HYPOTHALAMUS AND PITUITARY GLAND
HYPOTHALAMUS AND PITUITARY GLAND

- The pituitary gland, weighing 500 to 900 mg, lies at the base of the skull in the sella turcica, within the sphenoid bone. It may double in size during pregnancy.

- The cavernous sinus, which contains the carotid arteries and cranial nerves III, IV, and VI, borders laterally on the pituitary gland. The optic chiasm courses over the superior aspect, separated from the gland by the diaphragma sellae of the dura. The roof of the sphenoid sinus forms the floor of the sella turcica.

- Two thirds of the pituitary gland is the anterior lobe, and one third is the posterior lobe.

- The pituitary gland referred to as the "master gland" because, together with the hypothalamus its have a regulatory functions of multiple other endocrine glands. The anterior pituitary gland produces six major hormones: (1) prolactin (PRL), (2) growth hormone (GH), (3) adrenocorticotropic hormone (ACTH), (4) luteinizing hormone (LH), (5) follicle-stimulating hormone (FSH), and (6) thyroid-stimulating hormone (TSH). MSH
Posterior lobe of pituitary secretes 2 hormones: 1- Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and transported through long axons into the posterior lobe of the pituitary gland, where it is stored and available to be secreted when stimulated. Oxytocin is also stored in, and secreted by, the posterior lobe of pituitary. Pituitary hormones are secreted in a pulsatile manner.
What the letters stand for...

- TSH: thyroid-stimulating hormone
- ACTH: adrenocorticotrophic hormone
- FSH: follicle-stimulating hormone
- LH: luteinizing hormone
- GH: growth hormone
- PRL: prolactin
- MSH: melanocyte-stimulating hormone

- ADH: antidiuretic hormone
- Oxytocin
Nerve cells that produce hormones and secrete them into the bloodstream are called **NEUROSECRETORY CELLS**.

In humans, neurosecretory cells are found in the **HYPOTHALAMUS**.
What the letters mean...

- **Releasing hormones (releasing factors) of hypothalamus**
  - Secreted like neurotransmitters from neuronal axons into capillaries and veins to anterior pituitary (adenohypophysis)
  - TRH (thyroid releasing hormone) ----- turns on* TSH
  - CRH (corticotropin releasing hormone) ----- turns on ACTH
  - GnRH (gonadotropin releasing hormone) --- turns on FSH and LH
  - PRF (prolactin releasing hormone) ----- turns on PRL
  - GHRH (growth hormone releasing hormone) ---- turns on GH

- **Inhibiting hormones of hypothalmus**
  - PIF (prolactin inhibiting factor) ----- turns off PRL
  - GHIF (growth hormone) inhibiting hormone --- turns off GH

*The hypothalamus controls secretion of hormones which in their turn control the secretion of hormones by the thyroid gland, the adrenal cortex and gonads: in this way the brain controls these endocrine glands*

*Note: “turns on” means causes to be released*
Sella turcica of the sphenoid bone
• Blood supply by middle inferior and superior hypophysial arteries from the internal carotid arteries
Pituitary Gland Hormones

- Thyroid-stimulating hormone (TSH)
- Adrenocorticotropic hormone (ACTH)
- Growth hormone (GH)
- Gonadotropic hormones: Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- Antidiuretic hormone (ADH)
- Oxytocin
- Melanocyte-stimulating hormone (MSH)
- Prolactin (PRL)

Organs and tissues affected:
- Kidney tubules
- Muscles of uterus
- Melanocyte in amphibian
- Mammary glands
- Bone marrow
CLINICAL FEATURES
Local complications
- Headache
- Visual field defect
- Disconnection hyperprolactinaemia
- Diplopia (cavernous sinus involvement)
- Acute infarction/expansion (pituitary apoplexy)

Hormone excess
- Hyperprolactinaemia
  - Galactorrhoea
  - Amenorrhoea
  - Hypogonadism
- Acromegaly
  - Headache
  - Sweating
  - Change in shoe and ring size
- Cushing's
  - Weight gain
  - Bruising
  - Myopathy
  - Hypertension
  - Striae
  - Depression

