Pituitary Disorders

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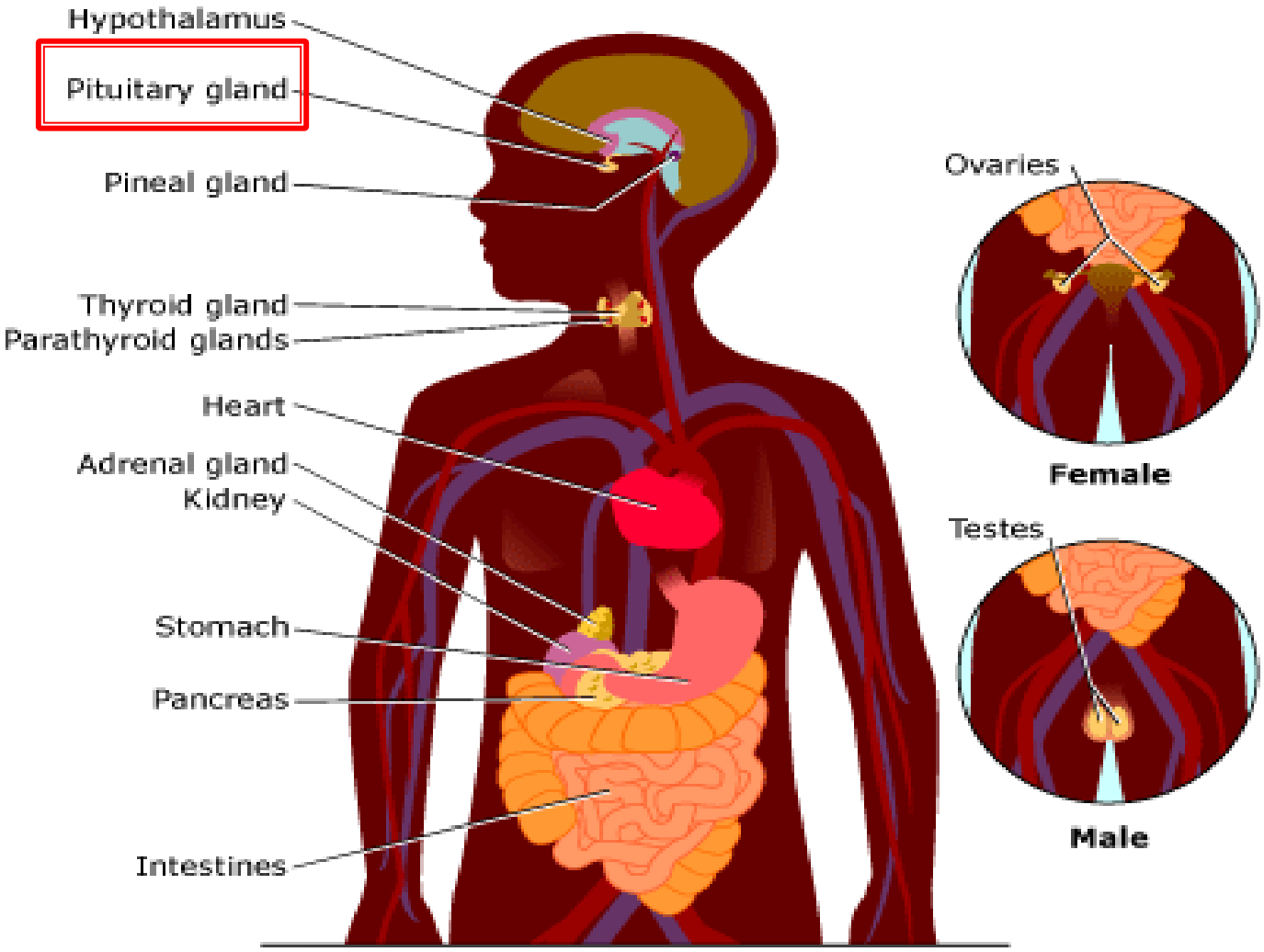
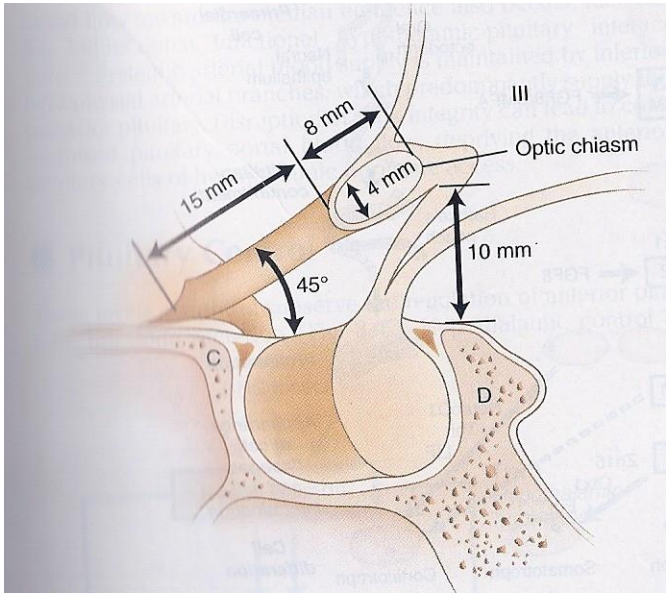
Objectives

- To understand basic pathophysiology and feedback for anterior pituitary hormones.
- Know about clinical approach for common anterior pituitary gland disorders:
  - Common clinical presentations.
  - Main laboratory investigations.
  - Radiological investigations
  - Describe lines of management for each of these conditions.

Endocrine system



Pituitary Gland



Pituitary Development

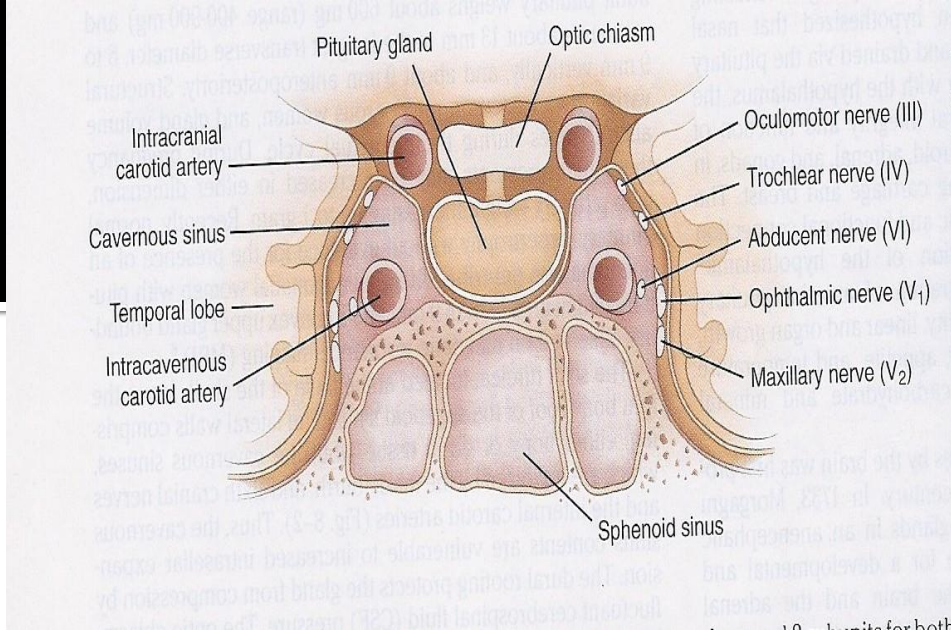
ANTERIOR PITUITARY

- Rathke's pouch, Ectodermal evagination of oropharynx
- Synthesis and secrete
  - (GH,LH,FSH,PRL,TSH,ACTH)
- recognizable by 4- 5th wk of gestation and full maturation by 20th wk
- Portion of Rathke's pouch →→ Intermediate lobe
- Remnant of Rathke's pouch cell in oral cavity →→ pharyngeal pituitary

POSTERIOR PITUITARY (NEUROHYPOPHYSIS)

- neural cells as an outpouching from the floor of 3rd ventricle
- Only storage:
  - Oxyctocin,ADH (hypothalamic hormones)

Sella turcica

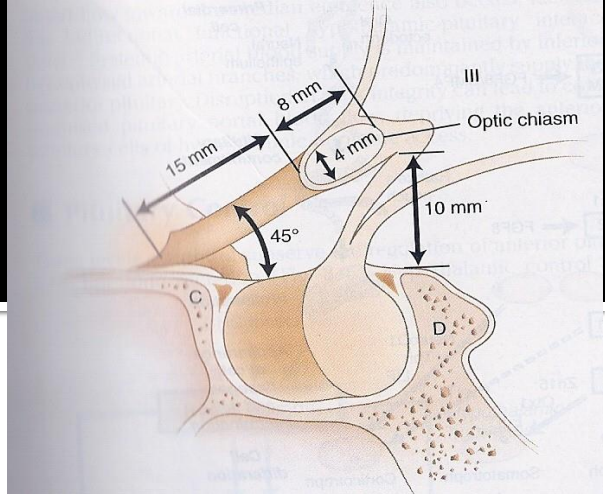


- Lies at the base of the skull
- **Roof :** diaphragma sellae
  - Pituitary stalk and its blood vessels pass through the diaphragm
- **Floor:** Sphenoid sinus
- **Lateral walls:** cavernous sinus
  - containing III, IV, VI, V1, V2 cranial nerves and internal carotid artery with sympathetic fibers.
  - Both adjacent to temporal lobes

Pituitary Development

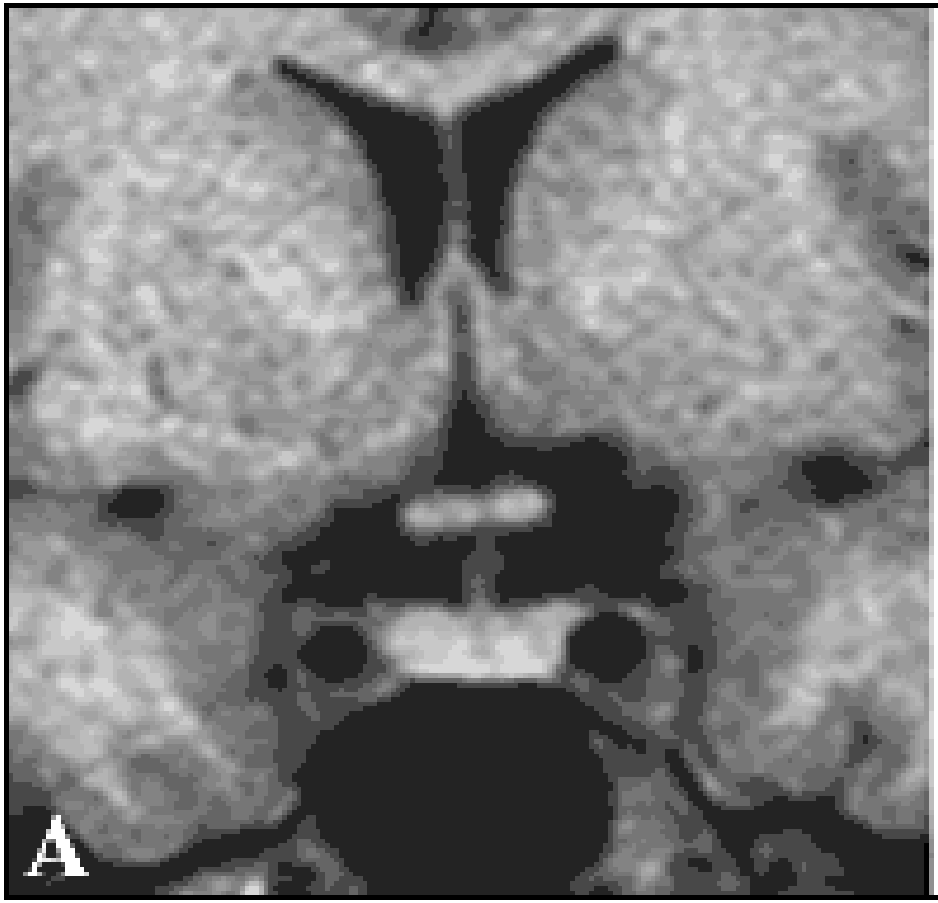
- Pituitary stalk in midline joins the pituitary gland with hypothalamus that is below 3rd ventricle
- Development of pituitary cells is controlled by a set of transcription growth factors like
  - Pit-1, Prop-1, Pitx2

