Disorders of the Pituitary Gland

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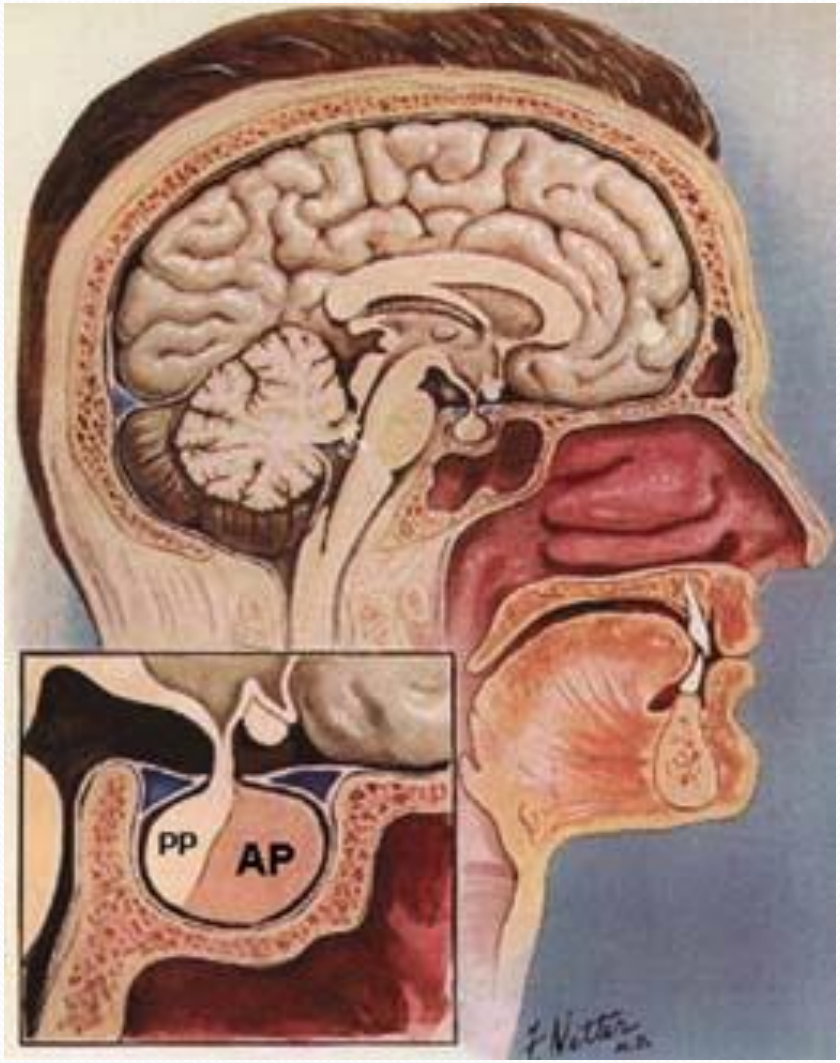
PITUITARY & FRIENDS
kidney
adrenal gland
muscle
ovary
ADH
ACTH
FSH LH
GH
testicle
MSH
FSH LH
skin
TSH
oxytocin
GH
oxytocin
prolactin
thyroid
uterus
liver
mammary gland

Anatomy

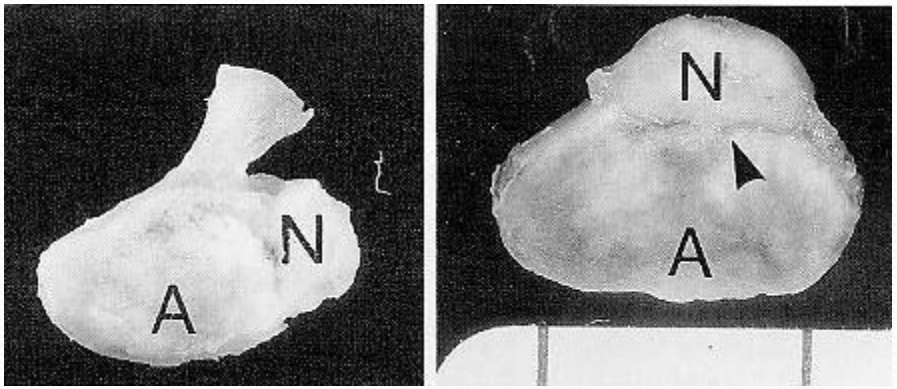


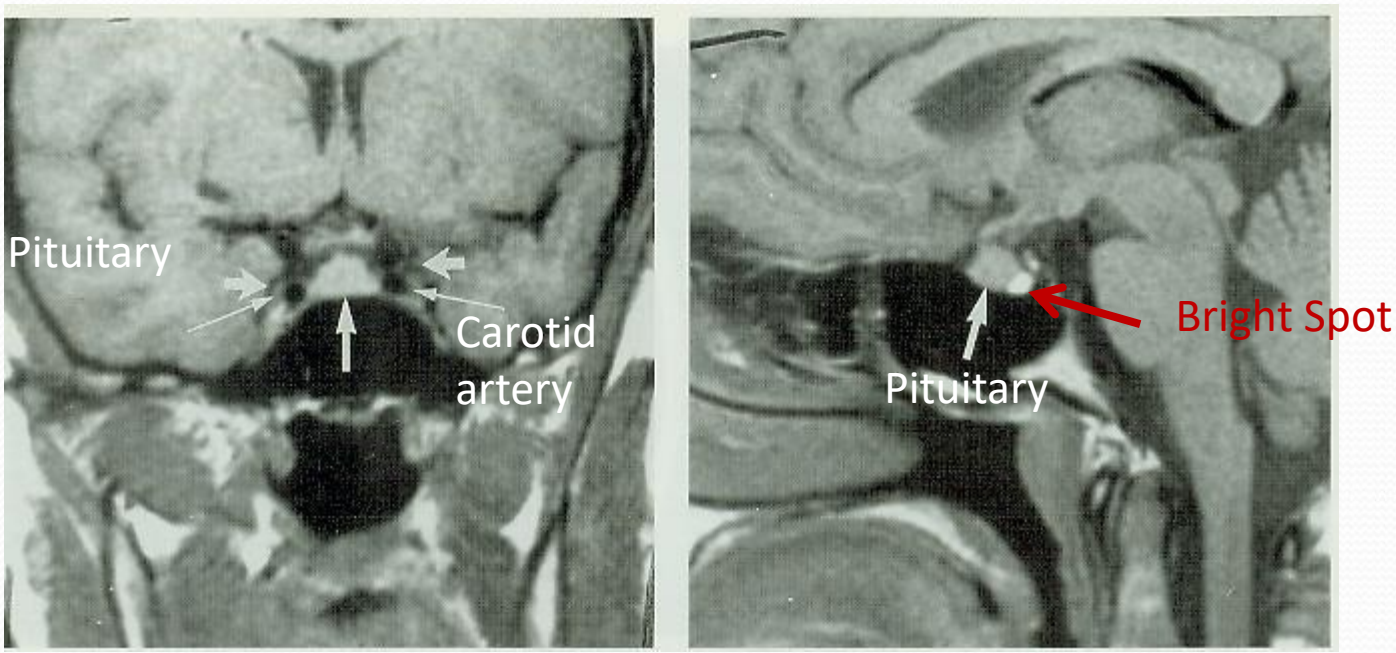
- Pituitary sits in the sella turcica of the sphenoid bone
- Separated into lobes:
  - Anterior
  - Intermediate
  - Posterior