Hypopituitarism
- Growth hormone
  - Lethargy
- Gonadotrophins
  - Lethargy
  - Loss of libido
  - Hair loss
  - Amenorrhoea
- ACTH
  - Lethargy
  - Postural hypotension
  - Pallor
  - Hair loss
- TSH
  - Lethargy
- Vasopressin
  - (usually post-surgical)
  - Thirst and polyuria

Macroadenoma > 10 mm diameter

Microadenoma < 10 mm diameter
Hypopituitarism: deficiency of the anterior pituitary hormones

- **CAUSES OF ANTERIOR PITUITARY HORMONE DEFICIENCY**
  - **Structural**
  - Primary pituitary tumour
    - Adenoma*
    - Carcinoma (exceptionally rare)
  - Secondary tumour (including leukaemia and lymphoma)
  - Craniopharyngioma*
  - Meningioma*
  - Chordoma
  - Germinoma (pinealoma)
  - Arachnoid cyst
  - Rathke's cleft cyst
  - Langerhans cell histiocytosis
  - Haemorrhage (apoplexy)
  - **Inflammatory/infiltrative**
  - Sarcoidosis
  - Lymphocytic hypophysitis
  - Infections, e.g. pituitary abscess, TB, syphilis, encephalitis
  - Haemochromatosis
  - **Congenital deficiencies**
  - GnRH (Kallmann's syndrome)*-gonadotrophin-releasing hormone
  - GHRH*-growth hormone-releasing hormone
  - TRH-thyrotrophin-releasing hormone
  - CRH-corticotrophin-releasing hormone
  - **Functional** Chronic systemic illness, Anorexia nervosa, Excessive exercise
  - **Other:** Head injury, *(Para-)sellar surgery*, *(Para-)sellar radiotherapy*, Post-partum necrosis (Sheehan's syndrome)
hypopituitarism

- Hypopituitarism is manifested by diminished or absent secretion of one or more PH.
- The development of sign and symptom is often slow and insidious.
- Hypo pit is either primary event caused by destruction of APG or secondary resulting from deficiency of hypothalamic SF.
- Treatment and prognosis depend on the extent of hypofunction, the underlying cause and the location of the lesion.
Hypopituitarism

- Is usually gradual and may have single hormone deficiency or multiple hormone deficiencies.

**CLINICAL FEATURES**

- **Local complications** (headache, visual field defect, diplopia, disconnection, hyperprolactinemia)

- **GH deficiency**
  - a. deficiency in children lead to short stature
  - b. deficiency in adult lead to vague non-specific symptoms, fatigue, decrease muscle mass,
Gonadotrophin H.D
(hypogonadism)

• In women
  a. before puberty primary amenorrhea and failure of puberty development
  b. after puberty 2ndary amenorrhea and regression of 2ndary sexual characteristic
  c. infertility
hypogonadism

• In men
  a. before puberty  failure of puberty development
  b. after puberty  decrease libido or impotence  loss of secondary sexual characteristic  infertility
TSH deficiency lead to secondary hypothyroidism

- Clinical feature
  - cold intolerance
  - dry skin, loss of hair
  - mental dullness
  - constipation
  - increase in wt
  - bradycardia, slow reflexes
  - hoarseness, puffiness of the face
ACTH deficiency lead to secondary adrenocortical insufficiency

- Clinical feature
  - Weakness
  - Nausea and vomiting
  - Anorexia
  - Wt loss
  - Postural hypotension
C.F