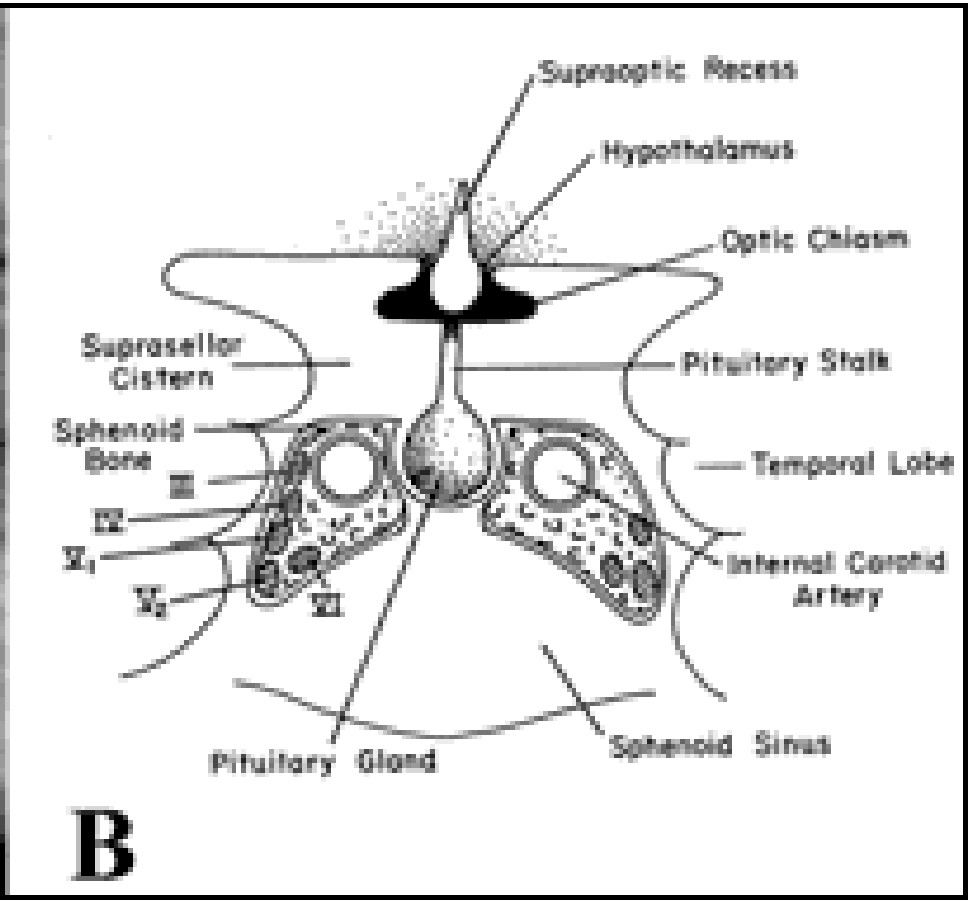
Pituitary Development



- Pituitary gland measures
  - 15 X 10 X 6 mm, weighs 500 mg but about 1 g in women
- Optic chiasm
  - lies 10 mm above the gland and anterior to the stalk
- Blood supply :
  - superior, middle, inferior hypophysial arteries (internal carotid artery) running in median eminence from hypothalamus
- Venous drainage:
  - to superior and inferior petrosal sinsuses to jugular vein

Normal Pituitary Anatomy





Pituitary Disorders

- Anterior pituitary disorders

- Posterior Pituitary disorders

Anterior Pituitary Disorders

- Function :
  - Hypersecretion: (GH,LH,FSH,PRL,TSH,ACTH)
  - Hyposecretion: hypopituitarism (isolated, multiple, pan)

- Masses
  - Functioning = Hypersecretion
  - **Non-** Functioning
  - **With /without mass-effect:**
    - **Space occupying lesion (compression symptoms,** hypopituitarism)

Posterior Pituitary disorders

- Diabetes insipidus

Anterior Pituitary Function

	Somatotroph	Gonadotroph	Lactotroph	Thyrotroph	Corticotroph
Stimulators	**GHRH** **GHS**	**GnRH** **E2**	**--------** **TRH,** E_2	**TRH**	**CRH** **AVP** **gp-130 cytokines**
Inhibitors	**IGF-1** **Somatostatin** **Activins**	Testosterone, E_2 **inhibin**		**T3, T4** **Dopamine** **Somatostatin** **GH**	**Steroid**
Hormone	GH	LH,FSH	PRL	TSH	ACTH,POMC
Target Gland	Liver & other tissues	**Ovary, Testes**	**Breast** **& other tissues**	Thyroid	**Adrenals**
Target Hormone	IGF-1	Testosterone, E_2		T_4	cortisol
Trophic Effects	**IGF-1 production, Growth induction, Insulin antagonism**	**Sex Steroid** **Follicular growth** **Germ Cell maturation**	**Milk Production**	**T4 synthesis and secretion**	**Steroid production** Androgen

Pituitary Function

- **Anterior Pituitary Hormones**
  - **G**o **L**ook **F**or **T**he **A**denoma **P**lease
  - GH , LH, FSH, TSH, ACTH, Prolactin
  - A compressive adenoma in pituitary will impair hormone production in this order
- **Posterior Pituitary Hormones**
  - Oxytocin
  - ADH(vasopressin)
  - Remember (storage not synthesis)

Etiology of Pituitary Masses

Anterior Pituitary Disorders

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Etiology of Pituitary-Hypothalamic Lesions

- **Non-Functioning Pituitary Adenomas**
- **Endocrine active pituitary adenomas**
  - Prolactinoma (PRL-oma)
  - Somatotropinoma (GH secreting adenoma, Acromegaly)
  - Corticotropinoma (ACTH secreting adenoma, Cushing's disease)
  - Thyrotropinoma (TSH-oma, rare)
  - Other mixed endocrine active adenomas
- **Malignant pituitary tumors:** Functional and non-functional pituitary carcinoma
- **Metastases in the pituitary (breast, lung, stomach, kidney)**
- **Pituitary cysts:** Rathke's cleft cyst, Mucocoeles, Others
- **Empty sella syndrome**
- **Pituitary abscess**
- **Lymphocytic hypophysitis**
- **Carotid aneursym**

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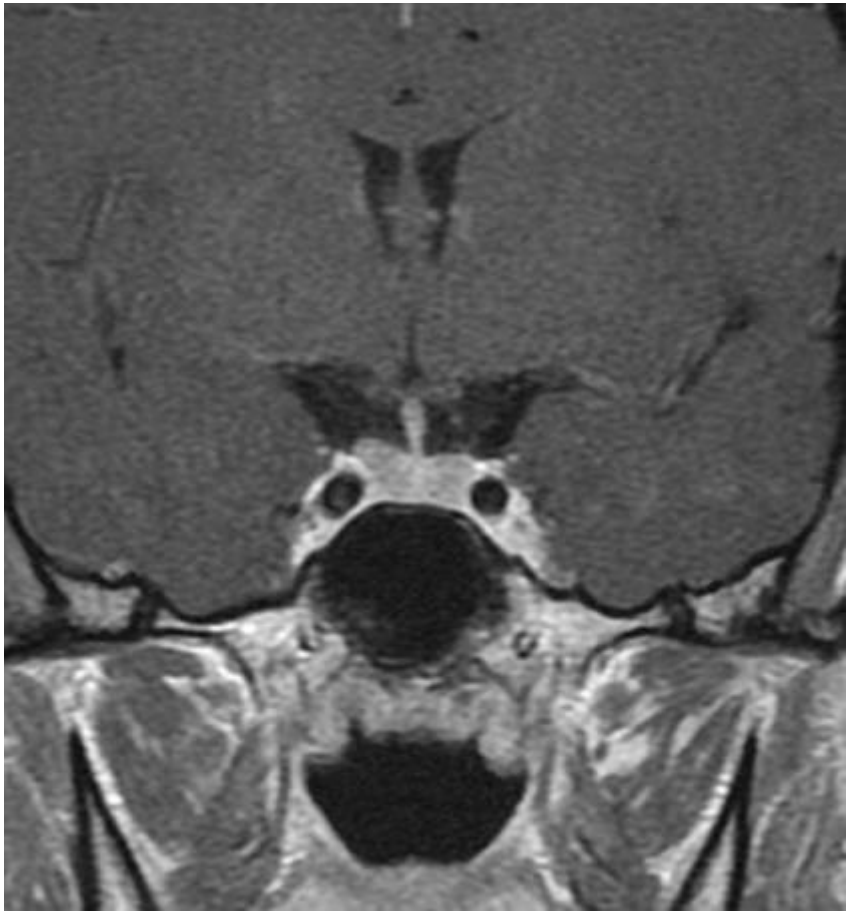