Normal Hypothalamus-Pituitary

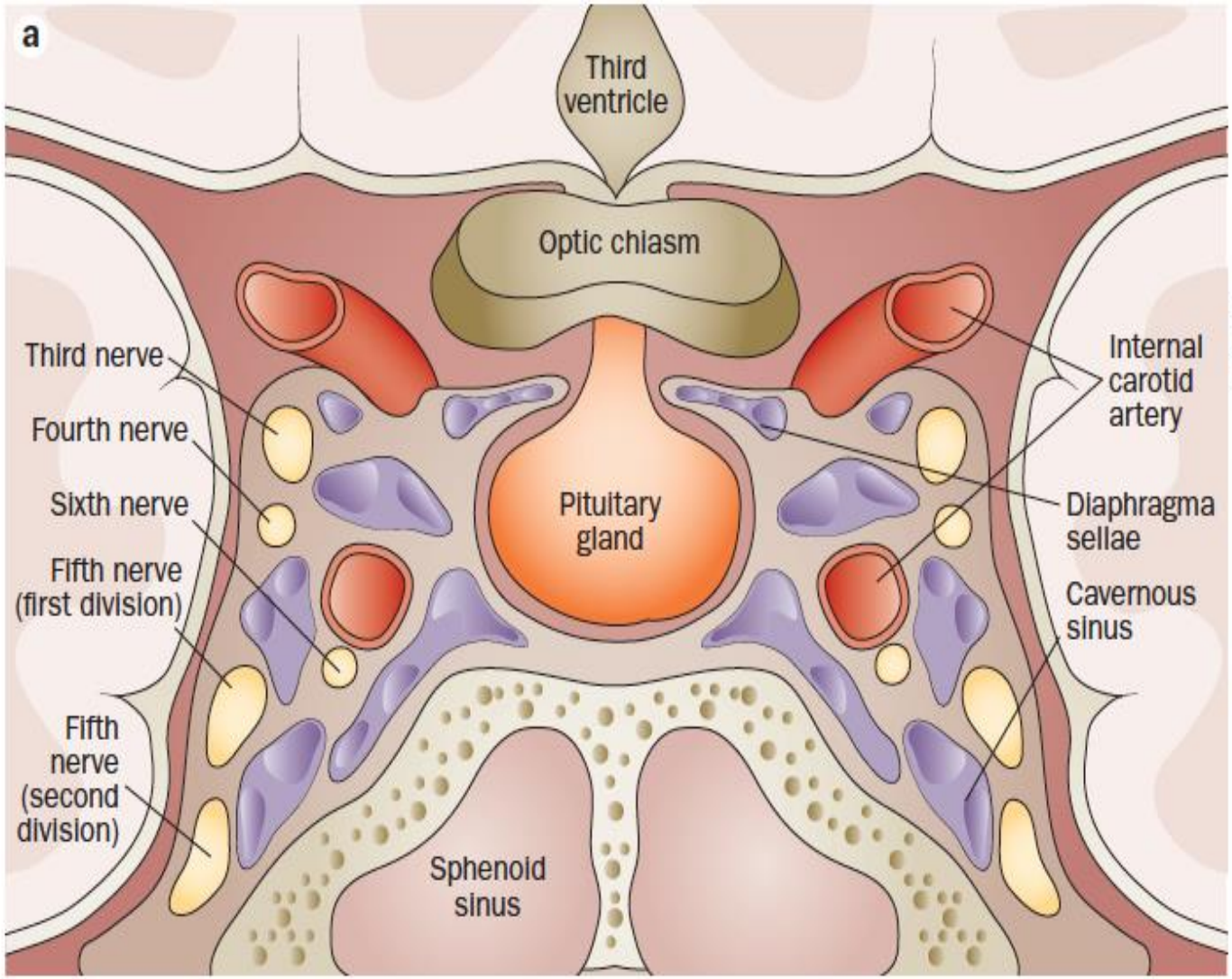
Adenohypophysis

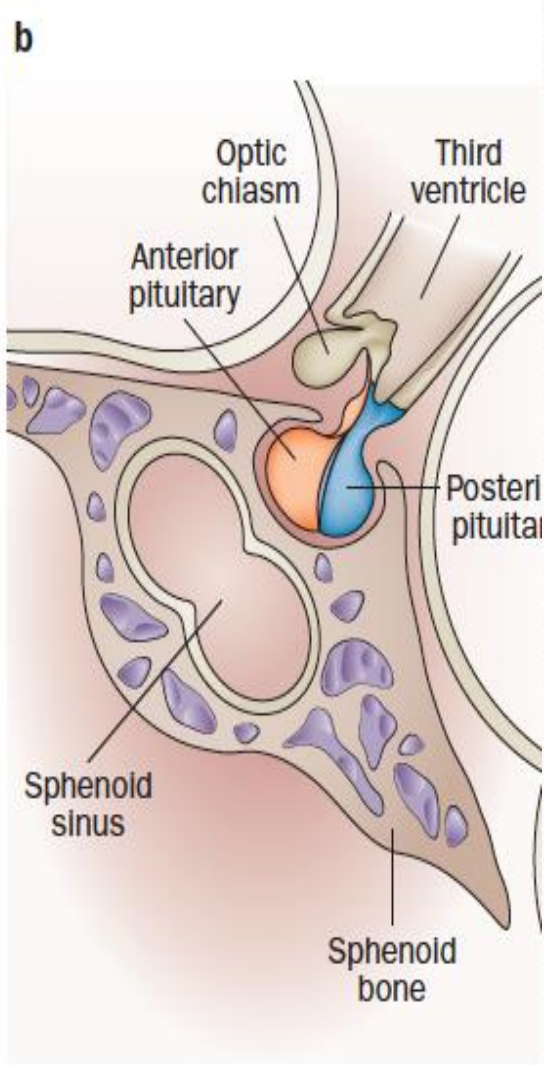
Neurohypophysis

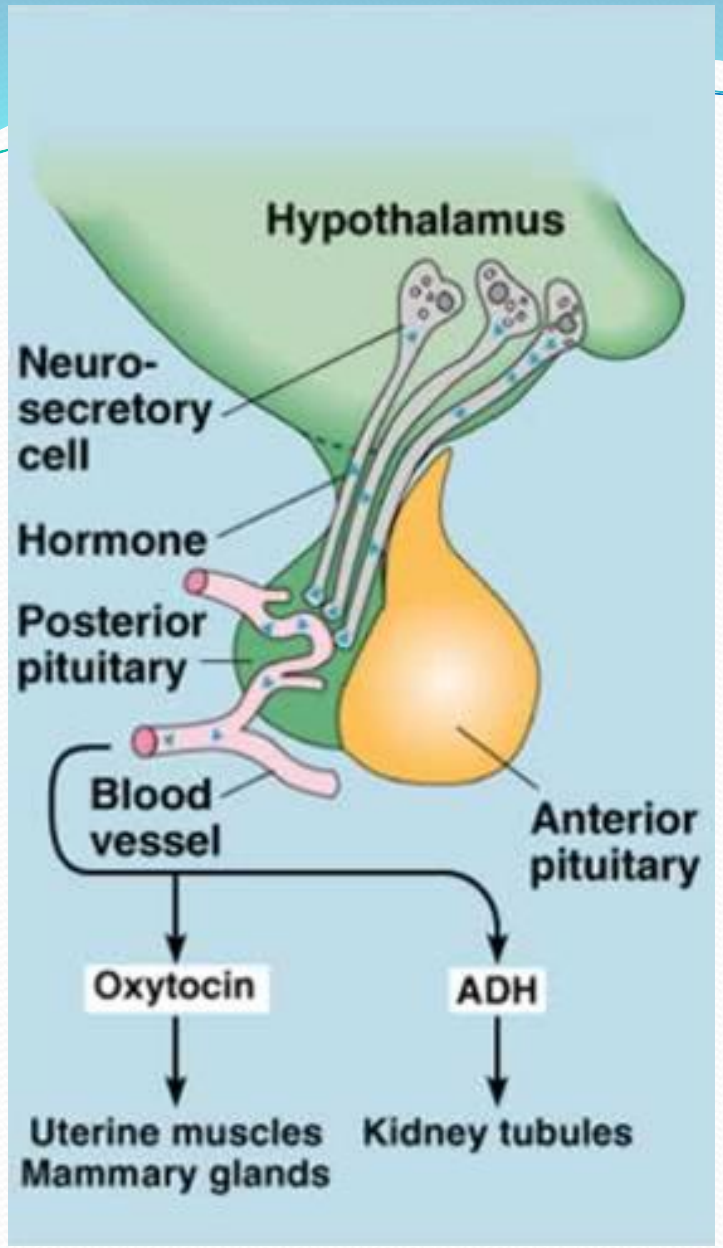


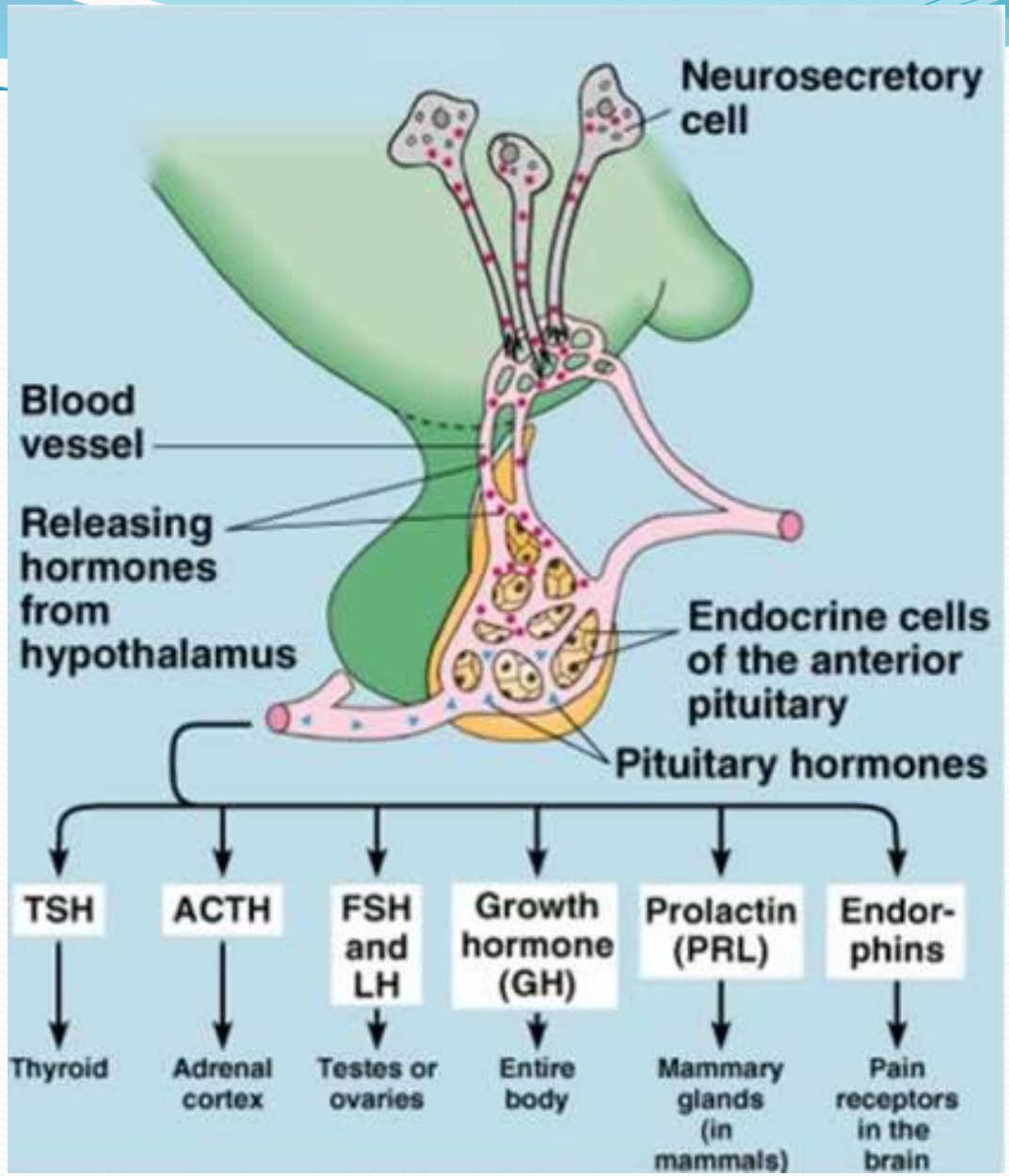


Pituitary Anatomy






Hypothalamus
Neuro-
secretory
cell
Hormone
Posterior
pituitary
Blood
vessel
Anterior
pituitary
Oxytocin
ADH
Uterine muscles
Mammary glands
Kidney tubules


Neurosecretory
cell
Blood
vessel
Releasing
hormones
from
hypothalamus
Endocrine cells
of the anterior
pituitary
Pituitary hormones
TSH
ACTH
FSH
and
LH
Growth
hormone
(GH)
Prolactin
(PRL)
Endor-
phins
Thyroid
Adrenal
cortex
Testes or
ovaries
Entire
body
Mammary
glands
(in
mammals)
Pain
receptors
in the
brain

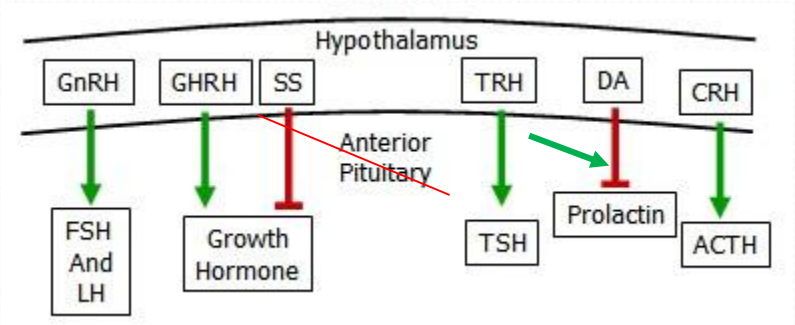
Hypothalamus Hormones

Releasing Hormones:

