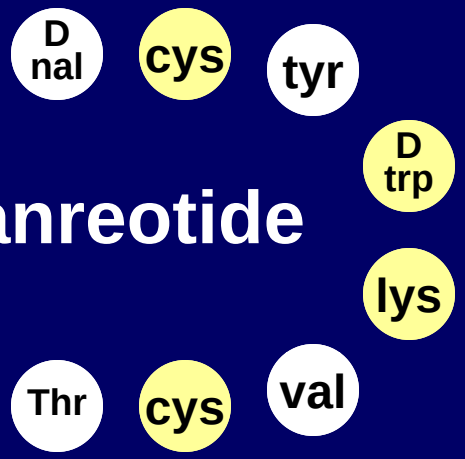


Somatostatin

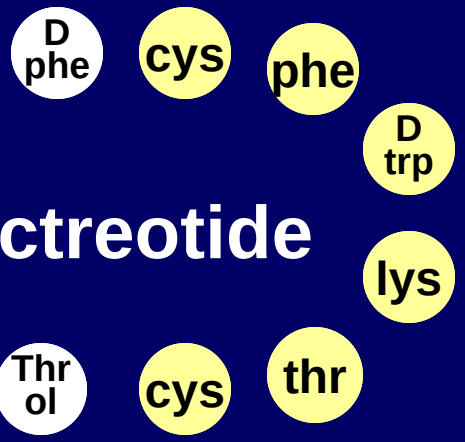


Somatostatin-14

Analogs: Clinical Use



Lanreotide

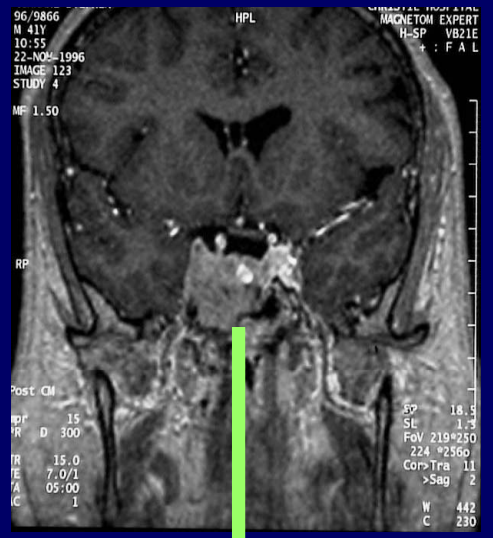


Octreotide

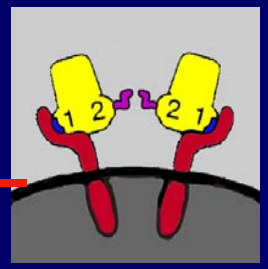
Amino acids common to native hormone & analog.