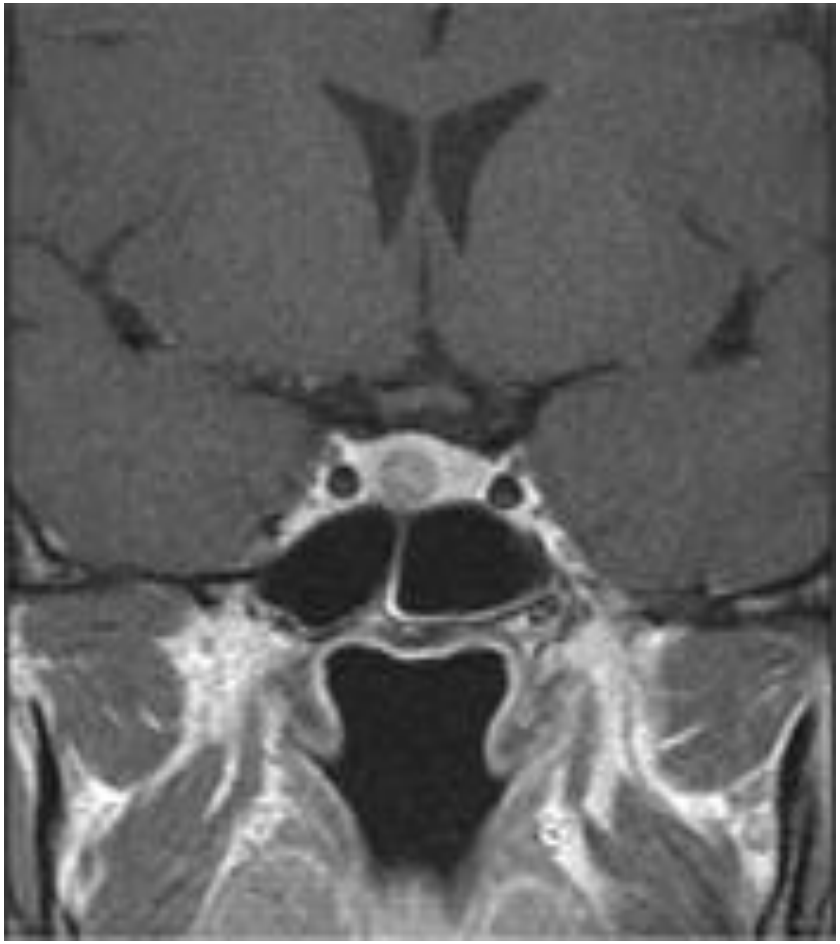

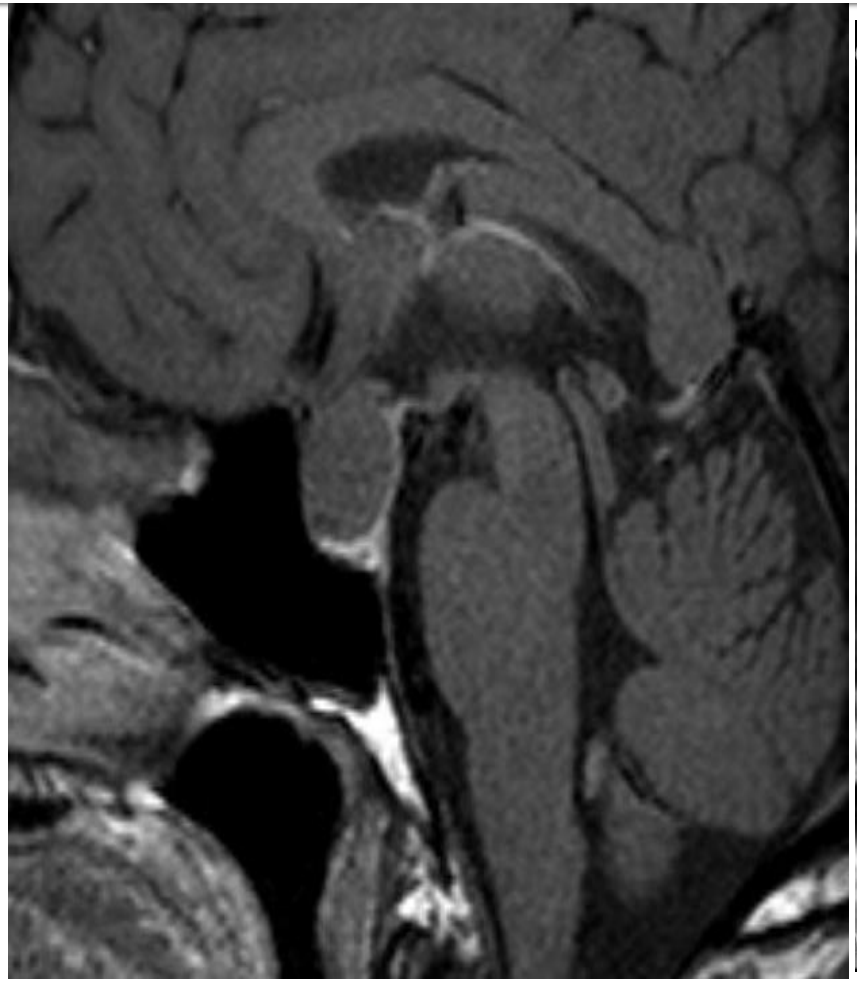

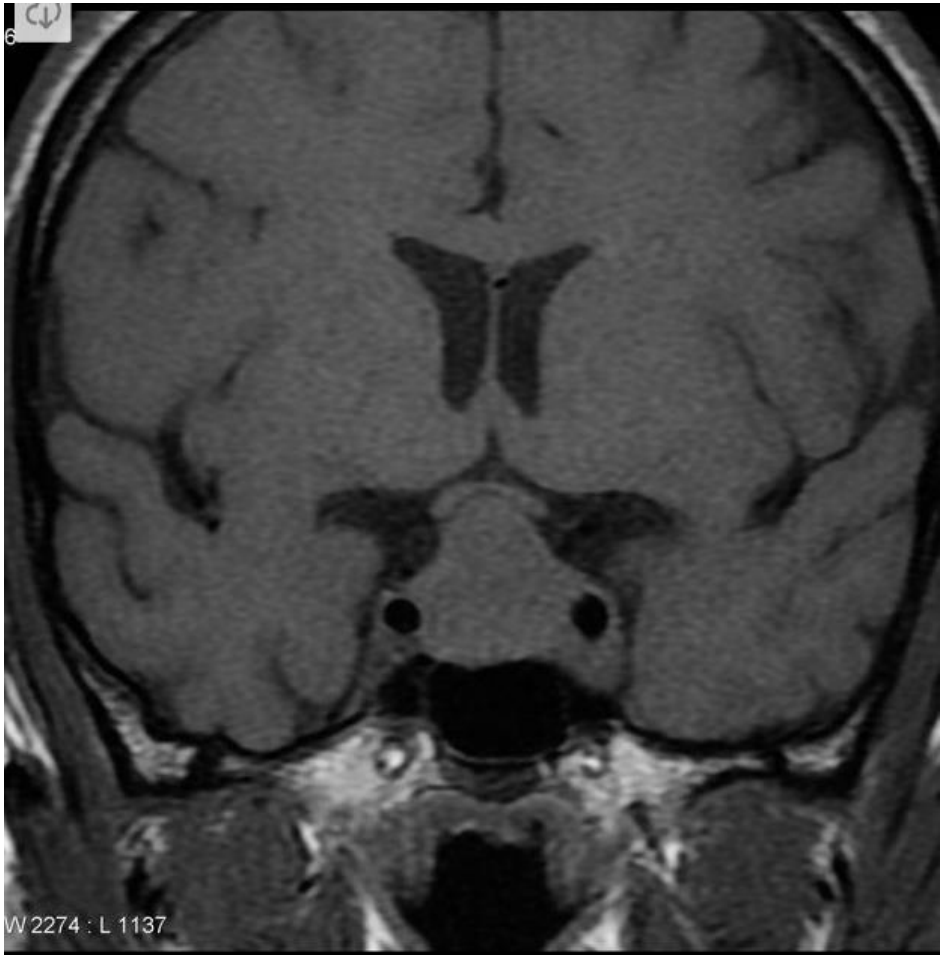
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Anterior Pituitary Disorders

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- Masses
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Disorders of Pituitary Function

- **Hypopituitarism**
  - Central hypoadrenalism, hypogonadism, hypothyroidism or GH deficiency
  - Panhypopituitarism
- **Hypersecretion of Pituitary Hormones**
  - Hyperprolactinemia
  - Acromegaly
  - Cushing's Disease

Evaluation of Pituitary mass

- Pituitary adenoma:
  - 10 % of all pituitary lesions
  - Genetic-related
    - MEN-1, Gs-alpha mutation, PTTG gene, FGF receptor-4
- Pituitary incidentaloma:
  - 1.5 -31 % in autopsy (prevalence)
  - 10 % by MRI most of them < 1 cm

Evaluation of Pituitary lesion

Table 1. Functioning Adenomas: Clinical Disease and Medical Therapy

Clinical disease	Hormone produced by tumor	Estimated frequency (%)	Medical therapy
Acromegaly	Growth hormone	5–10	Somatostatin analog (octreotide) Growth hormone receptor blocker
Cushing's disease	ACTH	10–15	Ketoconazole (blocks cortisol synthesis)
Gonadotroph	FSH, LH	5	None
Prolactinoma	Prolactin	20–30	Dopamine agonist (bromocriptine, cabergoline, pergolide)
Null cell	None	20–25	None
Thyrotropic	TSH	<3	Somatostatin analog (octreotide) Propylthiouracil
Other (including mixed cell adenomas)	None	20	None

ACTH = adrenocorticotropic hormone, FHS = follicle-stimulating hormone, LH = luteinizing hormone, TSH = thyroid-stimulating hormone.

Evaluation of Pituitary lesion

- **C: Clinical** (History and Examination)
  - function (oversection or hyposecretion)
  - Mass (headache, visual symptoms)
- **B: Biochemical**
  - Screen Test
  - Confirmatory Test
- **A: Anatomical**
  - MRI of sella turcica
- Then treatment:
  - Surgical – Medical – Radiation
  - Medical – Surgical – Radiation

Non- functional pituitary adenoma

C: Clinical	Asymptomtic , incidentaloma by imaging Mass-effect (mechanical pressure, hypopituitarism, visual (bitemproal hemianopia) Gonadal hypersecretion
B: Biochemical	GH,LH,FSH,TSH,ACTH: not high PRL : low ,high, normal
A: Anatomical	MRI
Treatment	**Surgery if indicated** **Observation** **Adjunctive therapy:** - Radiation therapy - Dopamine agonist - Somatostatin analogue