- TRH – thyrotropin releasing hormone
  - (stimulates TSH and prolactin)
- GnRH – gonadotropin releasing hormone
  - (stimulates FSH and LH)
- CRH – corticotropin releasing hormone
  - (stimulates ACTH, MSH, endorphins)
- GHRH – growth hormone releasing hormone
  - (stimulates growth hormone)

Inhibiting Hormones:

- DA (PIF) – dopamine/prolactin inhibiting factor
- Somatostatin – Inhibits growth hormone, TSH
  - (somatostatin also produced in the pancreas)



Testing

- Suppression tests

Used when HYPERfunction of the gland is suspected

  - Patient found to have excess cortisol
  - Dexamethasone suppression test
    - Administer dexamethasone (a synthetic glucocorticoid)

- Stimulation tests

Used when HYPOfunction of the gland is suspected

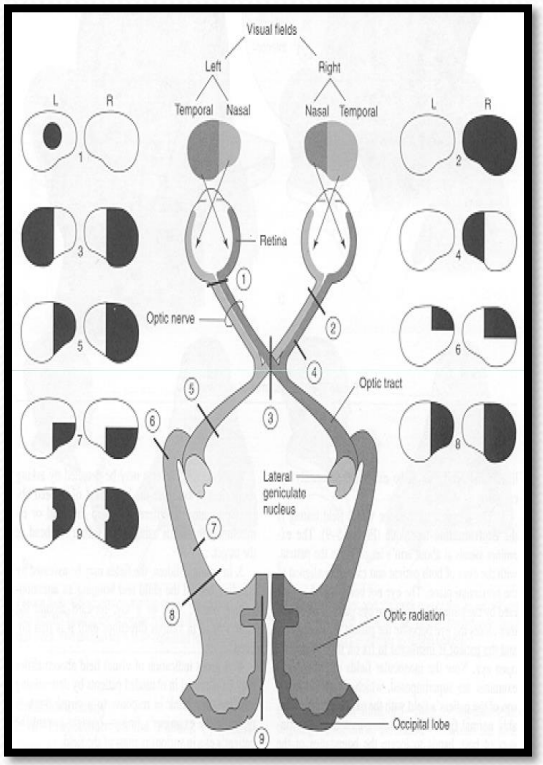
  - Patient found to have low cortisol
  - ACTH Stimulation test
    - Test adrenals response to synthetic ACTH

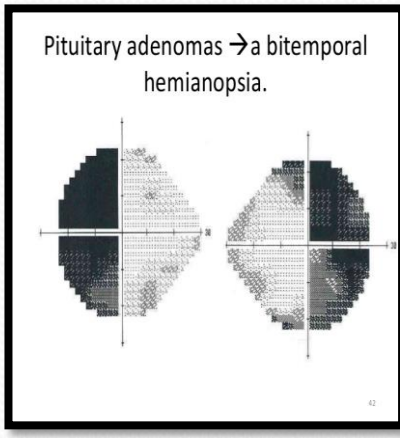
Pituitary macroadenomas: > 1 cm adenomas
Pituitary microadenomas: < 1 cm adenomas

Tests for pituitary lesions

- All patients should have a dedicated pituitary MRI *(Endo society strong recommendation, high-quality evidence)*
  - Includes fine cuts throughout the sella with and without administration of the contrast gadolinium

- All patients presenting with a pituitary lesions compressing the optic nerves or chiasm on MRI should undergo formal ophthalmic examination *(Endo society strong recommendation, high-quality evidence)*
  - Visual field
  - Extraocular movements
  - Ophthalmoscopy – primary optic atrophy





Disorders of the Hypothalamus

- Hypothalamus:
  - Tumors (e.g. craniopharyngioma)
  - Inflammation (lymphocytic hypophysitis)
  - Infiltration (sarcoidosis, histiocytosis, hemochromatosis)
  - Metastatic tumor (breast, lung)

Often associated with loss of posterior pituitary function i.e central diabetes insipidus

NEUROENDOCRINE PHARMACOLOGY

Hypothalamic/Posterior Pituitary Hormones

Vasopressin V- 2 agonist uses

"*Antidiuretic Hormone – ADH*"

- ***To decrease water excretion in central diabetes insipidus and nocturnal eneuresis***
- To increase circulating levels of factor VIII and improve platlet responsiveness (hemophilia A, vonWilibrand's disease, uremic coagulopathy)

Causes of Central Diabetes Insipidus

- Idiopathic: 30 – 50% (? autoimmune/inflamatory)
- CNS/pituitary surgery, ***trauma***, anoxic encephalopathy (NOT Pituitary Tumors)
- Primary tumors, craniophyrngioma, suprasella germinoma, pinealoma
- Metastatic tumors , leukemia and lymphoma
- Granulomatous Disease (e.g. TB)
- Hereditary: Autosomal dominant (onset at months to years)
- Pregnancy: unmasking of partial central diabetes or nephrogenic insipidus

  (markedly increased levels and activity of vasopressinase (oxytocinase)

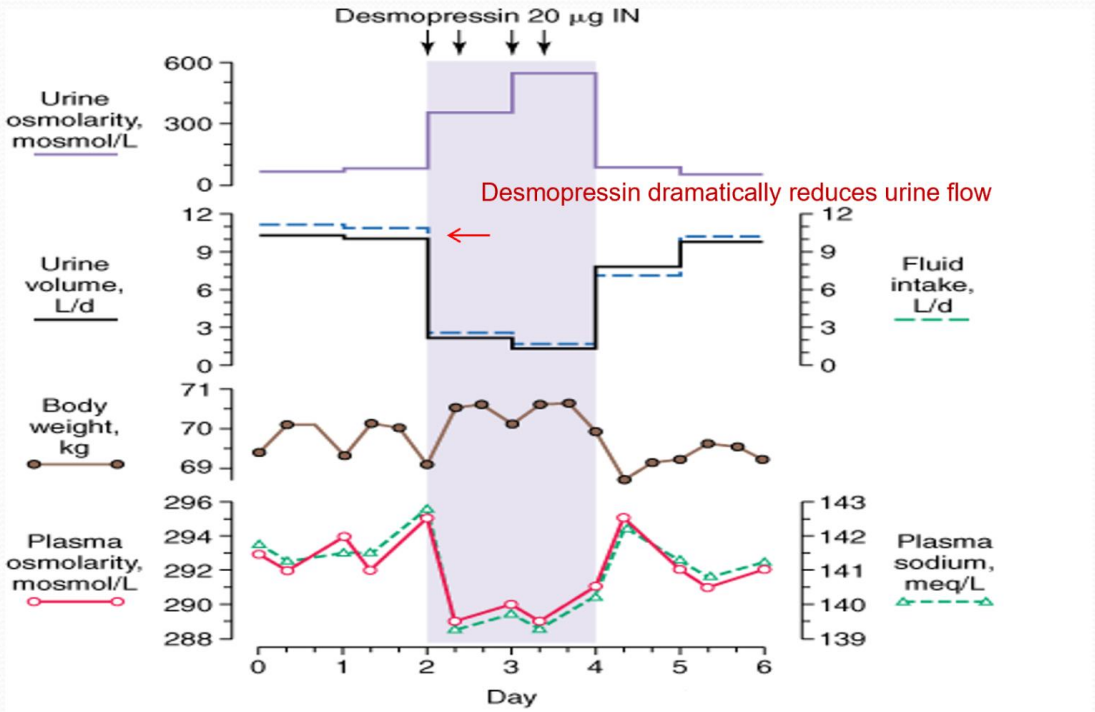
Symptoms:

Often ***acute*** presentation with ***unremitting*** sustained thirst and polyuria and preference for ***cold liquids*** especially water with continued thirst and polyuria ***day and night***

Central Diabetes Insipidus Dehydration Test

- Check g
- Screen v
- Easiest t … than 3-
- Diagnos
  - Expe
  - With Desr
  - ADH

Central Diabetes Insipidus



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Table 4-1.

Normal sub…		
Diabetes ins…		
Partial diabe…		
Nephrogenic diabetes insipidus	No	No

Treatment of Neurogenic (Central) DI

1)Desmopressin (DDAVP): potent anti-diuretic

- Oral pills, nasal spray, Injection (oral is less potent than nasal form)
- Can be given At night time to decrease nocturia
- Replacement of fluid losses is also important
  - Hypernatremia can occur if thirst is impaired or the patient has no access to water

2) Chlorpropamide

- Anti-diuretic drug
- Promoting renal response to ADH
- Higher doses may produce increase risk of hypoglycemia

3) Carbamazepine or Clofibrate

- Carbamazepine (anti-seizure medication)
  - Enhance the response to ADH
- Clofibrate (hyperlipidemia)
  - Increase ADH release
- Can lower the urine output by as much as 50%

Treatment of Nephrogenic DI

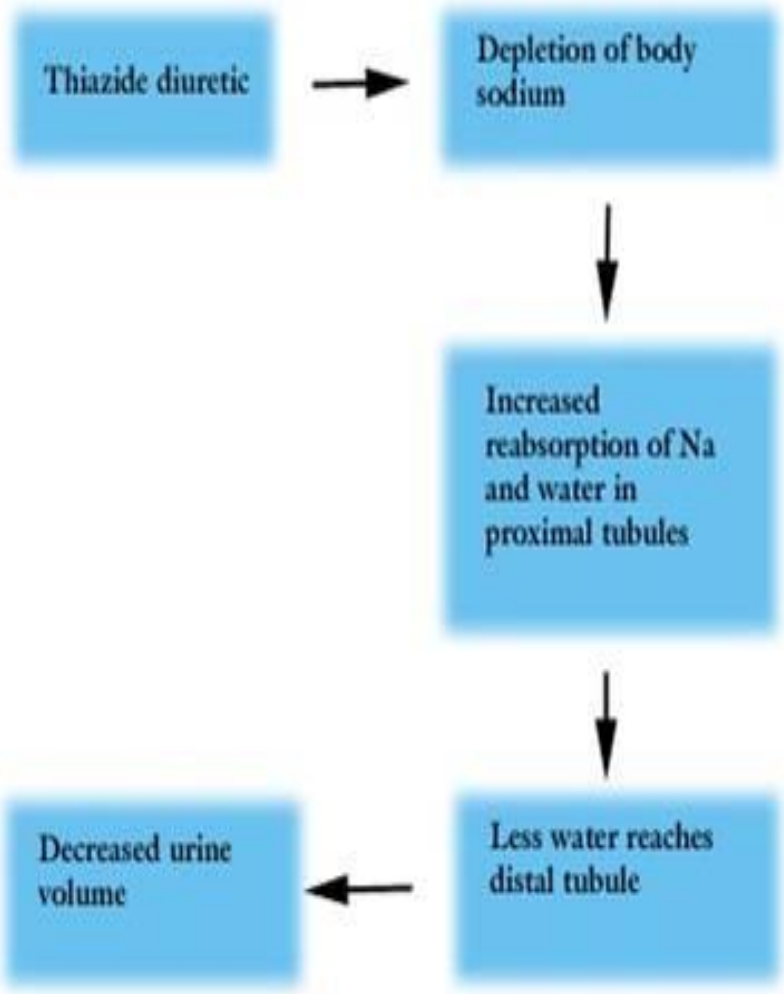
1)No response to DDAVP

2)In adults, nephrogenic DI most often due to chronic lithium use or hypercalcemia