- **Local complications**: (headache, visual field defect, diplopia, disconnection of the visual pathways, hyperprolactinemia)
- **Hormones deficiency**:  
  - **GH**: (lethargy, impaired growth, muscle weakness and increased fat mass)
  - **Gonadotrophin**: (lethargy, loss of libido, hair loss, amenorrhea, gynaecomastia in male, breast atrophy in girls, decreased frequency of shaving. In both sexes axillary and pubic hair eventually become sparse or even absent and the skin becomes characteristically finer and wrinkled. Chronic anaemia may also occur)
  - **ACTH**: (postural hypotension, pallor, lethargy, hair loss)
  - **TSH**: (lethargy, frank myxoedema is rare, )
- **Growth hormone** secretion is often the earliest to be lost. Next, **gonadotrophin** (LH and FSH) secretion becomes impaired, in the male (loss of libido and), in the female (oligomenorrhea or amenorrhea). Later, in the male there may be gynaecomastia and. The next hormone to be lost is usually **ACTH**, resulting in symptoms of cortisol insufficiency. In contrast to primary adrenal insufficiency, angiotensin II-dependent zona glomerulosa function is not lost and hence aldosterone secretion maintains normal plasma potassium. However, there may be postural hypotension and a dilutional hyponatraemia for three reasons:
  - 1- Failure of vasoconstriction in the absence of cortisol results in pooling of blood in the legs on standing.
  - 2- Antidiuretic hormone (ADH) release is enhanced by hypotension and cortisol deficiency.
  - 3- Cortisol is required for normal water excretion by the kidney.
Causes of hypopituitarism

- Infarction
  - postpartum necrosis (Sheehan syndrome)
  - vascular disease
  - head trauma
- Infections
  - tuberculosis, fungi
  - pyogenic, syphilis
  - toxoplasmosis
Hypopituitarism 2

- Granulomas
  - Sarcoidosis
  - Histiocytosis
- Autoimmune lymphocytic hypophysitis
- Neoplasms involving pituitary
  - Pituitary adenoma
  - Craniopharyngioma
- Metastasis or primary carcinoma (rare)
Hypopituitarism 3

- Aneurysm of internal carotid artery
- Hemochromatosis
- Idiopathic or genetic
  - deficient production of pituitary hormone
  - synthesis of abnormal hormone
- Iatrogenic
  - stalk section
  - radiation
  - hypophysectomy
Hypopituitarism 3

- Primary hypothalamic disorders
  - tumor (craniopharyngioma)
  - granulomas (histiocytosis x)
  - genetic or idiopathic releasing H.D
  - head trauma
  - structural anomalies of hypothalamus
Laboratory Investigation

- *demonstrating low levels* of trophic hormones in the setting of low target hormone levels
- **STIMULATING TEST** GH responses to insulin-induced hypoglycemia, arginine, L-dopa, growth hormone–releasing hormone (GHRH).
- GH levels are commonly undetectable, so a choice from the range of 'stimulation' tests is required:
  - 1 hour after going to sleep
  - Frequent sampling during sleep
  - Post-exercise
  - Insulin-induced hypoglycaemia
  - Arginine (may be combined with GHRH)
  - Glucagon
  - Clonidine
- Insulin-induced hypoglycemia is contraindicated in patients with active coronary artery disease or seizure disorders.
- Corticotropin-releasing hormone (CRH) administration induces ACTH release, and administration of synthetic ACTH (cortrosyn) evokes adrenal cortisol release as an indirect indicator of pituitary ACTH reserve
- *CT & MRI*
Treatment Hormone replacement therapy, including glucocorticoids, thyroid hormone, sex steroids, growth hormone, and vasopressin, is usually safe and free of complications. Treatment regimens that mimic physiologic hormone production allow for maintenance of satisfactory clinical homeostasis. Patients in need of glucocorticoid replacement require careful dose adjustments during stressful events such as acute illness, dental procedures, trauma, and acute hospitalization.

- ACTH
  - Hydrocortisone (10–20 mg A.M.; 5–10 mg P.M.)
  - Cortisone acetate (25 mg A.M.; 12.5 mg P.M.)
  - Prednisone (5 mg A.M.; 2.5 mg P.M.)
- TSH
  - L-Thyroxine (0.075–0.15 mg daily)
- FSH/LH
- Males
  - Testosterone enanthate (200 mg IM every 2 weeks)
  - Testosterone skin patch (5 mg/d)
- Females
  - Conjugated estrogen (0.65–1.25 mg qd for 25 days)
  - Progesterone (5–10 mg qd) on days 16–25
  - Estradiol skin patch (0.5 mg, every other day)
  - For fertility: Menopausal gonadotropins, human chorionic gonadotropins
- GH
  - Adults: Somatotropin (0.1–1.25 mg SC qd)
  - Children: Somatotropin [0.02–0.05 (mg/kg per day)]
- Vasopressin
  - intranasal desmopressin (5–20 g twice daily), Oral 300–600 g qd
DIABETES INSIPIDUS (decrease or defect action of ADH)

central (neurogenic) origin when there is failure of the posterior lobe of the pituitary to secrete adequate amounts of ADH,

nephrogenic origin, caused by failure of the kidney to respond to adequate amounts of circulating ADH.