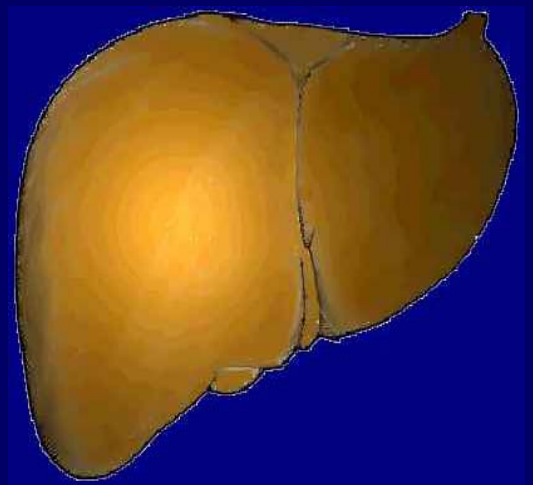
Pegvisomant

- 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





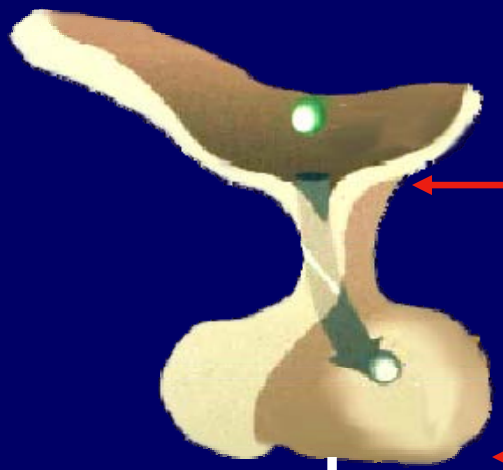
IGF-I Levels Fall

GHR Signal Transduction 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

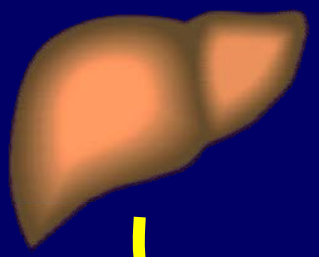


Hypothalamic Disease: GHRH Deficiency

Pituitary Disease: Failure to Secrete GH

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

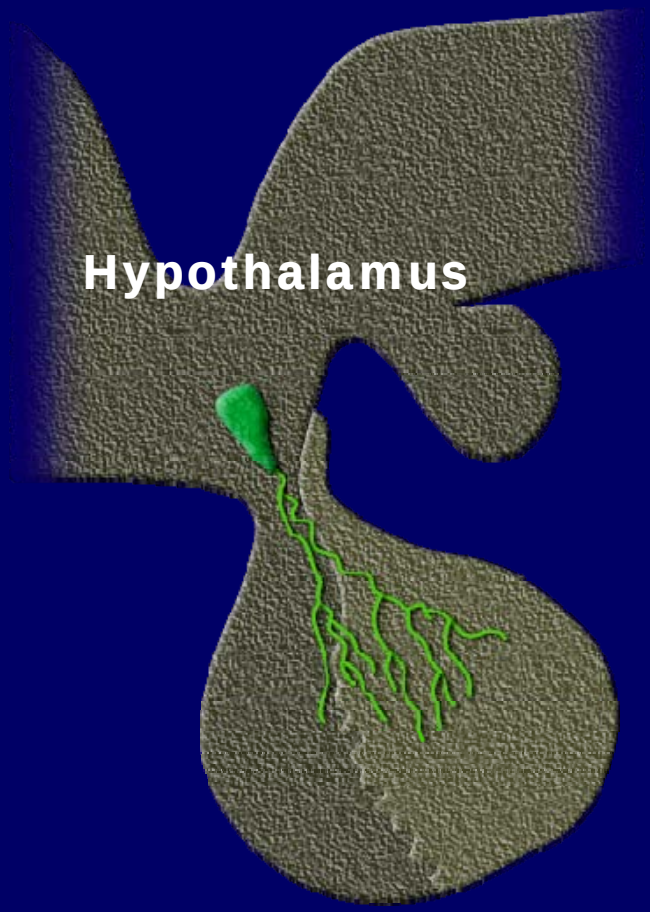
Therapy of GH Deficiency:

- 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 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

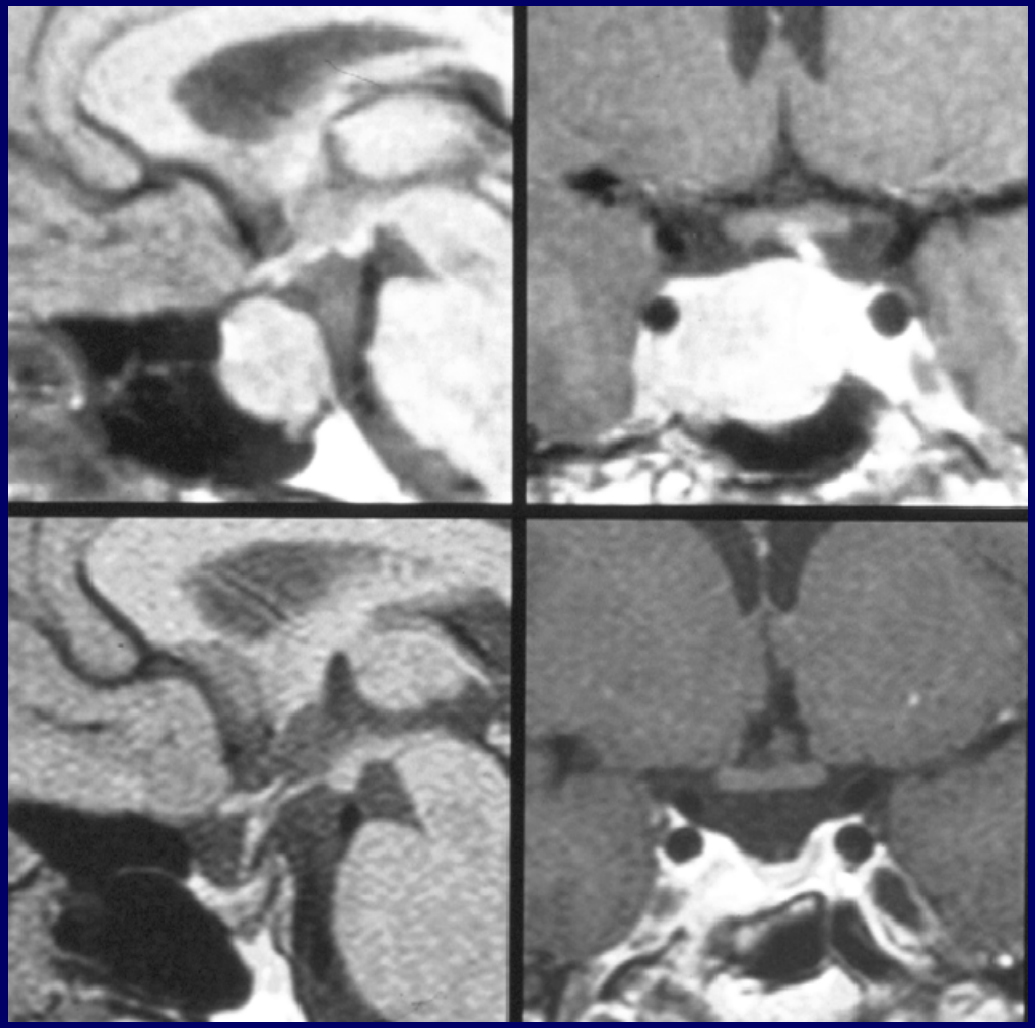
Hyperprolactinemia: Treatment Goals

- 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

Dopamine Agonists used to treat Hyperprolactinemia/Prolactinomas

- Bromocriptine
- Cabergoline

MRI Showing Tumor Reduction With Dopamine Agonist



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