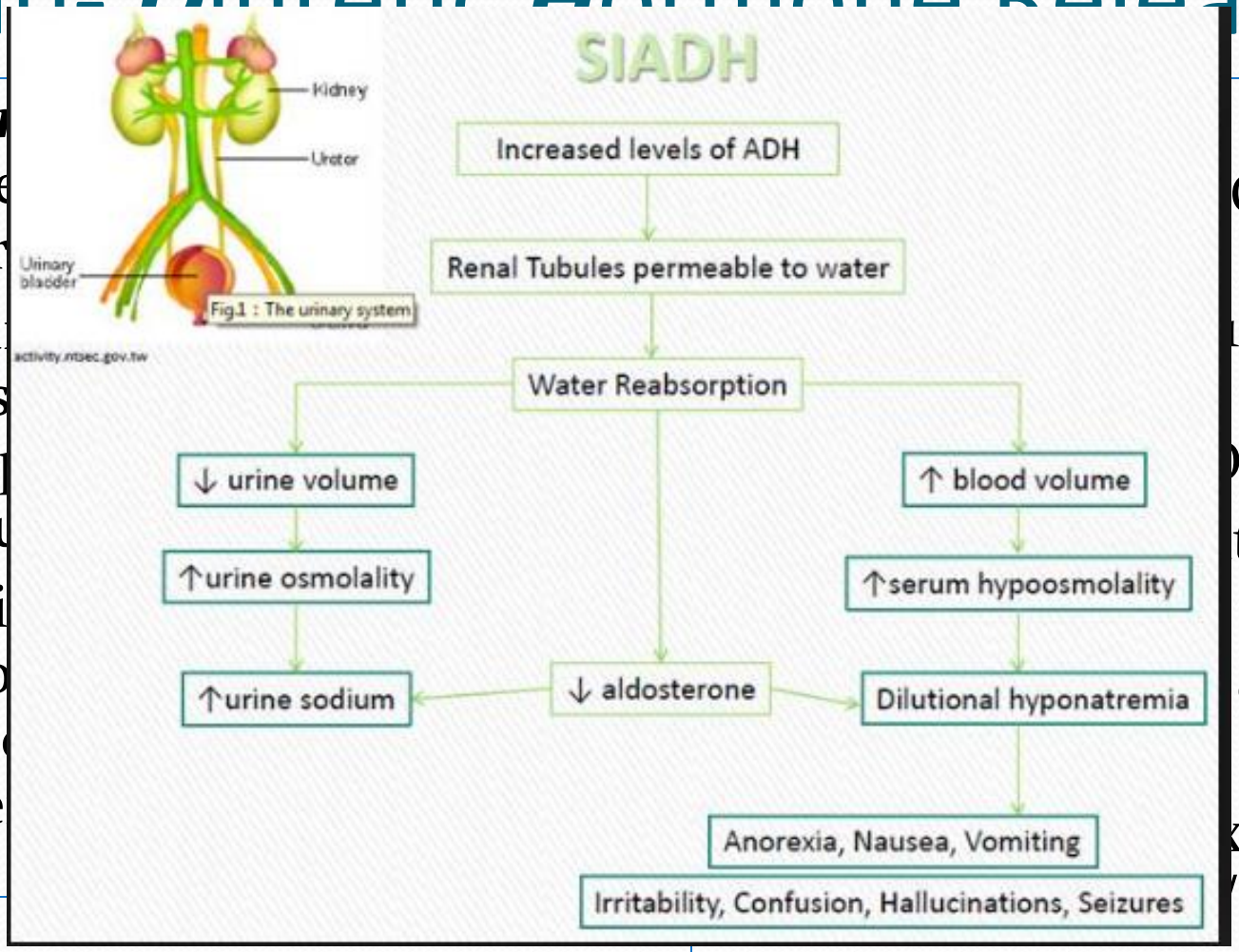
- Correct underlying disorder or discontinue offending drug
- Hypercalcemic patients – normalize plasma calcium concentration
- Lithium-induced nephrogenic DI - irreversible if patient already has renal damage

3)Thiazide diuretic in combination with a low salt diet

- Induces mild volume depletion
- Hypovolemia-induced increase in proximal tubule Na+ and water reabsorption
  - Reducing the urine output



Syndrome of Inappropriate Anti- Diuretic Hormone Release



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SIADH

Causes

- **Ectopic Production:**
  Malignancy: Small Cell Lung, GI, GU, Oropharnyx, etc
- **Baroreceptor Dysregulation:** (loss of inhibitory input)
  - CNS: Infection, Masses,Hemorrhage,MS.
  - Pulmonary: Pneumonia, Abscess,TB, etc (thoracic baroreceptor network)
  - Transient: Pain, Nausea , etc. (Post Surgery common)
- **Multifactorial** (central and peripheral):
  - Drugs: Antidepressants, Antipsychotics, Narcotics, Cancer chemotherapies etc.

Symptoms

- Decreased serum sodium and osmolality
- "Euvolemia" - no signs of edema or dehydration
- Inappropriate (increased) urine sodium loss despite low serum sodium
- Hyponatremia symptoms
  - Moderate/ severe :nausea without vomiting, confusion, headache,
  - Severe: vomiting, somnolence, seizures, glascow scale <8

Treatment

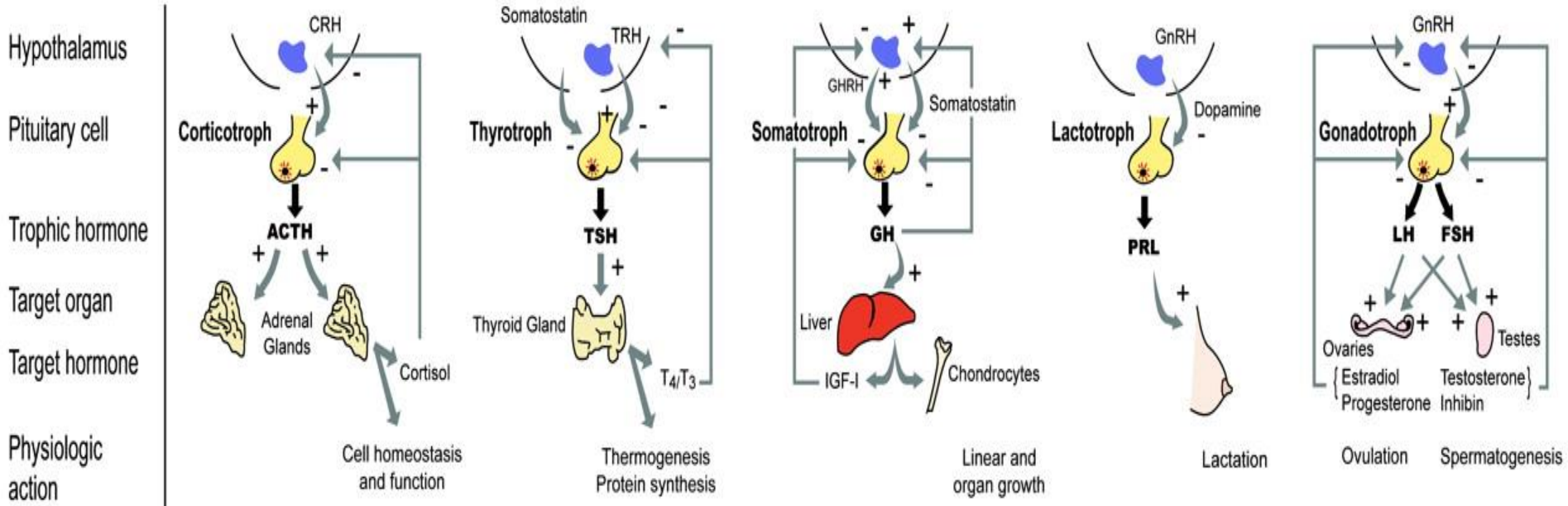
- Basic approach is to restrict fluid intake (problem is excess volume)
- Gentle administration of hypertonic fluids used to reverse symptoms (e.g. seizures)
- Drugs which impair renal responses to ADH i.e. demeclocline and lithium*
- Vasopressin antagonists*

SIADH and CSW[11]		
Characteristic	**SIADH**	**CSW**
Extracellular Fluid Volume	Normal, Increased	Decreased
Urine Osmolality	High	High
Plasma Osmolality	Low	Low
Serum Sodium	Low	Low
Urine Sodium	High	Very high
Urine Output	Normal or Low	High
Treatment	Fluid Restriction	Fluids &/or mineralocorticoids

Disorders of the Pituitary

- Functional pituitary tumors:
  - Excess growth hormone (Acromegaly)
  - Pituitary dependant Cushing's Disease (ACTH)
  - Prolactinomas with prolactin associated hypogonadism
  - Central hyperthyroidism due to TSH secretion
  - Rare increased LH or FSH with ↑ T or E_2
- Anatomic Damage
  - Visual field loss, cranial nerve injury etc
  - Hypopituitarism
  - CSF leak etc
  - Diabetes insipidus: uncommon

Hypothalamic-pituitary regulation and pituitary tumor pathogenesis



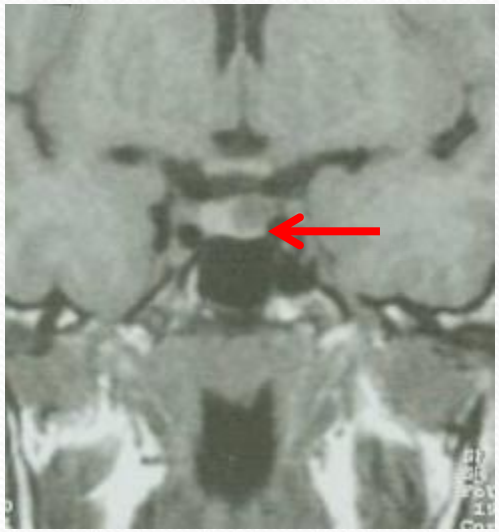
	Cushing's Disease	TSH-cell Adenoma	Acromegaly	Prolactinoma	Non-functioning Adenoma
Tumor phenotype	Hypercortisolism	Thyroid goiter	Acral enlargement	Galactorrhea	Central effects
	Central obesity	Hyperthyroxinemia	Soft tissue swelling	Amenorrhea	Hypogonadism
	Striae		Cardiac hypertrophy	Infertility	Hypergonadism (rare)
	Hyperglycemia		Hypertension	Hypogonadism	Clinically silent
	Osteoporosis		Hyperglycemia		
	Hirsutism		Sleep apnea		