Regardless of the cause, patients are polyuric, secreting large volumes of dilute urine. The patient may pass 5-20 litres or more of urine in 24 hours. This is of low specific gravity and osmolality. This causes cellular and extracellular dehydration, stimulating thirst, which results in polydipsia. The causes of central diabetes insipidus are entirely different from those of nephrogenic diabetes insipidus

Causes of Central Diabetes Insipidus
1-Idiopathic, 2-Familial, 3-Hypophysectomy,
3-Infiltration of hypothalamus and posterior pituitary, 4-Langerhans cell histiocytosis,
5-Granulomas Infection, 6-Tumors (intrasellar and suprasellar), 8-Autoimmune

Causes of Nephrogenic Diabetes Insipidus
1-Idiopathic, 2-Familial, 3-Chronic renal disease (e.g., chronic pyelonephritis, polycystic kidney disease, or medullary cystic disease), 4-Hypokalemia, 5-Hypercalcemia, 6-Sickle cell anemia, 7-Drugs Lithium Fluoride Demeclocycline Colchicine
• **DIAGNOSES**

• **water deprivation test.** (To establish a diagnosis of diabetes insipidus, and differentiate cranial from nephrogenic causes)

• No coffee, tea or smoking on the test day

• No fluids from 0730 hrs on the morning of the test

• Attend at 0830 hrs for body weight, plasma and urine osmolality

• Record body weight, urine volume, urine and plasma osmolality and thirst score on a visual analogue scale every 2 hours for up to 8 hours

• Stop the test if the patient loses 3% of body weight

• If plasma osmolality reaches > 300 mOsm/kg and urine osmolality < 600 mOsm/kg, then administer DDAVP 2 μg i.m.

• Interpretation Diabetes insipidus is confirmed by a plasma osmolality > 300 mOsm/kg with a urine osmolality < 600 mOsm/kg

• Cranial diabetes insipidus is confirmed if urine osmolality rises by at least 50% after DDAVP

• Nephrogenic diabetes insipidus is confirmed if DDAVP does not concentrate the urine

• Primary polydipsia is suggested by low plasma osmolality at the start of the test

• Diabetes insipidus is confirmed if, in the face of elevated plasma osmolality (i.e. > 300 mOsm/kg), either ADH is not measurable in serum or the urine is not maximally concentrated (i.e. is < 600 mOsm/kg).

• **An alternative** is to.. infuse hypertonic saline (5% saline) and measure ADH secretion in response to increasing plasma osmolality

• In primary polydipsia the urine may be excessively dilute because of chronic diuresis which 'washes out' the solute gradient across the loop of Henle, but plasma osmolality is low rather than high. DDAVP (should not be administered to patients with primary polydipsia, since it will prevent excretion of water and risks severe water intoxication if the patient continues to drink fluid to excess.

• **In nephrogenic diabetes insipidus** appropriate further tests include plasma electrolytes, calcium and investigation of the renal tract ,GUE,US ,CT of abd. .......
Treatment

**Central Diabetes Insipidus.** Desmopressin acetate des-amino-des-aspartate-arginine vasopressin (desmopressin, DDAVP) a synthetic analogue of ADH, is usually administered intranasally or orally in the treatment of diabetes insipidus. Frequency of administration is determined by the severity of the disease. Adequacy of replacement is monitored by regular measurement of serum osmolarity and sodium. In sick patients, DDAVP is given by intramuscular injection. The dose of DDAVP required to keep the patient in water balance must be determined by measuring plasma sodium concentrations and/or osmolality. The principal hazard is excessive treatment resulting in water intoxication and hyponatraemia. Inadequate treatment results in thirst and a compensatory increase in fluid intake in the conscious patient. The ideal dose prevents nocturia, but allows a degree of polyuria from time to time before the next dose (e.g. DDAVP nasal dose 5 µg in the morning and 10 µg at night

**Nephrogenic Diabetes Insipidus.** underlying disease should be reversed. Specific treatment of nephrogenic diabetes insipidus aims to maintain a state of mild sodium depletion with reduction in the solute load on the kidneys and subsequent increased proximal tubular reabsorption. Diuretics coupled with dietary salt restriction can be used to achieve this goal.