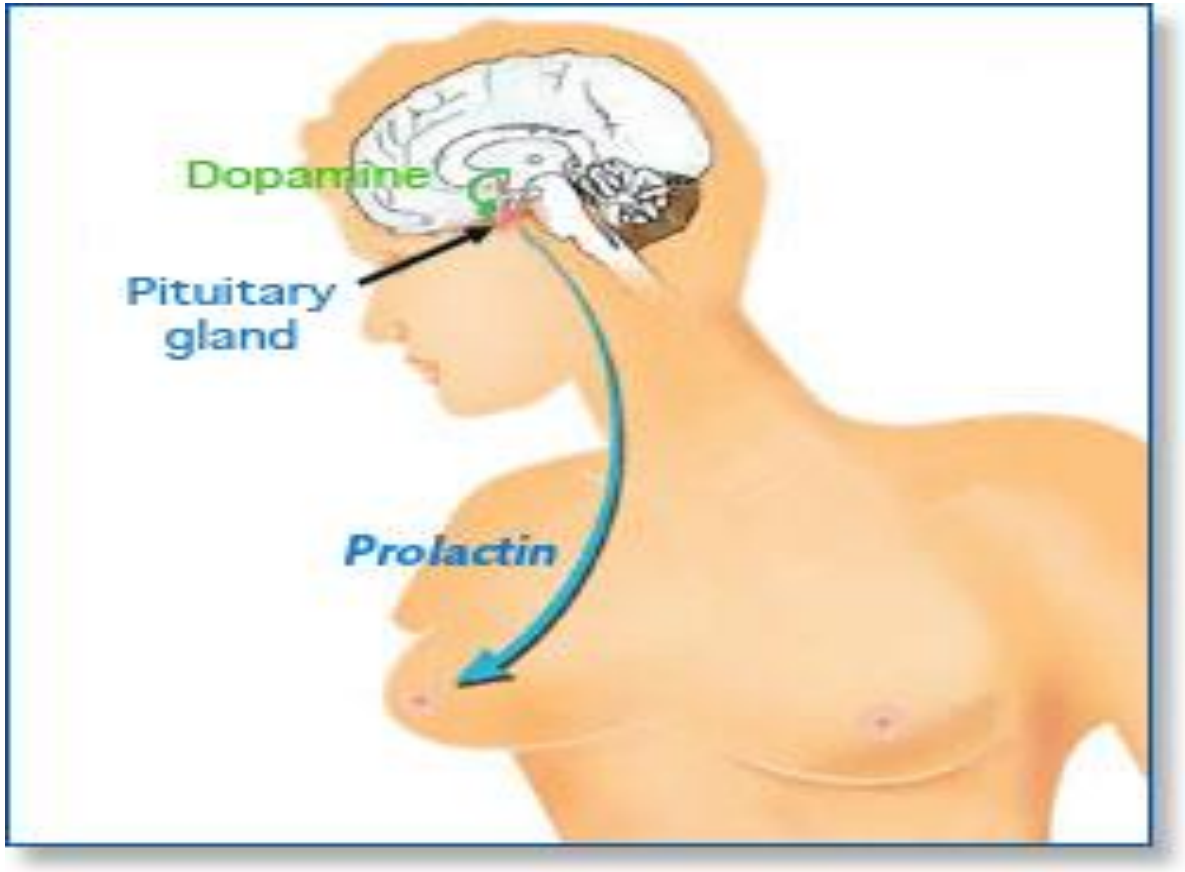
Non- functional pituitary adenoma

Table 2
Clinical characteristics of NFPA patients.

	Nomikos et al[15]	Losa et al[16]	Chang et al[17]	Ferrante et al[51]	Total
Number of patients	721	491	663	295	2170
Mean age	54.2 ± 19	–	53 (median)	50.4 ± 14.1	
Gender (M/F)	401/320	276/215	394/269	161/134	1232/938 (56.7% M)
Incidental finding	57 (7.9%)	57 (11.6%)	49 (7.4%)	_	163/1875 (8.7%)
Headaches	70 (9.7%)	–	212 (32%)	122 (41.4%)	404/1679 (24%)
Visual deficits	222 (30.8%)	287/486 (59.1%)	327 (49%)	200 (67.8%)	1036/2170 (47.7%)
Pressure on cranial nerves	_	22 (4.5%)	26 (3.9%)	–	48/1154 (4.2%)
Apoplexy	27 (3.7%)	48 (9.8%)	24 (3.6%)	–	99/1875 (5.3%)
Symptoms of Hypopituitarism	345 (47.8%)	_	342 (51.6%)	118 (40%)	805/1679 (48%)
Documented Hypopituitarism	614 (85%)		–	183 (62%)	797/1016 (78.4%)
Hypogonadism	512/659 (77.7%)	335/474 (70.7%)		128 (43.3%)	975/1261 (77.3%)
Hypoadrenalism	230 (31.9%)	115/478 (24.1%)		77 (26.2%)	422/1494 (28.2%)
Hypothyroidism	129/658 (19.6%)	116/462 (25.1%)		72 (24.5%)	317/1415 (22.4%)
Hyperprolactinemia	199 (27.6%)	251/462 (54.3%)	–	82 (27.6%)	532/1478 (35.9%)

Functional pituitary mass

Prolactin

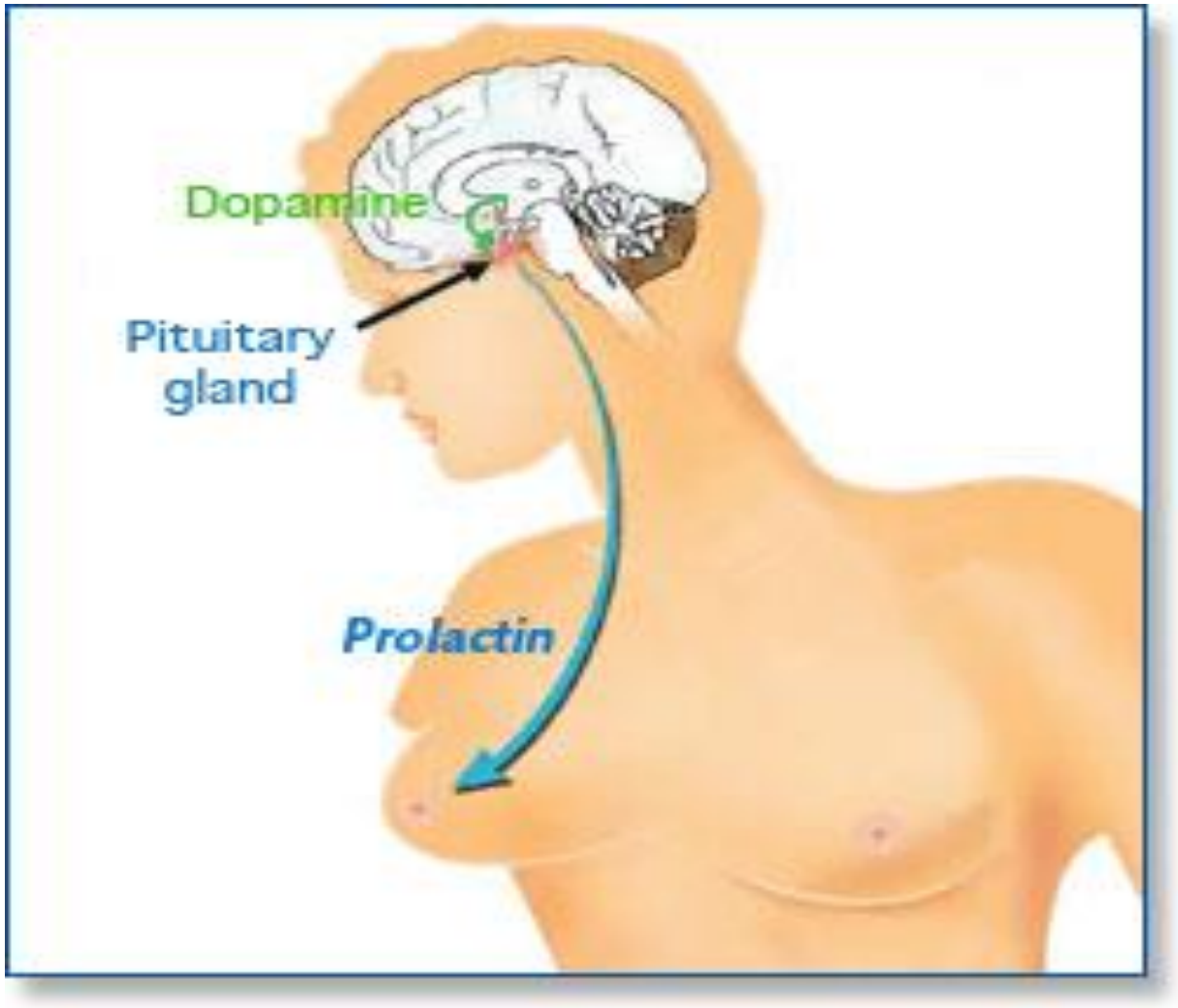


Prolactin - Low

- No clinical significant if there is no mass invading the hypothalamus.

- N.B. :
  - PRL is the only pituitary hormone that is inhibited by hypothalamus.

Prolactinoma (Mass + high level)



Prolactinomas

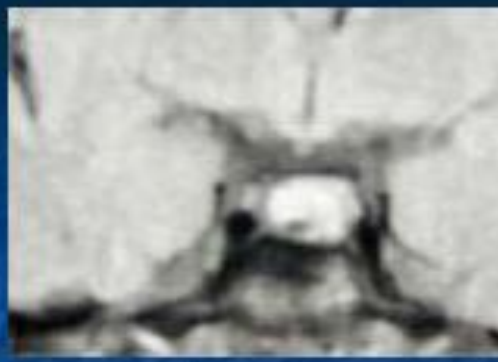
- **Most common** of functional pituitary adenomas
- 25-30% of all pituitary adenomas
- Some growth hormone (GH)–producing tumors also co-secrete PRL
- Prolactinomas **women:**
  - 90% present with **micro**prolactinomas

- Prolactinomas in **men** :
  - 60% present with **macro**prolactinomas

Hyperprolactinemia

- Causes:
  - 1. disruption of dopamine (tumor, trauma, infiltrative lesions)
  - 2. hypothyroid (increases TRH)
  - 3. estrogen increase (pregnancy)
  - 4. chest wall burns – nueronal effect like suckling
  - 5. chronic renal failure, returns to nml after transplant
  - 6. drugs (verapamil, H2 blockers, estrogens, opiates, dopamine receptor antagonists, reserpine, a-methyldopa)

Prolactinomas

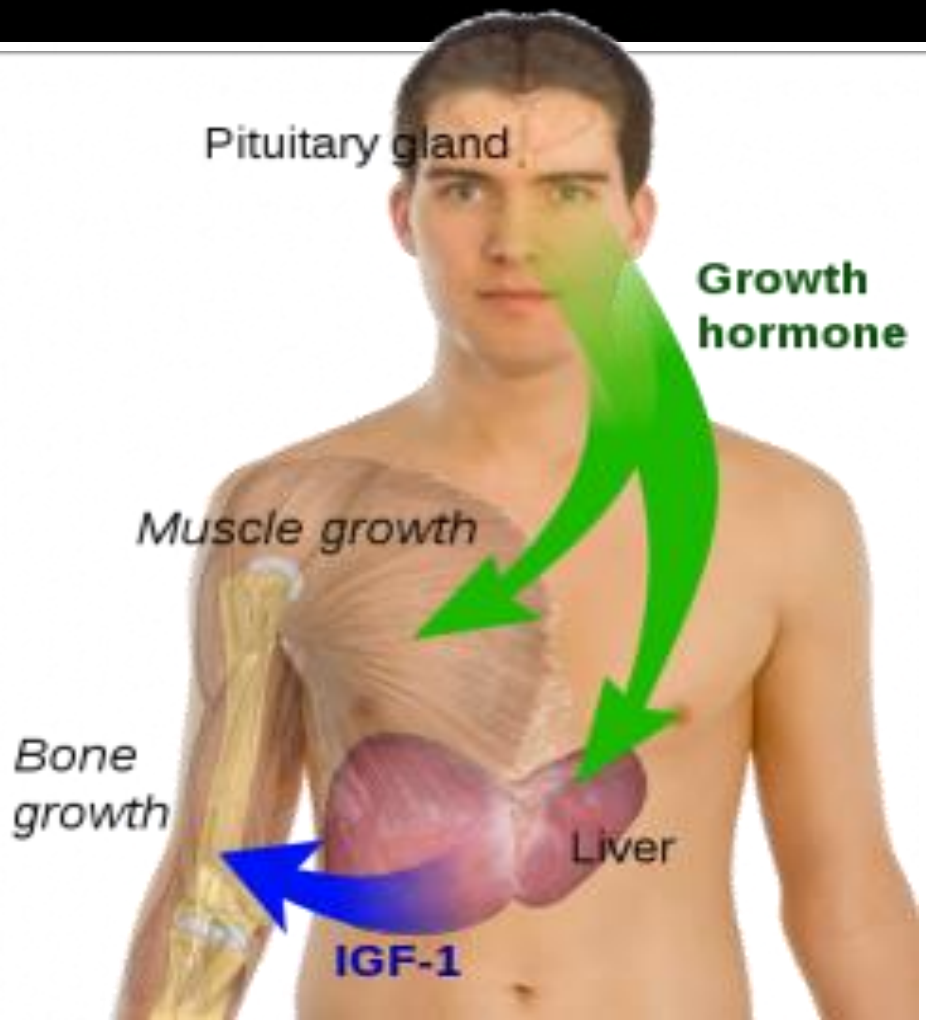


- Most common functional pituitary tumor
- 10% are lactotroph and somatotroph such as GH producing
- Presents with amenorrhea and infertility
- Prolactinomas lose TRH response
- Microadenomas <10mm on MRI
- Macroadenomas >10mm