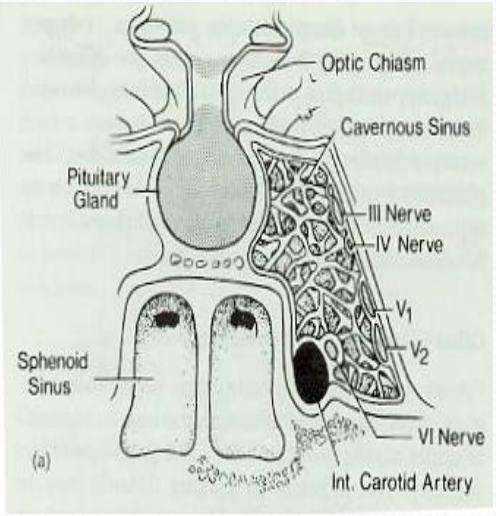
Melmed, S. J. Clin. Invest. 2003;112:1603-1618

TYPE	Prevalence %	Hormone Staining	Clinical Manifestations
Prolactinoma	40-45	Prolactin	Signs of Increased Prolactin
Somatotroph Adenoma	20	GH +/- prolactin	Acromegaly
Corticotroph Adenoma	10-12	ACTH +/- others	Cushing's Disease
Gonadotroph Adenoma	15	FSH, LH αSU, βSU	Compression Sx Hypopituitarism
Null Cell	5-10	None	Compression Sx Hypopituitarism
Thyrotroph Adenoma	1-2	TSH,αSU, =/- GH	Hyperthyroidism Compression Sx

Pituitary Incidentaloma

Not a bad idea to warn all patients before MRI of CNS





Prevalence: Autopsy: 11% (90 % stain for prolactin)
Hormonal Activity: none
Prognosis: Generally < 0.5% chance of subsequent significant clinical events

" Up-to-Date" Recommendations: measure prolactin, if wnl

< 5mm no additional study required

6- 9mm repeat MRI over subsequent 2 years

Macroadenomas – consider diluted PRL to avoid possible "hook effect"

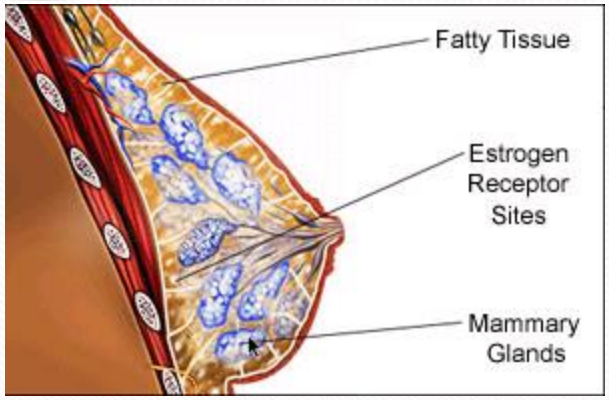
Endo Society Recommendations
Measure prolactin, IGF-1, free T4,
AM cortisol, consider LH/FSH
<1cm - MRI in 1 year
> 1cm - 6 mos then yearly x 3

Symptoms:

- Intrasellar: Headache, Pituitary hypofunction
- Tumor associated loss: GH>LH/FSH>TSH>ACTH
- Suprasellar: Impingement on Optic Chiasm
- Other Mass Effects: obstruction of 3rd ventricle, hydrocephalus, altered sensorium

➢ Lateral Extension: Impingement on Cr N iii, iv, vi
➢ Inferior Erosion: Spinal Fluid Leak, Meningitis

Prolactin



- Physiologic function of PRL includes:
  - Milk production
  - Metabolism of fats and carbohydrates
  - Vitamin D metabolism
  - Fetal development
- Main function of PRL is:
  - Mammary gland development (puberty)
  - Initiation of lactation postpartum (pregnancy)
- Secreted by lactotrophs of the anterior pituitary(in a pulsatile manner)

<u>Regulation:</u>

- ❑ *Inhibited by hypothalamic Prolactin Inhibitory Factor (dopamine)*
- ❑ *Stimulated by high Thyrotropin Releasing Hormone (TRH)*
- ❑ *Increased by chest wall motion and nipple stimulation*
  - *Smaller increases after sleep, exercise, intercourse, stress, pregnancy and lactation*
- ❑ *Suppresses GnRH → suppress LH and FSH*
- ❑ *Stimulates adrenal androgen production*

Etiologies of Hyperprolactinemia

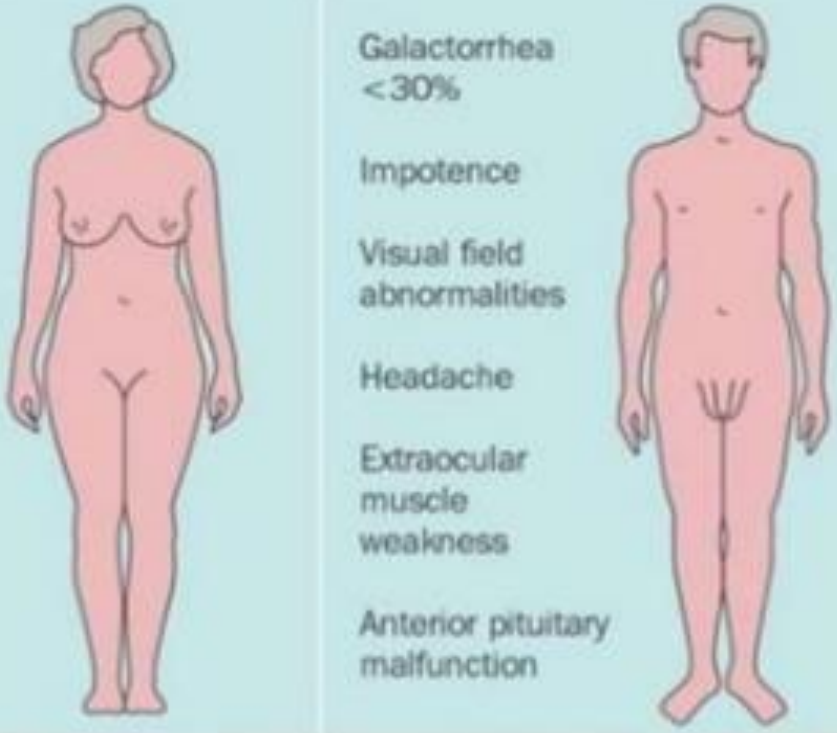
- Prolactinoma (autonomous production)
- Other pituitary tumors (GH, ACTH)
- Hypothalamic disease
- Chronic Kidney Failure (decreased clearance by kidneys) or Liver Disease
- Chest wall
- Severe Prin
- Medication
  - Anti-ps and Reglan
  - Dopam
  - Others (INH, danazol, tricyclic antidepressants, verapamil, estrogens, antiandrogens, cyproheptadine, opiates, H2-blockers)
- Radiation, Surgery
- Idiopathic , Pregnancy

Testing:

- Serum assays: Fasting PRL, FSH, LH, estradiol, testosterone, TSH, renal/hepatic panels, and ß-hCG in females
- MRI of pituitary and brain
- Visual field examination/Neurological testing-if mass effect suspected

Clinical manifestations of hyperprolactinemia

Women	Men
Galactorrhea 30–80%	Galactorrhea <30%
Menstrual irregularity	Impotence
Infertility	Visual field abnormalities
	Headache
	Extraocular muscle weakness
	Anterior pituitary malfunction



Microadenoma seen more in women

Macroadenomas seen more in men

- Hypogonadism in both women and men by supressing GnRH secretion and pulsutility, resulting in low levels of LH and FSH

NEUROENDOCRINE PHARMACOLOGY

- Prolactin is under tonic *inhibitory* control and predominant inhibitor is Dopamine

Treatment:

- First line of treatment is Dopamine agonists (may have dramatic effects on prolactin secreting tumors)
- Cabergoline (weekly) or bromocriptine (twice daily)
- Microadenomas respond dramatically; often with resumption of menses and restoration of fertility
- +/- surgical resection

NEUROENDOCRINE PHARMACOLOGY

Dopamine Agonists

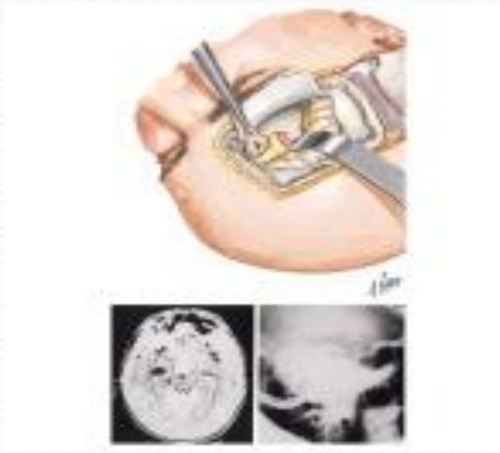
1)Bromocriptine: excellent drug with strong record of clinical success; drug of choice in infertility; troublesome side effects can occur

2)Cabergoline: most tolerable preparation with less side effects biweekly dosing;

High doses of cabergoline and pergolide(in Parkinsonism) are associated with valvular heart disease due to activation of valvular serotinin receptors

Surgical treatment

- Transsphenoidal resection
- Surgical resection
- Radiation therapy



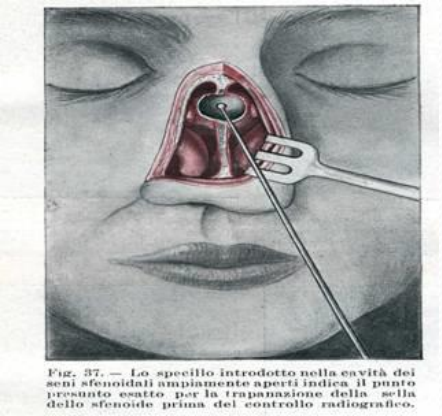
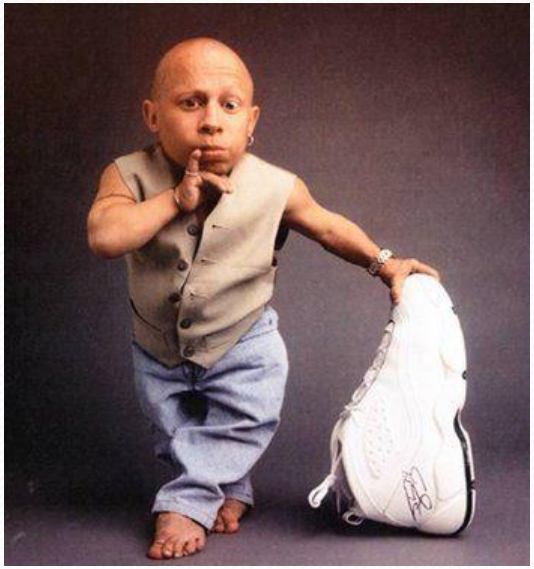


Fig. 37. — Lo specillo introdotto nella cavità dei seni sfenoidali ampiamente aperti indica il punto presunto esatto per la trapanazione della sella dello sfenoide prima del controllo radiografico.