). Polyuria in nephrogenic diabetes insipidus is improved by thiazide diuretics (e.g. bendroflumethiazide 2.5-5 mg/day), amiloride (5-10 mg/day) and NSAIDs (e.g. indometacin 15 mg 8-hourly), although the last of these carries a risk of reducing glomerular filtration rate.
Pituitary tumors

- Nearly always benign account for 10% of intracranial neoplasm
- Pituitary microadenoma is intrasellar adenoma less than 1 cm in diameter
- Pituitary macroadenoma are those larger than 1 cm in diameter
## Type of pituitary tumors

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prl secreting</td>
<td>26%</td>
</tr>
<tr>
<td>nonfunctioning</td>
<td>23%</td>
</tr>
<tr>
<td>ACTH secreting</td>
<td>15%</td>
</tr>
<tr>
<td>GH-secreting</td>
<td>14%</td>
</tr>
<tr>
<td>plurihormonal</td>
<td>12%</td>
</tr>
<tr>
<td>LH or FSH secreting</td>
<td>8%</td>
</tr>
<tr>
<td>TSH-secreting</td>
<td>1%</td>
</tr>
</tbody>
</table>
Clinical presentation of pituitary tumours

- Hormone hypersecretion
- Space occupying lesion
  - Headaches
  - Visual loss (field defect)
- Hormone deficiency states
  - Interference with surrounding normal pituitary
Tumours of the anterior pituitary can cause syndromes of hormone excess

- GH: Acromegaly
- ACTH: Cushing’s disease
- TSH: Secondary thyrotoxicosis
- LH/FSH: (Non-functioning pituitary tumour)
- PRL: Prolactinoma
Treatment of P.T

• Surgical
  Transfrontal or transsphenoidal

• Radiological
  Conventional irradiation, heavy particle I

• Medical
  Dopamine agonist (bromocriptin)
  Somastatin analog (octreotid)
Acromegaly is caused by growth hormone (GH) secretion from a pituitary tumour, usually a macroadenoma. The Clinical features include:

- Headache
- Enlargement of lips, nose, and tongue
- Cardiomyopathy
- Cardiovascular disease (2–3 × T)
- Hypertension
- Enlargement of liver
- Enlargement of hands
- Arthropathy
- Carpal tunnel syndrome
- Skull growth—prominent supraorbital ridges with large frontal sinuses
- Prognathism (growth of lower jaw)
- Increased sweating
- Thickened skin
- IGT (25%)/type 2 diabetes (10%)
- Colonic cancer (2–3 × T)
- Myopathy
- Enlargement of feet
- Increased heel pad thickness
manifestations of GH and IGF-I hypersecretion are indolent and often are not clinically diagnosed for 10 years or more.

- frontal bossing, increased hand and foot size, mandibular enlargement with prognathism, and widened space between the lower incisor teeth. In children and adolescents, initiation of GH hypersecretion prior to epiphyseal long bone closure is associated with development of pituitary gigantism. Soft tissue swelling results in increased heel pad thickness, increased shoe or glove size, ring tightening, characteristic coarse facial features, and a large fleshy nose. hyperhidrosis, deep and hollow-sounding voice, oily skin, arthropathy, kyphosis, carpal tunnel syndrome, proximal muscle weakness and fatigue, acanthosis nigricans, and skin tags. Generalized visceromegaly occurs, including cardiomegaly, macroglossia, and thyroid gland enlargement.
1.28 Overbiting lower teeth

1.29 Prognathism

1.30 Normal and acromegalic hands

1.31 Large, square feet

1.32 Acromegalic skin fold

1.33 Normal skinfold
• GH excess may cause Coronary heart disease, cardiomyopathy with arrhythmias, left ventricular hypertrophy, decreased diastolic function, and hypertension occur in about 30% of patients.