Prolactinomas

C: Clinical	**oligomenorrhea, amenorrhea or infertility** **Galactorrhea** **Mass-effect (mechanical pressure, hypopituitarism)** **Sexual dysfunction (in male)** ***asleep, stress, pregnancy, lactation and chest wall stimulation or trauma, Renal failure, Liver failure*** ***medication*** **O/E: Visual field defect (Bitemporal hemianopia)** **Nipple discharge**
B: Biochemical	GH,LH,FSH,TSH,ACTH: normal or low PRL : High TSH: R/O Hypothyroidism(primary) IGF-1: R/O acromegaly co-secrtion
A: Anatomical	MRI
Treatment	**Medical – Medical – Medical (Dopamine agonist)** **Surgical- Radiation**

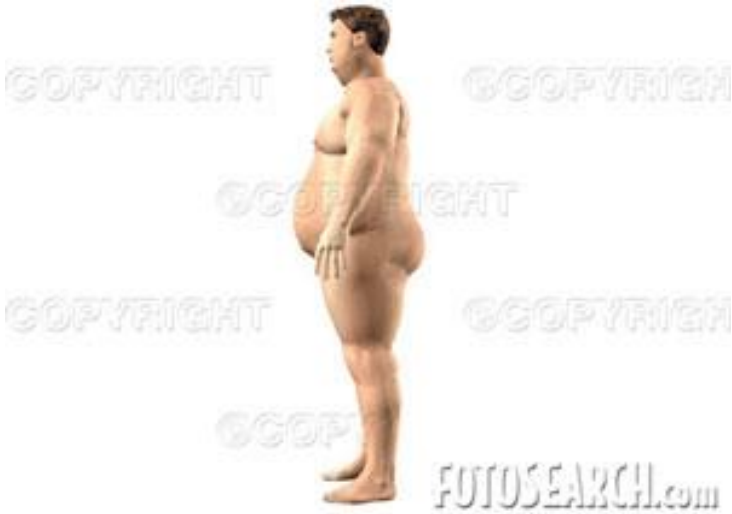
Growth hormone disorder



Growth hormone deficiency

- Isolated, pan hypopituitarism
- Pituitary tumor as mass effect →→ Growth hormone deficiency
- Disease :
  - Children: Short stature
  - Adult: ??

Growth hormone deficiency

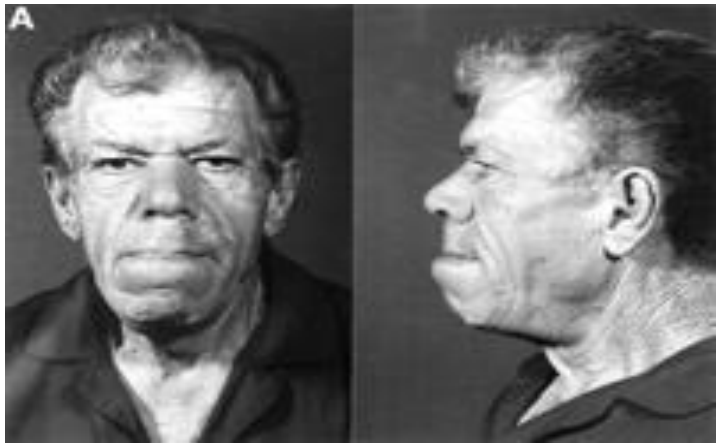


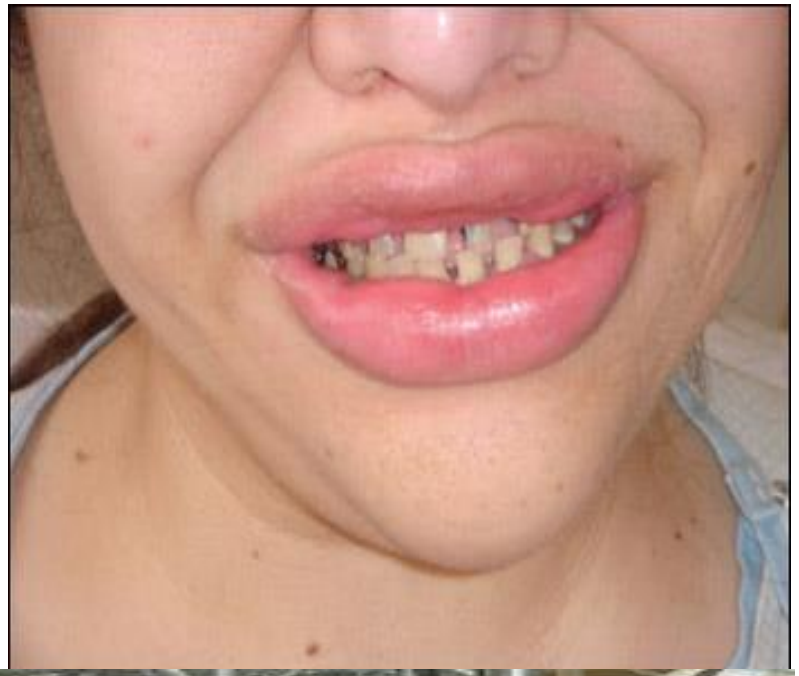
- Diagnosis in children and adult

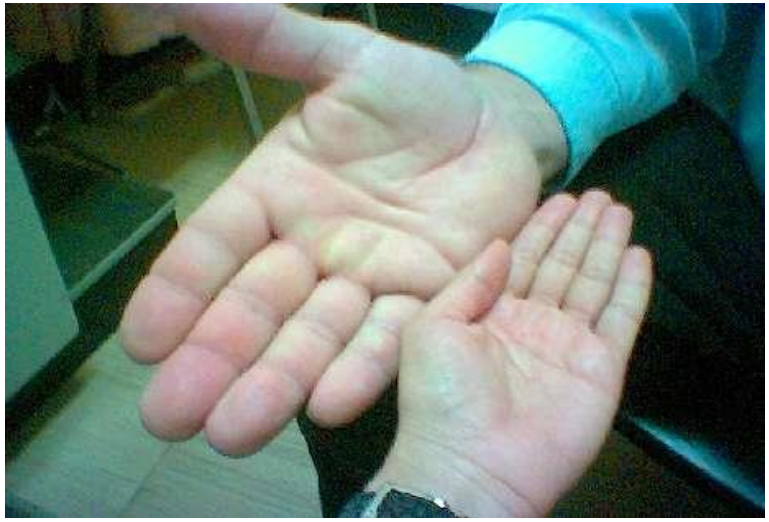
Growth hormone deficiency

C: Clinical	**Function : Short stature** **Mass-effect (mechanical pressure, hypopituitarism)**
B: Biochemical	Pituitary Function (LH,FSH.PRL, TSH, ACTH, cortisol,testesterone, T_4) Screen: IGF-1 Dynamic testing: clonidine stimulation test glucagon stimulation exercise testing, arginine-GHRH **insulin tolerance testing**
A: Anatomical	X-ray of hands: delayed bone age MRI
Treatment	GH replacement