Growth Hormone disorders



Physiology of GH

Growth hormone (GH) - most abundant pituitary hormone - somatotrope cells

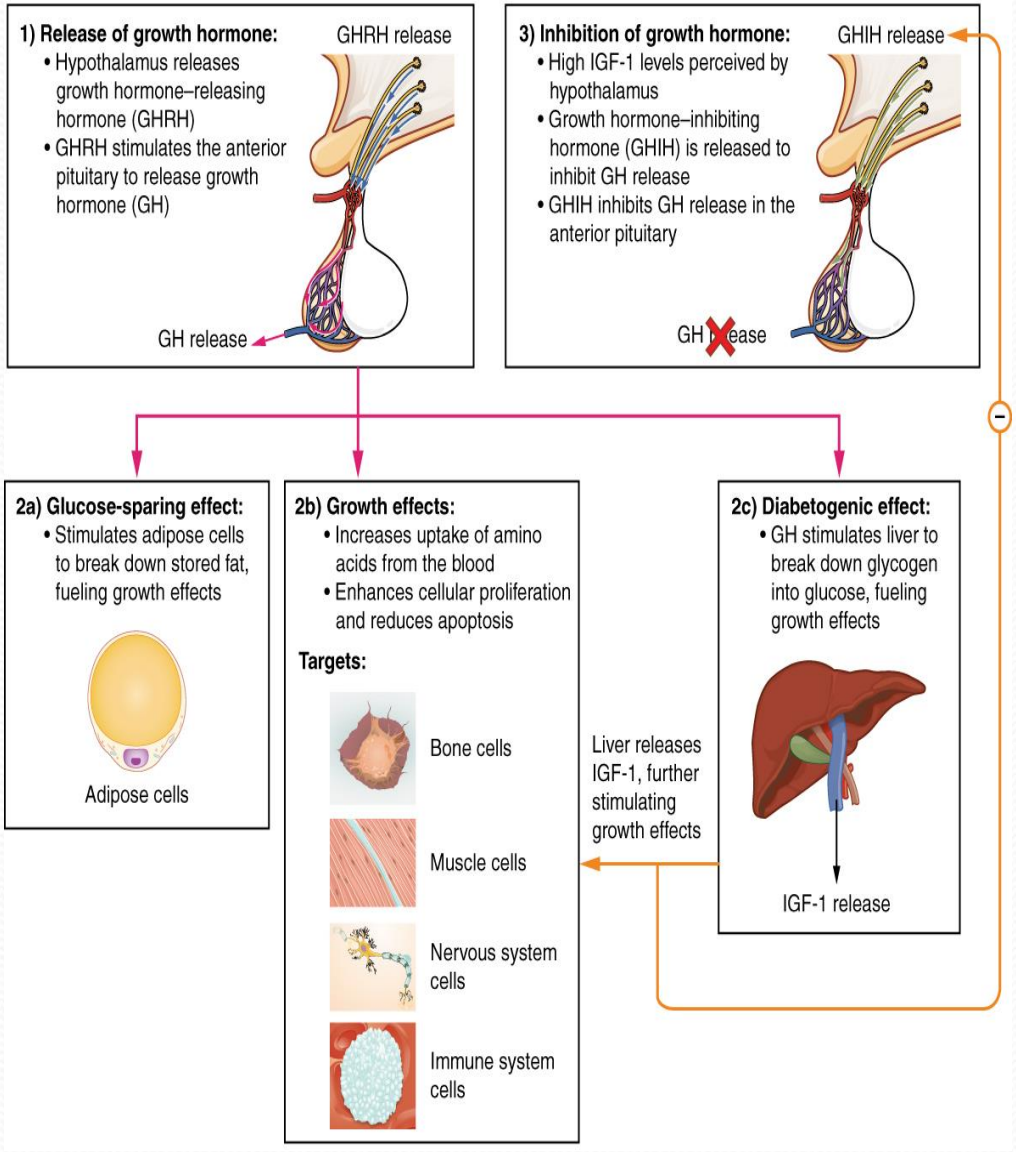
GH secretion - controlled by hypothalamic and peripheral factors

- GHRH – stimulates GH secretion
- GHIH (somatostatin) - inhibits GH secretion

GH secretion is pulsatile, undetectable between the pulses

Peak GH - within an hour after the onset of deep sleep

Insulin like Growth Factor-1 is produced in liver after stimulation by GH



Etiology of Growth Hormone Deficiency

- Incidence of GH deficiency ~1 per 4000-10,000
  - Hypothalamic causes:
    - Idiopathic ↓ GHRH secretion
    - Hypothalamic tumors
  - Pituitary causes:
    - Pituitary tumors
    - Trauma
    - Surgical removal
    - Irradiation
    - Idiopathic
    - Secretion of abnormal GH molecules

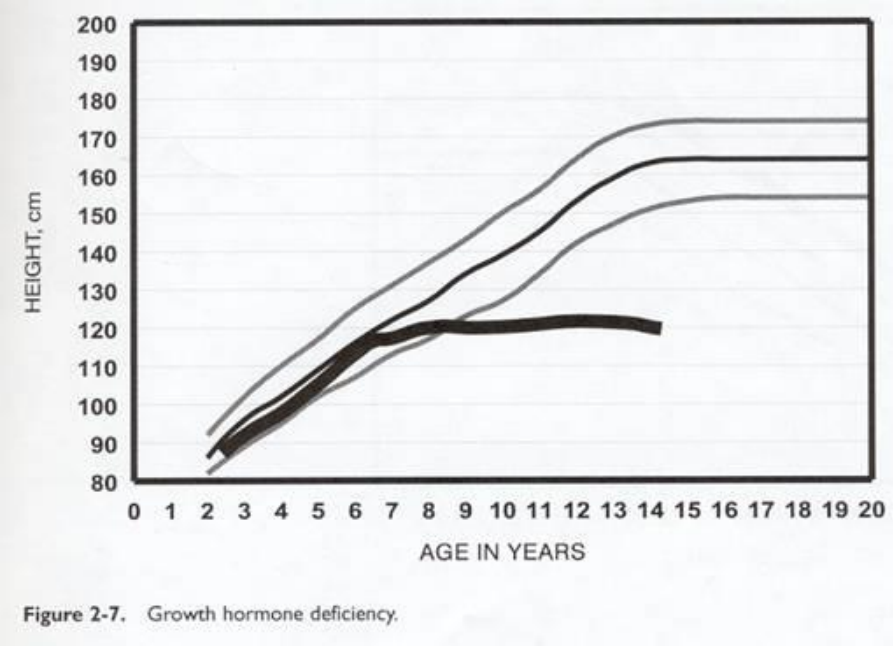


Figure 2-7. Growth hormone deficiency.

Diagnostic Approach to Short Stature

- Three basic steps:
  1. History and Clinical Presentation
     - Pattern of growth, medical history, genetic factors, and physical findings(dysmorphic features), and other causes like hypothyroidism,DM and
  2. I
  3. (

Treatment of Growth Hormone Deficiency in Children

- Most common preparations subcutaneous administration Somatropin
- Several brands available

- *In*

Humatrope Pen

  - 60, 90 and 120
    - Most available in multiple-dose pen devices
- *Arginine stimulation test*
  - Measure serum GH at 0, 30, 60, 90 and 120 minutes

Pituitary Gigantism

- Excessive linear growth due to excess growth hormone secretion in infants, children and adolescents who have open epiphiseal growth plates; often accompanied by obesity, acral enlargement, etc.
- Causes:
  - Growth hormone secreting tumors
  - GhRH secreting tumors ?
- *Rule out genetic tall stature, precocious puberty, or hyperthyroidism*
- *Dysmorphic & disproportionate features and/or neurocognitive problems suggest a chromosomal cause (Klinefelter's syndrome)*
- Initial evaluation requires determination of bone age, thyroid function tests, sex steroid hormone concentrations, karyotype, and GH-related studies

Di

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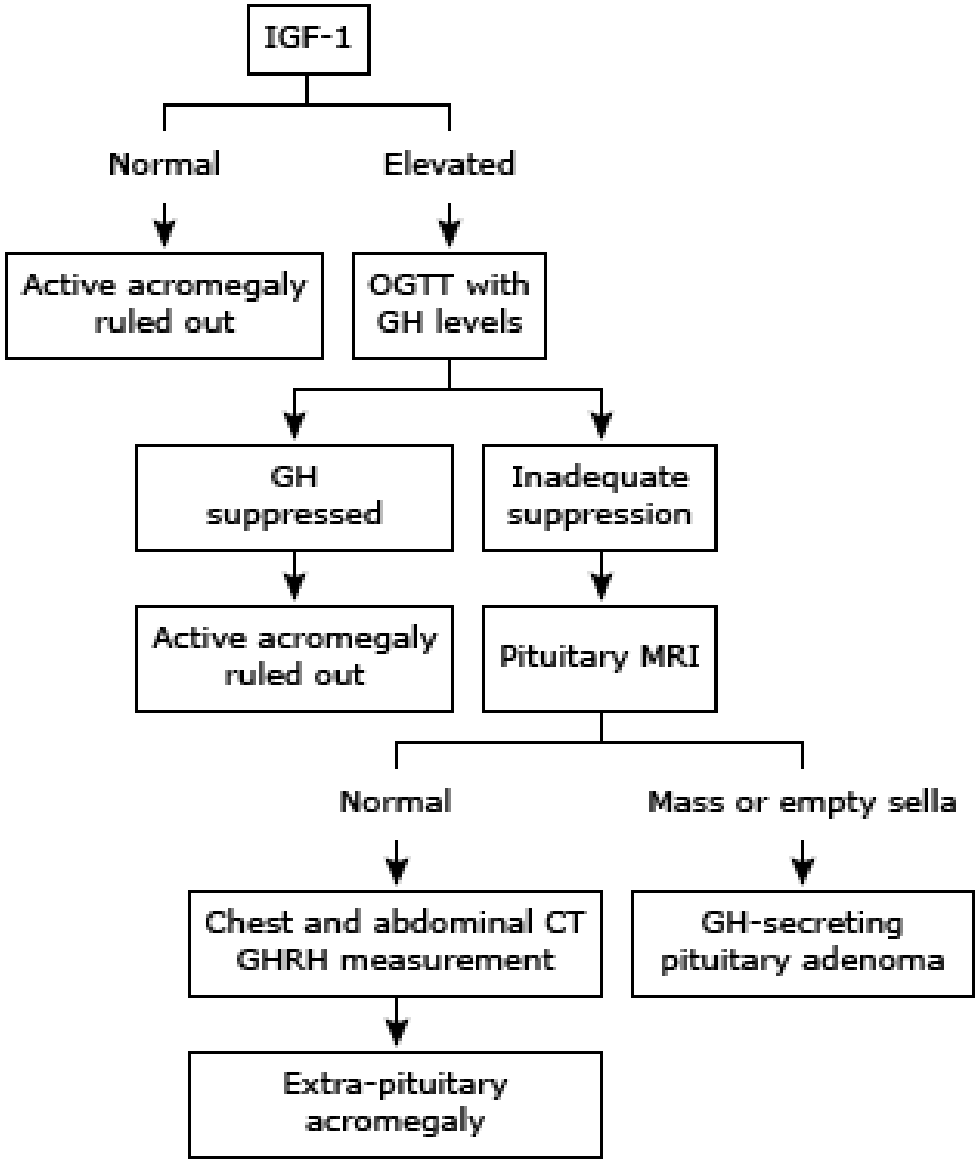
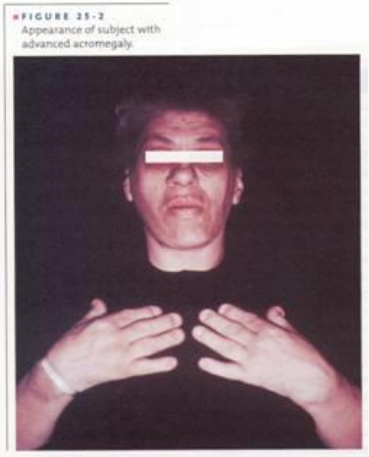
Algorithm for the diagnosis of acromegaly