• Upper airway obstruction with sleep apnea occurs in more than 60% of patients and is associated with both soft tissue laryngeal airway obstruction and central sleep dysfunction.

• Diabetes mellitus develops in 25% of patients with acromegaly, and most patients are intolerant of a glucose load (as GH counteracts the action of insulin).

• increased risk of colon polyps and mortality from colonic malignancy; polyps are diagnosed in up to one-third of patients.

• Overall mortality is increased about threefold and is due primarily to cardiovascular and cerebrovascular disorders and respiratory disease.
• Laboratory Investigation

1- Serum IGF-I levels are elevated in acromegaly. Consequently, an IGF-I level provides a useful laboratory screening measure when clinical features raise the possibility of acromegaly. Due to the pulsatility of GH secretion, measurement of a single random GH level is not useful for the diagnosis or exclusion of acromegaly and does not correlate with disease severity.

2- The diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to <1 g/L within 1–2 h of an oral glucose load (75 g). About 20% of patients exhibit a paradoxical GH rise after glucose.

3- PRL should be measured, as it is elevated in ~25% of patients with acromegaly patients due to co-secretion of prolactin from the tumour.

4- The rest of pituitary function should be investigated. Thyroid function, gonadotropins, and sex steroids may be attenuated because of tumor mass effects.

5- Screening for colonic neoplasms with colonoscopy

6- CT & MRI
• **Management**

  • **Surgical** Trans-sphenoidal surgery is usually the first line of treatment and may result in cure of GH excess, especially in patients with microadenomas. More often, surgery serves to debulk the tumour and further second-line therapy is required, according to post-operative imaging and glucose tolerance test results.

  • **Radiotherapy** External radiotherapy is usually employed as second-line treatment if acromegaly persists after surgery, to stop tumour growth and lower GH levels. However, GH levels fall slowly (over many years) and there is a risk of hypopituitarism.

  • **Medical therapy** In patients with persisting acromegaly after surgery, most centres employ to lower GH levels to < 5 mU/l. Medical therapy may be discontinued after several years in patients who have received radiotherapy.

    • **1-Somatostatin analogues** (e.g. octreotide or lanreotide) can be administered as slow-release injections every few weeks. In some centres, somatostatin analogues are used as primary therapy for acromegaly, as they can cause modest tumour shrinkage in a proportion of patients.

    • **2-Dopamine agonists** Oral dopamine agonists (cabergoline or bromocriptine) are less potent in lowering GH but may be helpful, especially in patients with associated prolactin excess.

    • **3-A peptide GH receptor antagonist** (*pegvisomant*). 'Daily subcutaneous pegvisomant improves IGF-1 levels and symptoms in patients with acromegaly.' is available for daily self-injection in patients whose GH concentrations fail to suppress following somatostatin analogue therapy.
• **Hyperprolactinemia**

• Normal adult serum PRL levels are about 10–25 g/L in women and 10–20 g/L in men. PRL secretion is pulsatile, with the highest secretory peaks occurring during sleep.

• (Peak serum PRL levels up to 30 g/L) occur between 4:00 and 6:00 A.M. The circulating half-life of PRL is about 50 min.

• Hyperprolactinemia is the most common pituitary hormone hypersecretion syndrome in both men and women. PRL-secreting pituitary adenomas (prolactinomas) are the most common cause of PRL levels >100 g/L. Microadenomas are classified as <1 cm in diameter and do not usually invade the parasellar region. Macroadenomas are >1 cm in diameter and may be locally invasive and impinge on adjacent structures. The female:male ratio for microprolactinomas is 20:1, whereas the gender ratio is near 1:1 for macroadenomas.
• Etiology of Hyperprolactinemia

I. Physiologic hypersecretion
• Pregnancy, Lactation, Chest wall stimulation, Sleep, Stress

II. Hypothalamic—pituitary stalk damage
• Tumor (Craniopharyngioma, Suprasellar pituitary mass, Meningioma, Dysgerminoma, Metastases)
• Empty sell, Lymphocytic hypophysitis, Adenoma with stalk compression, Granulomas, Rathke's cyst, Irradiation, Traum Pituitary stalk section, Suprasellar surgery