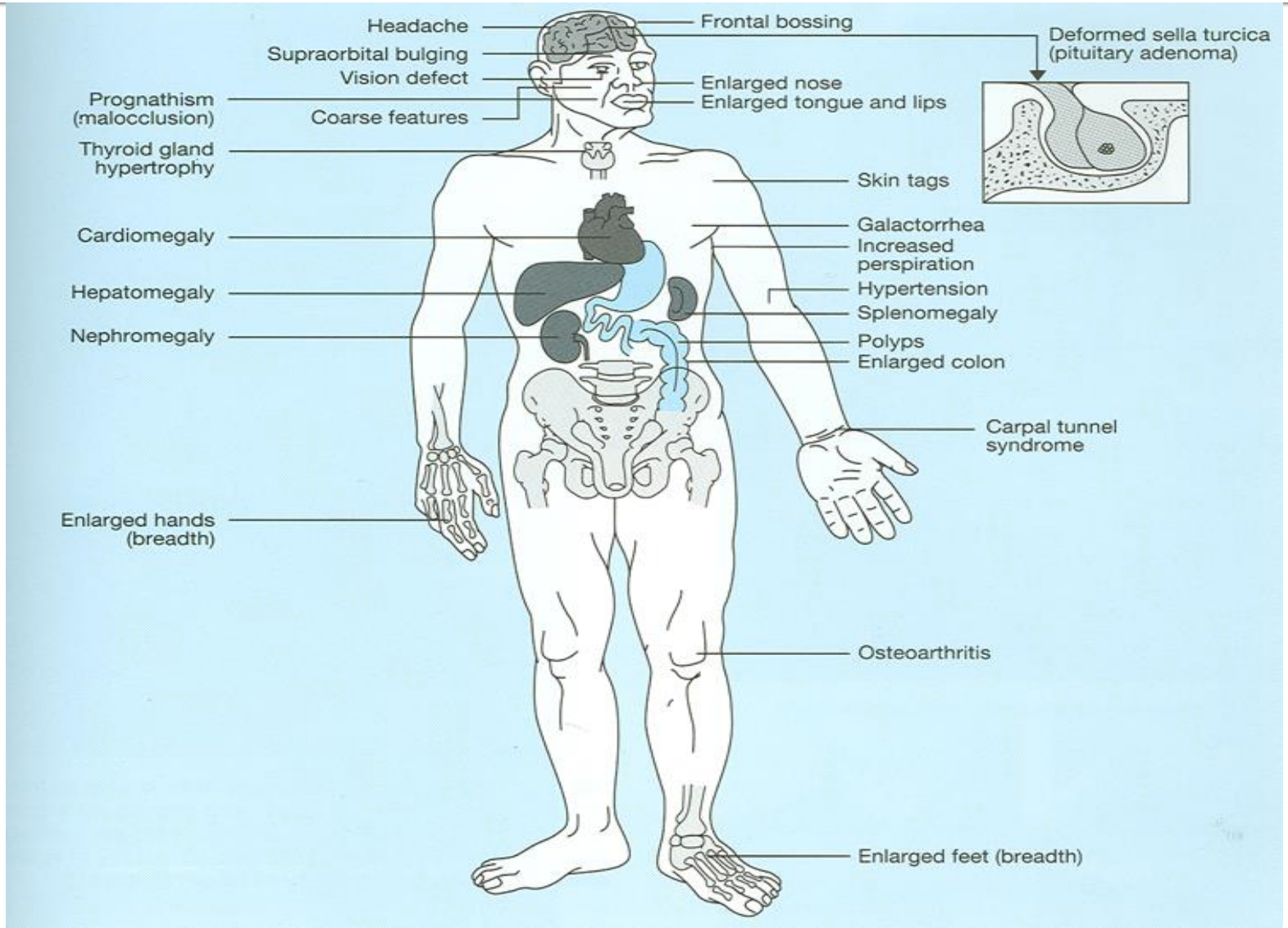
Acromegaly







Growth hormone - Acromegaly



Growth hormone - Acromegaly

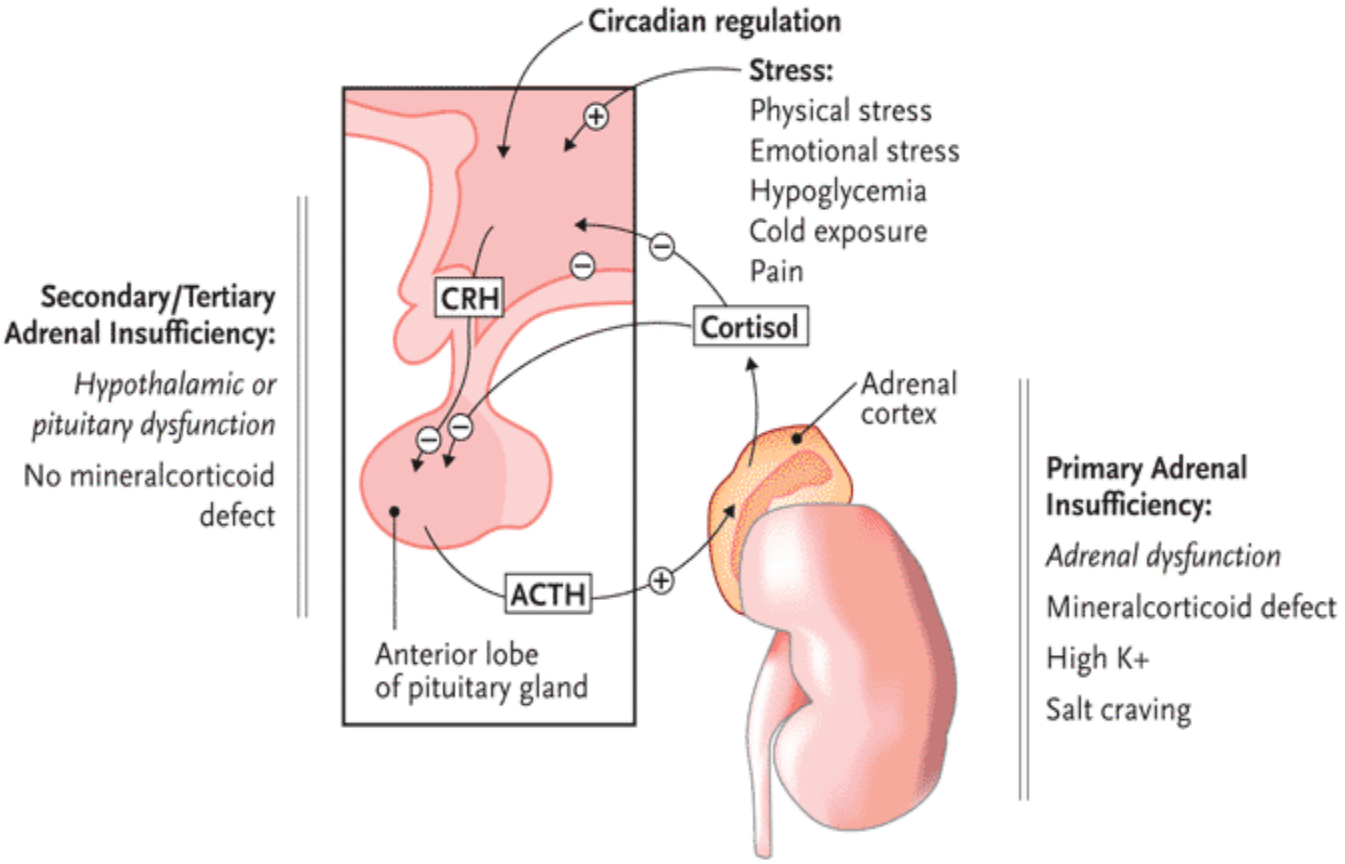
Table 1. Clinical Features of Acromegaly.

Local tumor effects	**Visceromegaly**
Pituitary enlargement	Tongue
Visual-field defects	Thyroid gland
Cranial-nerve palsy	Salivary glands
Headache	Liver
Somatic systems	Spleen
Acral enlargement, including thickness of soft tissue of hands and feet	Kidney
	Prostate
Musculoskeletal system	**Endocrine and metabolic systems**
Gigantism	Reproduction
Prognathism	Menstrual abnormalities
Jaw malocclusion	Galactorrhea
Arthralgias and arthritis	Decreased libido, impotence, low levels of sex hormone–binding globulin
Carpal tunnel syndrome	
Acroparesthesia	Multiple endocrine neoplasia type 1
Proximal myopathy	Hyperparathyroidism
Hypertrophy of frontal bones	Pancreatic islet-cell tumors
Skin and gastrointestinal system	Carbohydrate
Hyperhidrosis	Impaired glucose tolerance
Oily texture	Insulin resistance and hyperinsulinemia
Skin tags	Diabetes mellitus
Colon polyps	Lipid
Cardiovascular system	Hypertriglyceridemia
Left ventricular hypertrophy	Mineral
Asymmetric septal hypertrophy	Hypercalciuria, increased levels of 25-hydroxyvitamin D_3
Cardiomyopathy	Urinary hydroxyproline
Hypertension	Electrolyte
Congestive heart failure	Low renin levels
Pulmonary system	Increased aldosterone levels
Sleep disturbances	Thyroid
Sleep apnea (central and obstructive)	Low thyroxine-binding–globulin levels
Narcolepsy	Goiter

Acromegaly

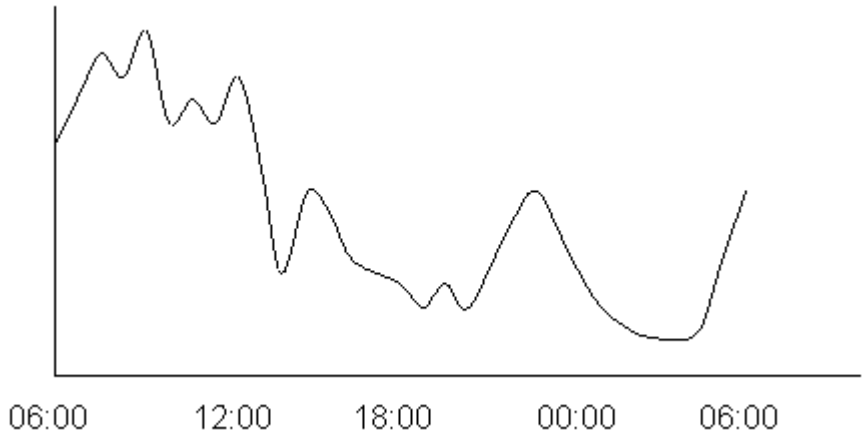
C: Clinical	**Function : Sweating, Enlargement (acral, face gross features, heart, tongue Jaw, gigantism in children , Galactorrhea** **Mass-effect (mechanical pressure, hypopituitarism)** ***HTN,CHF, OSA,constipation*** **O/E: Visual field defect (Bitemporal hemianopia)** **Gross features of Acromegaly**
B: Biochemical	Pituitary Function (LH,FSH.PRL, TSH, ACTH, cortisol,testesterone, T_4) Screen: IGF-1 Confirmatory Test : 75 g OGTT tolerance test for GH suppression Fasting and random blood sugar, HbA1c Lipid profile
A: Anatomical	MRI Echo: Cardiac disease is a major cause of morbidity and mortality 50 % died before age of 50 HTN in 40%, LVH in 50% , Diastolic dysfunction as an early sign of cardiomyopathy
Treatment	**Surgical – Medical (**Somatostatin analogue)- **Radiation**

ACTH-disorders



HPA-axis

- Circadian rhythm of cortisol secretion
- Early morning cortisol between 8-9 am



ACTH-disorders

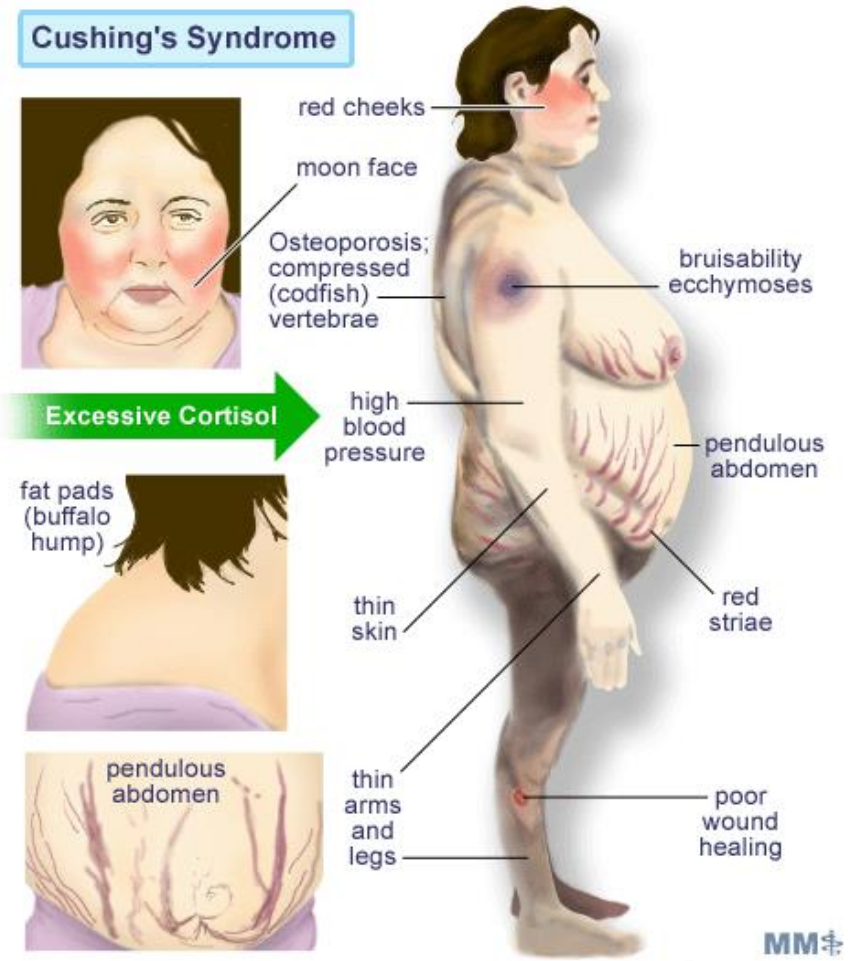
Cortisol low (Hypoadrenalism)