Acromegaly

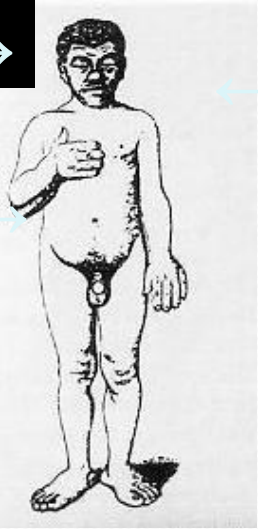
- Clinical syndrome of hypertrophic and degenerative injury to soft tissues, joints, the heart and cardiovascular system accompanied by disturbances in respiration and intermediary metabolism.
- Macroadenoma in > 70 %
- Onset of Sx 10 – 12 years before diagnosis
- Excessive growth hormone (GH) after puberty



- Incidence – 3-4 per million/yr and Mean age - 40-45 years
  - *Diagnosis delayed due to slow progression of signs and symptoms*
- Most common cause - GH secreting adenoma of the pituitary

ACROMEGALY

Frontal Bossing →

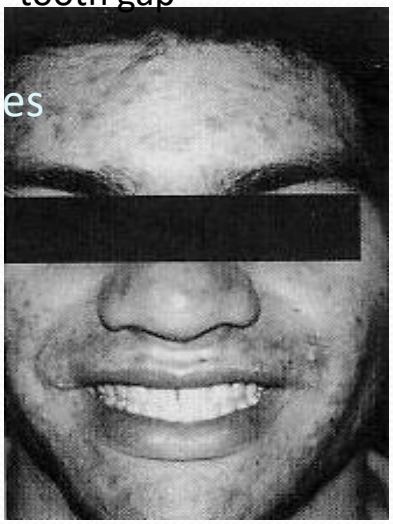


←Facies

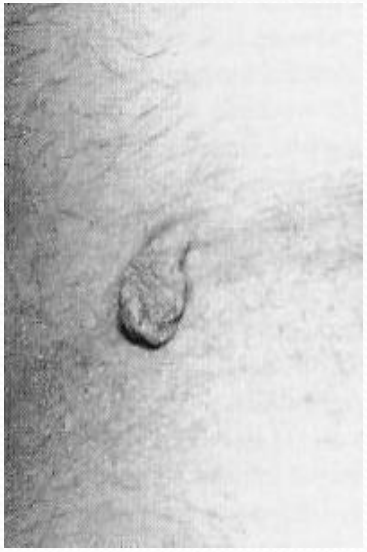
Fleshy → fingers

Fleshy toes→

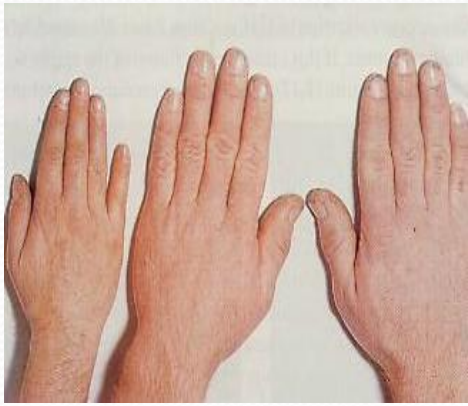
Active perspiration, oily skin, acne, wide tooth gap



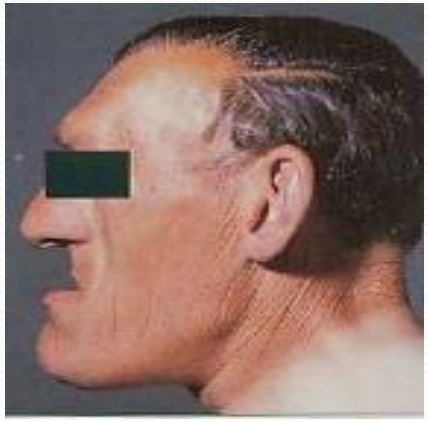
Prominent skin tags may be associated with colonic polyps



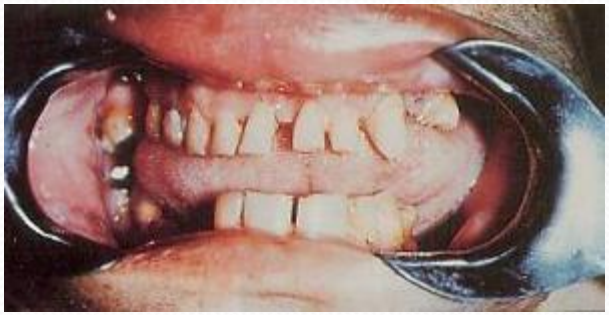
Acromegalic hands



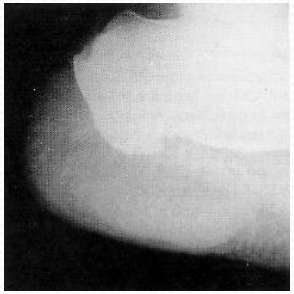
Prognathism, Frontal bossing



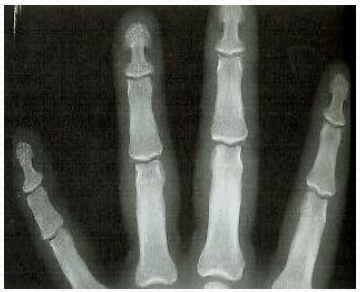
Mandibular growth results in increased tooth separation



Increased heal pad thickness (> 22mm)



Distal tufting of the terminal phalanges



Summary of Clinical Manifestations of Acromegaly

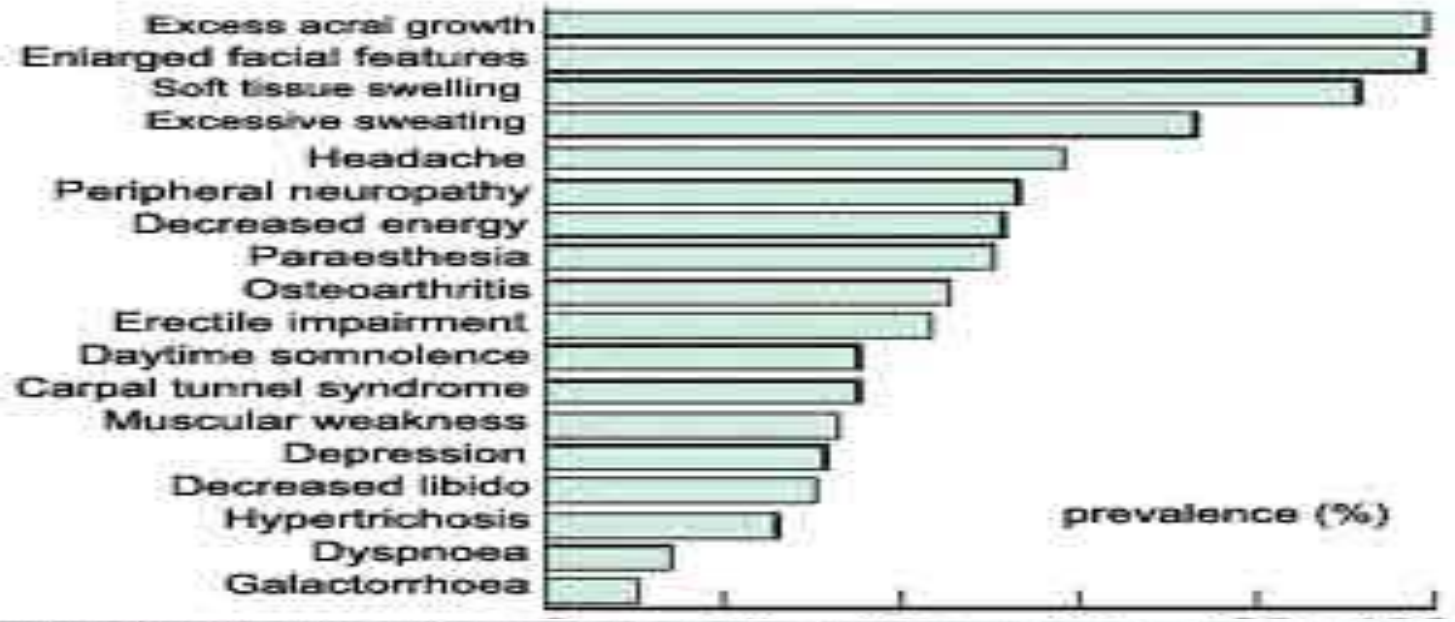


Table 3-1. Manifestations of Acromegaly

Skeletal and soft tissue changes
Enlargement of hands (especially fingertips) and feet
Increased ring, glove, shoe size
Coarsening of facial features
Thick skinfolds: brow, nasolabial creases
Enlargement of nose and mandible, with prognathism, spreading of teeth
Enlargement of internal organs: heart, lungs, liver, spleen, kidneys
Skin thickening and interstitial edema, with swelling and firmness of soft tissue
Osteoarthritis
Entrapment neuropathies, especially carpal tunnel syndrome
X-ray changes: enlargement of sinuses, tufting of distal phalanges, cortical thickening
Metabolic changes
Decreased glucose tolerance (anti-insulin actions of growth hormone)
Hyperphosphatemia (increased tubular reabsorption of phosphate caused by growth hormone)

Acromegaly treatment

1)Surgical treatment :Trans-sphenoidal surgery is the treatment of choice

2) Adjuvant Radiation therapy→ can lead to panhypopituitarism

3) Medical:

- Somatostatin and Somatostatin Analogues
  - **Octreotide**: short acting somatostatin analogue
  - **Octreotide LAR**: long acting release preparation given monthly
  - **Lanreotide gel**: now available in US similar activity to octreotide
  - **pasireotide:** potent analog, especially useful in Cushing's Disease; effective against wider range of SST's and associated with hyperglycemia
- Bromocriptine, a dopamine analog, was the agent used most commonly until recently
- Growth Hormone receptor antagonists: Pegvisomant
- Combination therapy - bromocriptine and octreotide

Long Term Management

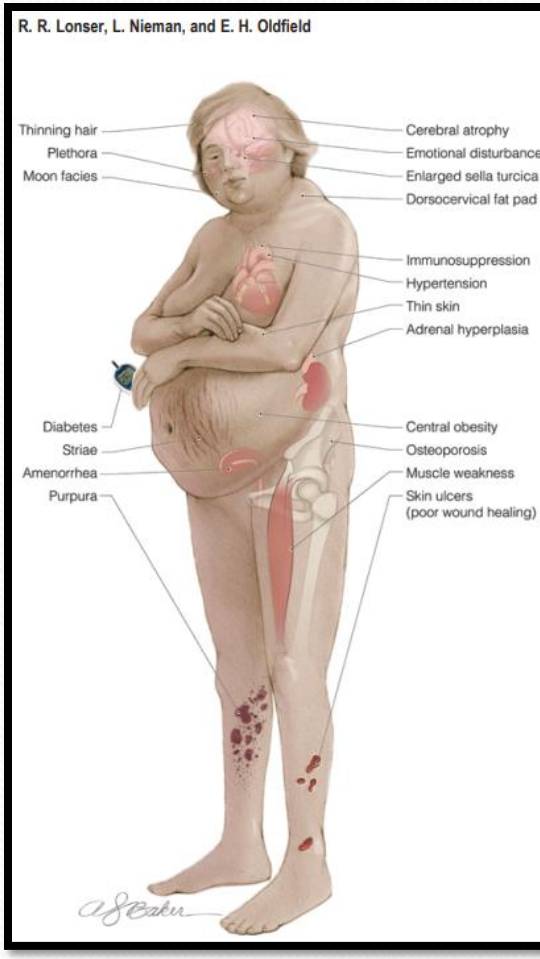
- Clinical evaluation and assessment of GH secretion : Evaluate every 3-4 months
  - Clinical exams
  - Serum IGF-1
  - OGTT
- Adenoma size
  - MRI - repeat yearly for the first several years after surgery
  - Semiannual visual field assessment
    - Visual problems before surgery, Macroadenomas and Residual extra-sellar adenoma after surgery
- Systemic evaluation
  - Colonoscopy at 3 to 4 year intervals in patients over 50 years
  - Annual cardiovascular evaluation (echocardiography)
  - Thyroid Ultrasound to rule out nodules and cancer
  - Sleep studies to rule out OSA
  - Other systemic manifestation as Fasting blood glucose, A1C , lipid profile, assessment of anterior pituitary hormones panel (TSH , am cortisol)

Corticotroph adenoma/Cushing disease

- Signs and symptoms of cushing
- Elevated ACTH → confirm hypercortisolism
  - 1 mg dexamethasone suppression test
  - Salivary cortisol
  - 24 hr urine free cortisol

- Dex-CRH stimulation test
  - Cushing's disease: ACTH is elevated

- Inferior petrosal sinus sampling
  - Compare ratio of inferior petrosal vs peripheral ACTH level



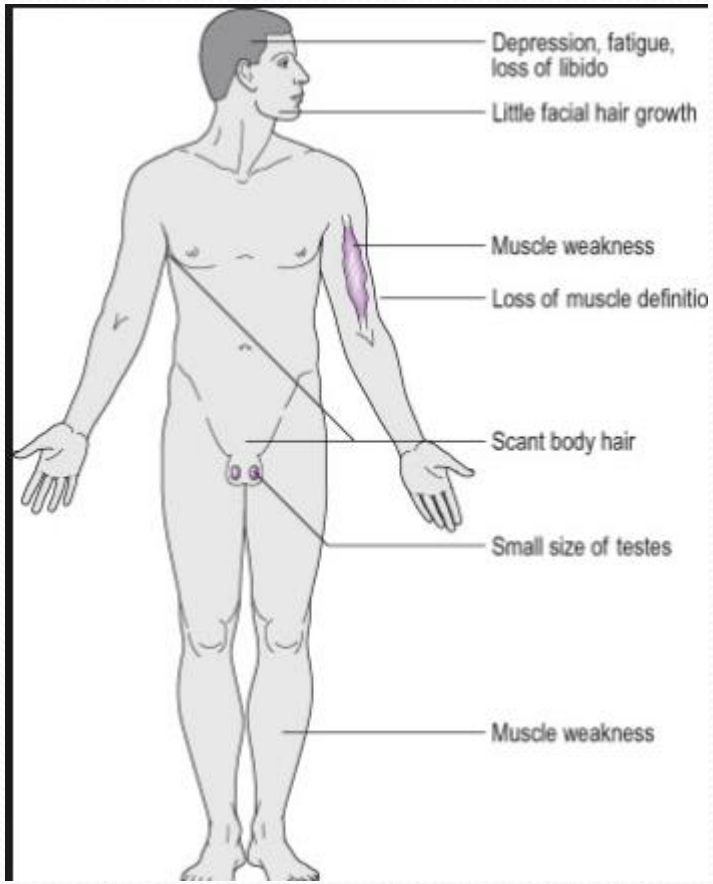
Causes of hypopituitarism

Hypothalamic diseases
Mass lesions – Benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc)
Radiation – For CNS and nasopharyngeal malignancies
Infiltrative lesions – Sarcoidosis, Langerhans cell histiocytosis
Infections – Tuberculous meningitis
Other – Traumatic brain injury, stroke
Pituitary diseases
Mass lesions – Pituitary adenomas, other benign tumors, cysts
Pituitary surgery
Pituitary radiation
Infiltrative lesions – Hypophysitis, hemochromatosis
Infection/abscess
Infarction – Sheehan syndrome
Apoplexy
Genetic mutations
Empty sella

Evaluation of Hypopituitarism

A)Hypogonadism

- Men: low libido, impaired fertility, decreased muscle mass and strength
- Women: **abnormal menstrual history**, infertility, low libido, further loss of body hair if in conjunction with adrenal insufficiency
- Labs: decreased LH & FSH, low testosterone(in males), low Estrogen (in Females)

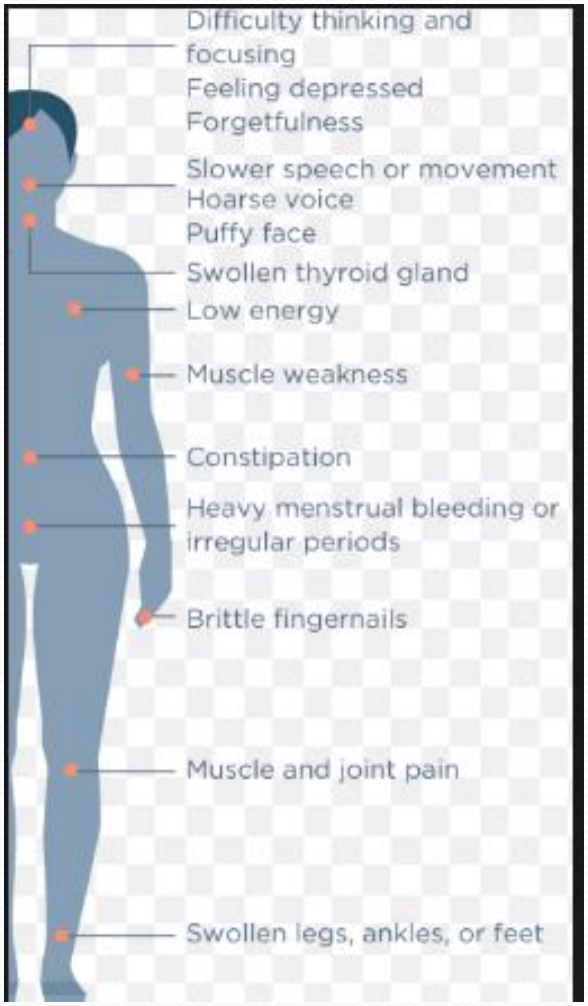


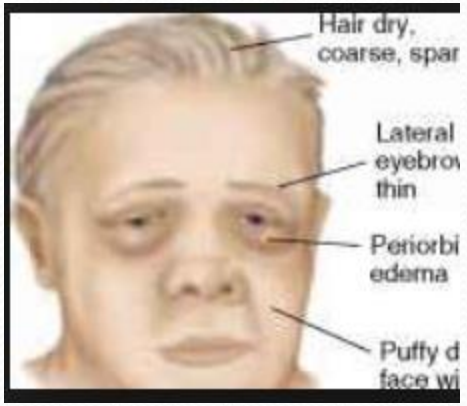
Evaluation of Hypopituitarism

B)Hypothyroidism

- Signs & symptoms: fatigue, cold intolerance, constipation, slow relaxing reflexes
- Hyponatremia (exacerbated by cortisol deficiency), normocytic anemia (exacerbated by secondary hypogonadism and GH deficiency)
- Low FT4, low or inappropriately normal TSH

Remember that we follow up Free T4 when we gave thyroid replacement therapy (unlike primary hypothyroidism when you follow up by normalization of TSH level)





Evaluation of Hypopituitarism

C)Adrenal insuffiency

- Symptoms: fatigue, weakness, dizziness, nausea, vomiting, hypotension, hypoglycemia
- Hyponatremia (particularly if also TSH deficiency)
- Treatment by replacement with prednisone (no need of fludrocortisone)
- *Remember that central adrenal insufficiency has normal aldosterone production so no hyperkalemia and since ACTH level is suppressed , no hyperpigmentation in contrary to primary adrenal insufficiency/Addison disease)*
- Educate your patient about sick days rule (double or triple the dose for 3 days)
- Remember to prescribe emergency kit/Dexamethazone injection

Evaluation of Hypopituitarism

C)Adrenal insufficiency

- Laboratory testing
  - Screen AM cortisol
    - Cortisol < 5 mcg/dL: highly suggestive of adrenal insufficiency
    - Cortisol > 15: unlikely adrenal insufficient
    - Cortisol 5-15: equivocal → ACTH stimulation test
  - ACTH stimulation test (alternative - insulin tolerance test)--. Can be falsely negative at initial time of diagnosis
    - Baseline, 30 minutes, 60 minutes
    - Test is abnormal if stimulated cortisol < 18
  - Baseline ACTH low or inappropriately normal in setting of low cortisol

Thanks for your attention