III. Pituitary hypersecretion
• Prolactinoma, Acromegaly

IV. Systemic disorder
Chronic renal failure, Hypothyroidism, Cirrhosis, Epileptic seizures

V. Drug-induced hypersecretion
• Dopamine receptor blockers: Phenothiazines: chlorpromazine, perphenazine
• Butyrophenones: haloperidol, Thioxanthenes, Metoclopramide
• Dopamine synthesis inhibitor: Methyldopa
• Catecholamine depletors: Reserpine, Opiates
• H₂ antagonists, Cimetidine, ranitidine
• Imipramines
• Amitriptyline, amoxapine
• Fluoxetine
• Calcium channel blockers: Verapamil
• Hormones: Estrogens, Antiandrogens
• **Presentation and Diagnosis**

1-, Women usually present with amenorrhea, infertility, and galactorrhea (galactorrhea present in up to 80% of hyperprolactinemic women). If the tumor extends outside of the sella, visual field defects or other mass effects may be seen.. If hyperprolactinemia develops prior to menarche, primary amenorrhea results

2-In men with hyperprolactinemia, diminished libido, infertility, or visual loss (from optic nerve compression) are the usual presenting symptoms. Gonadotropin suppression leads to reduced testosterone, impotence, and oligospermia. True galactorrhea is uncommon in men with hyperprolactinemia.

3-If the disorder is longstanding, secondary effects of hypogonadism are evident, including osteopenia (particularly when associated with pronounced hypoestrogenemia.), reduced muscle mass, and decreased beard growth. weight gain, and mild hirsutism

4-central CNS compression including headaches and visual defects
• **Laboratory Investigation**

• 1-Basal, fasting morning PRL levels (normally <20 g/L) should be measured to assess hypersecretion. Because hormone secretion is pulsatile and levels vary widely in some individuals with hyperprolactinemia, both false-positive and false-negative results may be encountered.

• Hypothyroidism should be excluded by measuring TSH and T₄ levels.

• 4-investigation for other medical causes of PRL
  
  Eg: CRF  CXR

• 5-CT & MRI
• **TREATMENT**

• **Oral dopamine agonists** *(cabergoline or bromocriptine)* are the mainstay of therapy for patients with micro- or macroprolactinomas. Dopamine agonists suppress PRL secretion and synthesis as well as lactotrope cell proliferation.

• About 20% of patients are resistant to dopaminergic treatment;

• **1-Bromocriptine**

• In microadenomas bromocriptine rapidly lowers serum prolactin levels to normal in up to 70% of patients, decreases tumor size, and restores gonadal function.

• In macroadenomas, prolactin levels are also normalized in 70% of patients and tumor mass shrinkage (50%) is achieved in up to 40% of patients.

• Therapy is initiated by administering a low bromocriptine dose *(0.625–1.25 mg)* at bedtime with a snack, followed by gradually increasing the dose. Most patients are successfully controlled with a daily dose of 7.5 mg *(2.5 mg tid)*.
2- **cabergoline** is a long-acting dopamine agonist. The drug effectively suppresses PRL for >14 days after a single oral dose and induces prolactinoma shrinkage in most patients. **Cabergoline (0.5 to 1.0 mg twice weekly)** achieves normoprolactinemia and resumption of normal gonadal function in ~80% of patients with microadenomas; galactorrhea improves or resolves in 90% of patients. Cabergoline normalizes PRL and shrinks ~70% of macroprolactinomas. Mass effect symptoms, including headaches and visual disorders, usually improve dramatically within days after cabergoline initiation; improvement of sexual function requires several weeks of treatment but may occur before complete normalization of prolactin levels. After initial control of PRL levels has been achieved, cabergoline should be reduced to the lowest effective maintenance dose.

- In ~5% of treated patients, hyperprolactinemia may resolve and not recur when dopamine agonists are discontinued after long-term treatment. Cabergoline may also be effective in patients resistant to bromocriptine. Adverse effects and drug intolerance are encountered less commonly than with bromocriptine.