- Nausea, Vomiting, abdominal pain, Diarrhea
- Dizziness and weakness, Tiredness, Muscle ache
- Hypotension
- Weight loss

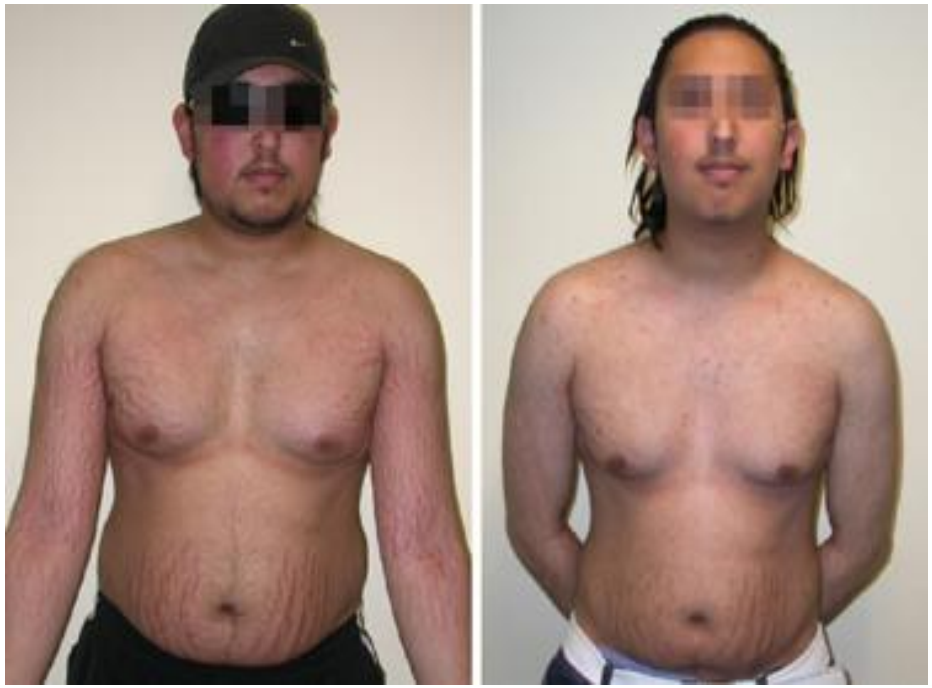
Management of hypoadrenalism

- Cortisol replacement

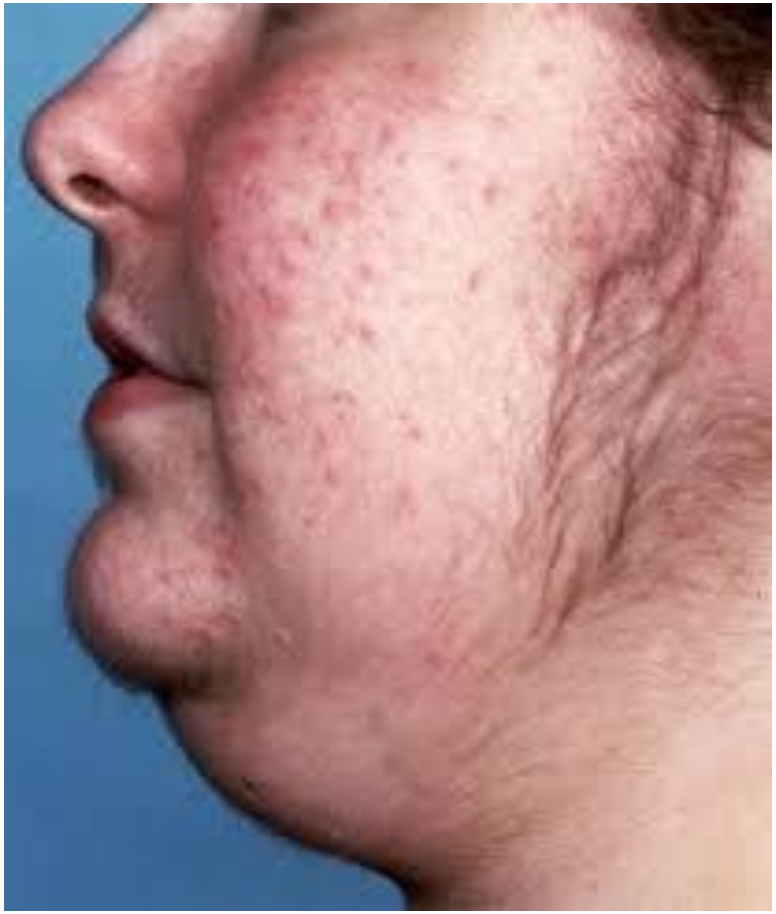
HPA-axis (excessive cortisol)



ACTH-Adenoma

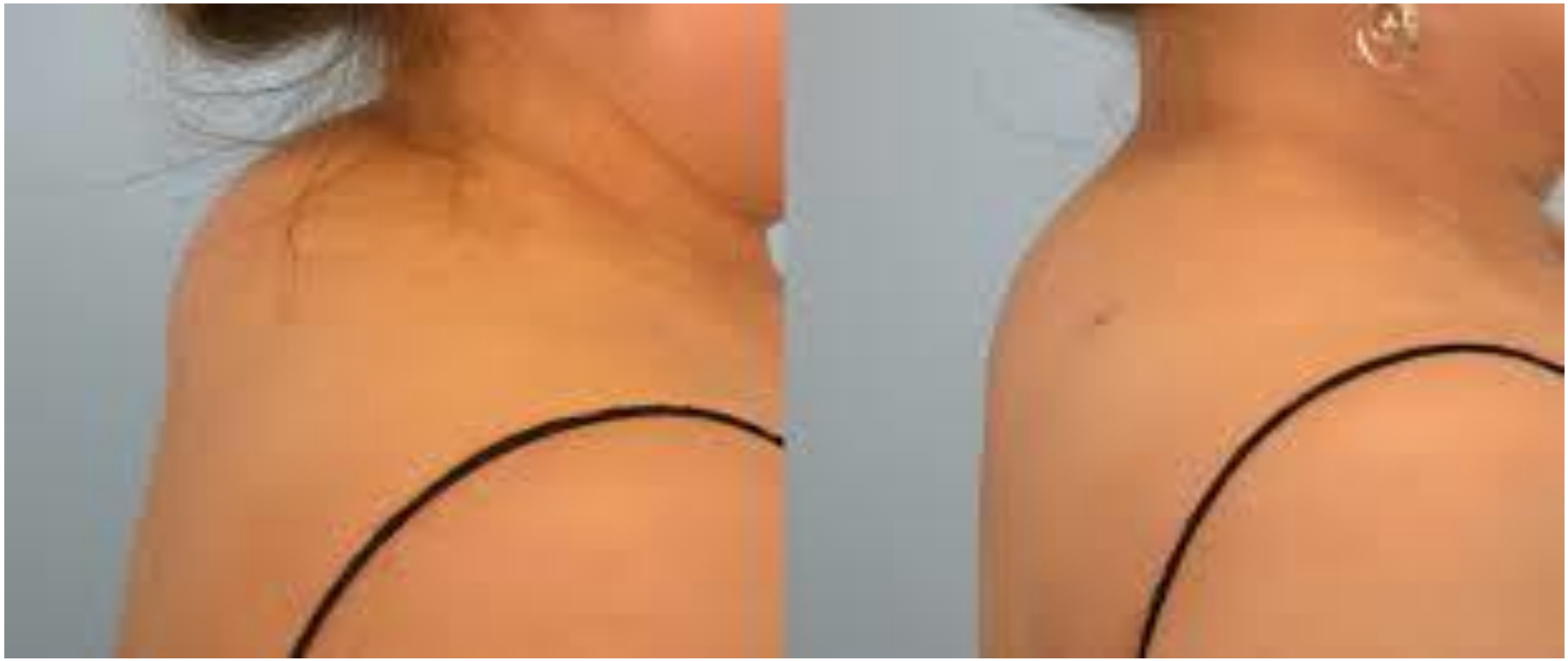


excessive cortisol (Cushing's)
Hirsutism in women

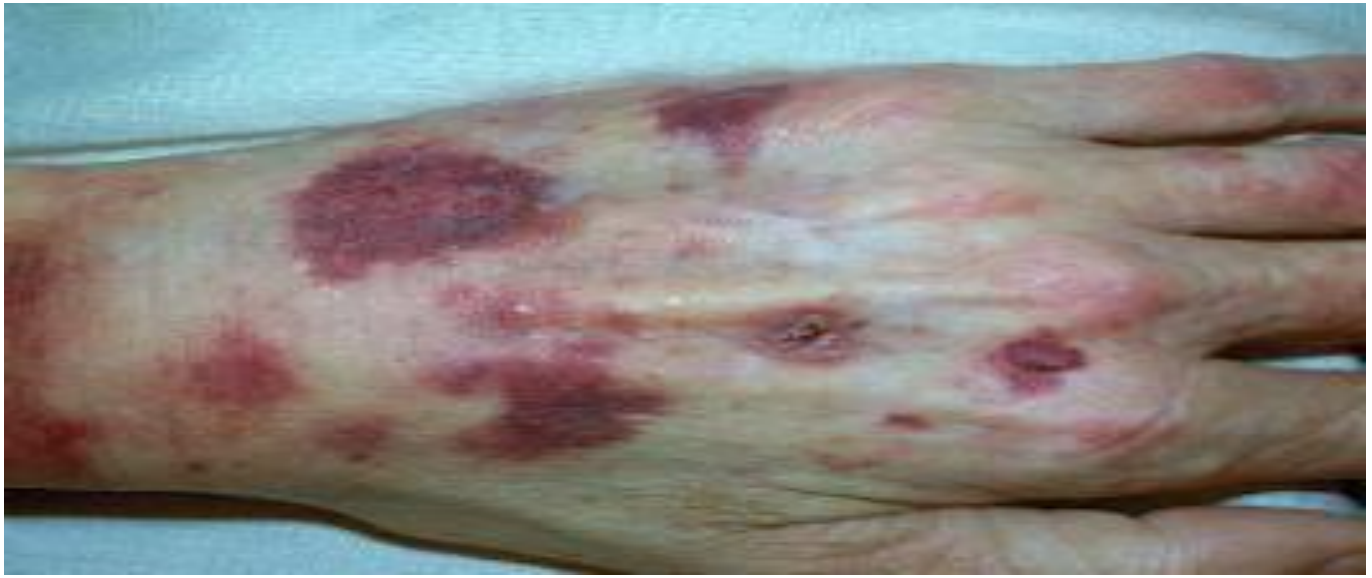


excessive cortisol (Cushing's)
Stria (purple, wide >1cm)

excessive cortisol (Cushing's)



excessive cortisol (Cushing's) ecchymosis



HPA-axis (excessive cortisol)

- 80 % HTN
- LVH
- Diastolic dysfunction, intraventricular septal hypertrophy
- ECG needed: high QRS voltage, inverted T-wave
- Echocardiogram preop
- OSA: 33% mild, 18% severe. Needs respiratory assessment and careful use of sedative during surgery
- Glucose intolerance in 60%, control of hyperglycemia
- Osteoporosis with vertebral fracture→→ positioning of patient in OR (50 %), 20 % with fracture
- thin skin→→ difficult IV cannulation, poor wound healing

Cushing's (excessive cortisol)

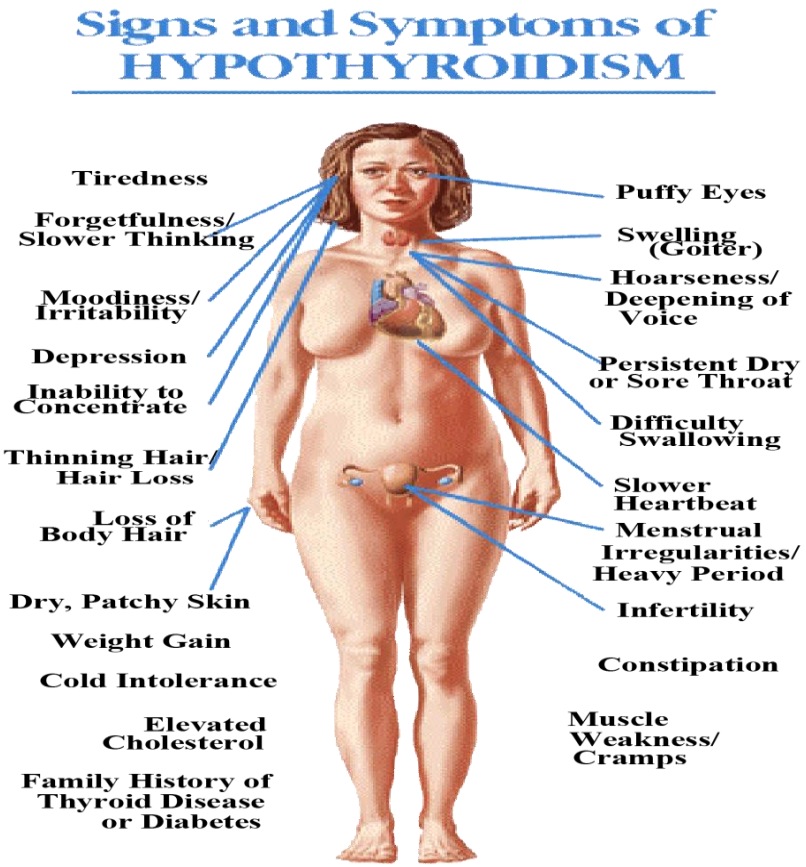
C: Clinical	**Function : Hirsutism, acne, easily bur DM,HTN, irregular period, proximal weakness, recurrent infections, depression** **O/E: hirsutism, acne, moon face, central obesity, stria, proximal weakness, supraclavicular fat pad,**
B: Biochemical	High cortisol , high ACH 24hrs for UFC 1MG DST Midnight salivary cortisol
A: Anatomical	MRI
Treatment	Surgical – Medical - Radiation

TSH-Hypothyroid

Fig. 2 A patient before and after successful treatment of primary hypothyroidism.

Central Hypothyroidism

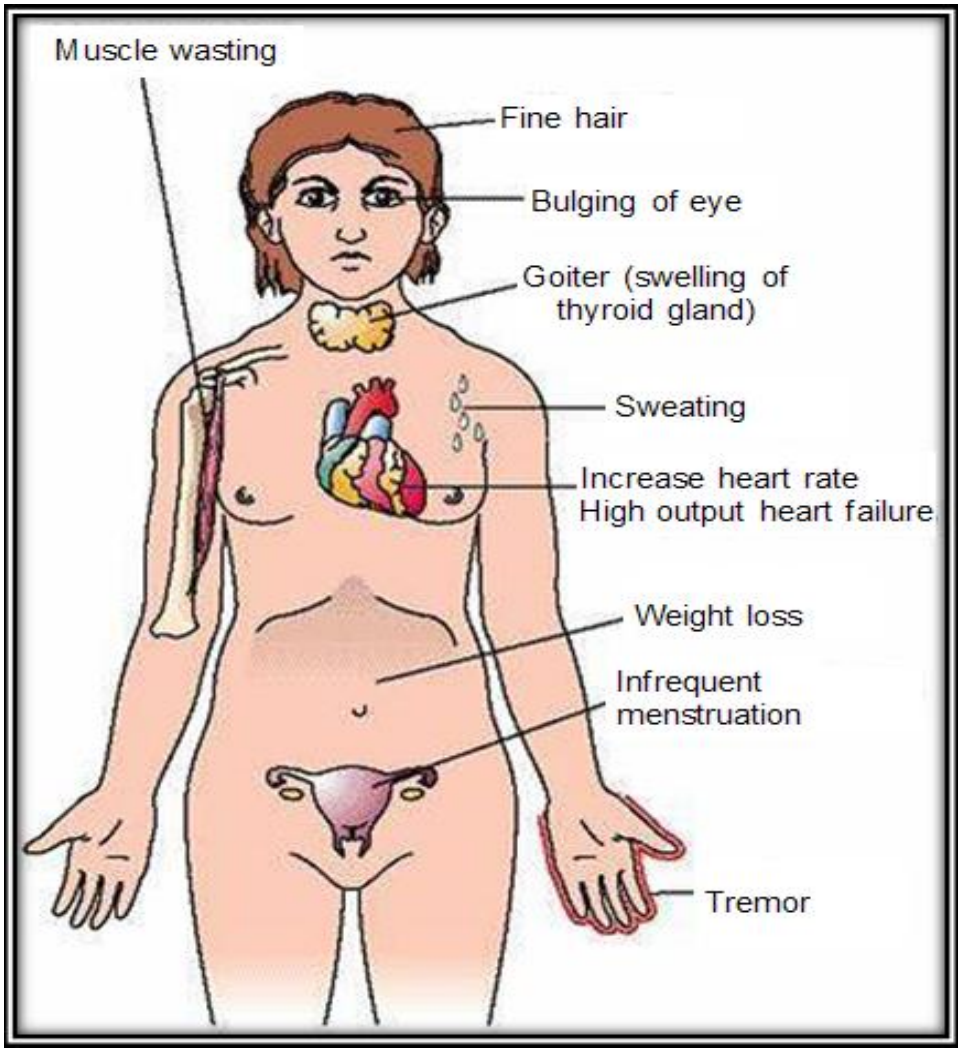
- Low TSH
- Low free T4 and T3



Central Hypothyroidism

C: Clinical	**Function : fatigue, weight gain, irregular menses, dry skin, depression, cold intolerance, increase sleep, slow thinking** **O/E: obesity, ? Depressed face, eye brow**
B: Biochemical	Low T_4 , Low TSH
A: Anatomical	MRI
Treatment	Thyroxine replacement Surgical removal of pituitary adenoma if large

TSH-hyperthyroid


Muscle wasting
Fine hair
Bulging of eye
Goiter (swelling of thyroid gland)
Sweating
Increase heart rate
High output heart failure
Weight loss
Infrequent menstruation
Tremor

TSH-Producing adenoma

- Very rare < 2.8 %
- Signs of hyperthyroidism
- High TSH, FT_4, FT_3
- Treatment preop with anti-thyroid meds
- Surgical resection of adenoma
- Medical therapy: Somatostatin Analogue

Gonadotroph adenoma vs. menopause and ovarian failure

- High FSH with low LH
- High serum free alpha subunit
- High estridiol, FSH, thickened endometrium and polycystic ovaries

Gonadotroph Adenoma

- Surgical resection if large
- Radiation therapy

Hypopituitarism

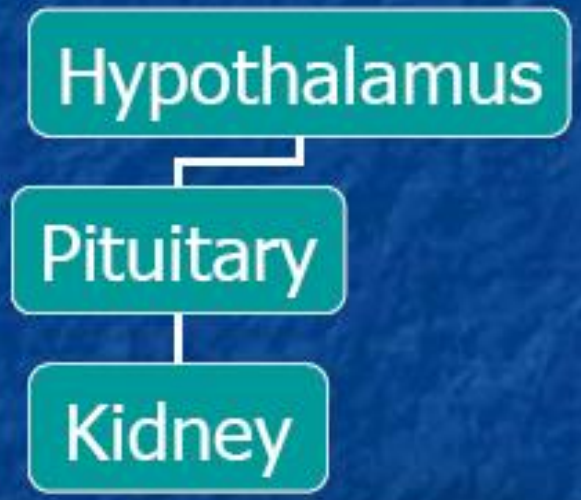
- 76% tumor or treatment of tumor
  - Mass effect of adenoma on other hormones
  - Surgical resection of non-adenomatous tissue
  - Radiation of pituitary
    - Check hormones 6 mos after and then yearly
- 13% extrapituitary tumor
  - Craniopharyngioma
- 8% unknown
- 1% sarcoidosis
- 0.5% Sheehan's syndrome

Infiltrative Lesions

- Hereditary Hemochromatosis
  - Fe deposition in pituitary
  - Gonadotropin deficiency most common
  - Tx repeat phlebotomy
- Pituitary Apoplexy
  - Sudden hemorrhage into pituitary
  - Severe, sudden HA; diplopia; hypopituitarism
  - Sudden ACTH def. is life-threatening hypotension
  - Tx: surgical decompression

Central Diabetes Insipidus

- Polydipsia and Polyuria (2-15 Liters/day)
- Abrupt onset
- 30-50% are idiopathic
  - Dec. production by hypothalamus
- Surgery or Trauma
- Rare with Sheehan's
  - Mild, undetectable degree



Dx of Central DI

- Water Deprivation test:
  - Restrict p.o. fluids or administer hypertonic saline to increase serum osmolality to 295-300 mosmol/kg (nml: 275-290)
  - Central DI: urine osmolality still low and returns to normal after administer vasopressin
  - Nephrogenic DI: exogenous vasopressin does not alter urine osmolality much

Treatment of Central D.I.

- DDAVP (Desmopressin Acetate)
  - Synthetic analog
  - Not catabolized by vasopressinase
  - No vasopressor action
  - Administered intranasally (rec.) or p.o.
  - Titrate 10-20ug qd or bid
  - Safe in pregnancy and breastfeeding

assessment of pituitary function

- Baseline:
  - TSH, FT_4
  - LH, FSH, and (Testosterone or Estradiol)
  - Prolactin
  - GH, IGF-I
  - ACTH, cortisol and electrolyte
- MRI brain
- Neuropthalmic evaluation of visual field
- Cardiac and respiratory assessment
- Anesthesiologist for airway and perioperative monitoring
- Neurosurgeon
- ENT for Endonasal evaluation for surgical approach
- Preop hormonal replacement:
  - maybe need to be covered with stress dose of HC