- **Other Dopamine Agonists**

  - These include **pergolide mesylate**, an ergot derivative with dopaminergic properties; **lisuride**, an ergot derivative; and **quinagolide** (CV 205-502, Norprolac), a nonergot oral dopamine agonist with specific D₂ receptor activity.
Side effects of dopamine agonists include:
- constipation, nasal stuffiness, dry mouth, nightmares, insomnia, and vertigo; decreasing the dose usually alleviates these problems.
- Nausea, vomiting, and postural hypotension with faintness may occur in ~25% of patients after the initial dose. These symptoms may persist in some patients. In general, fewer side effects are reported with cabergoline. For the approximately 15% of patients who are intolerant of oral bromocriptine, cabergoline may be better tolerated.
- Auditory hallucinations, delusions, and mood changes have been reported in up to 5% of patients.
- Rare reports of leukopenia, thrombocytopenia, pleural fibrosis, cardiac arrhythmias, and hepatitis have been described.

Surgery:
- 2-surgery: Indications for surgical adenoma debulking include dopamine resistance or intolerance, or the presence of an invasive macroadenoma with compromised vision that fails to improve after drug treatment. Initial PRL normalization is achieved in about 70% of microprolactinomas after surgical resection, but only 30% of macroadenomas can be successfully resected.
- Follow-up studies have shown that hyperprolactinemia recurs in up to 20% of patients within the first year after surgery; long-term recurrence rates exceed 50% for macroadenomas.
- 3- Radiotherapy for prolactinomas is reserved for patients with aggressive tumors that do not respond to maximally tolerated dopamine agonists and/or surgery.
ELEVATED PROLACTIN LEVELS

Exclude secondary causes of hyperprolactinemia
MRI evidence for pituitary mass

Symptomatic Prolactinoma

Microadenoma
- Titrate dopamine agonist
  - Serum PRL
    - <20: Maintenance Rx
    - 20–50: Reassess diagnosis
    - >50 (μg/L): Increase dose
    - >50 (μg/L): Consider Surgery

Macroadenoma
- Test visual fields
- Test pituitary reserve function
- Titrate dopamine agonist
  - Repeat MRI within 4 months
    - No tumor shrinkage or tumor growth or persistent hyperprolactinemia
- Tumor shrinkage and prolactin normalized
  - Monitor PRL and repeat MRI annually
• CRANIOPHARYNGIOMA
• Abenign tumours that develop in cell rests of Rathke's pouch, and may be located within the sella turcica, or commonly in the suprasellar space. They are often cystic and/or calcified
• In young people, they are diagnosed more commonly than pituitary adenomas. They may present with pressure effects on adjacent structures, hypopituitarism and/or cranial diabetes insipidus. In addition, other clinical features that are directly related to hypothalamic damage may also occur. These include hyperphagia and obesity, loss of the sensation of thirst and disturbance of temperature regulation
• Surgery is unlikely to be curative, and radiotherapy is usually given
• Unfortunately, craniopharyngiomas often recur, requiring repeated surgery. They often cause considerable morbidity, usually from hypothalamic obesity, water balance problems and/or visual failure.
MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES

- **MEN 1 (Werner's syndrome)**
  - Primary hyperparathyroidism
  - Pituitary tumours
  - Pancreatic neuro-endocrine tumours (e.g. insulinoma, gastrinoma)

- **MEN 2 (Sipple's syndrome)**
  - Primary hyperparathyroidism
  - Medullary carcinoma of thyroid
  - Phaeochromocytoma
  - In addition, in MEN 2b syndrome there are phenotypic changes (including marfanoid habitus, skeletal abnormalities, abnormal dental enamel, multiple mucosal neuromas)
* Type 1 (APECED)
  - Addison's disease
  - Hypoparathyroidism
  - Type 1 diabetes
  - Primary hypothyroidism
  - Chronic mucocutaneous candidiasis
  - Nail dystrophy
  - Dental enamel hypoplasia

**Type 2 (Schmidt's syndrome)**
  - Addison's disease
  - Primary hypothyroidism
  - Graves' disease
  - Pernicious anaemia
  - Primary hypogonadism
  - Type 1 diabetes
  - Vitiligo
  - Coeliac disease
  - Myasthenia gravis
• **Pituitary Apoplexy**
  - Acute intrapituitary hemorrhagic can cause substantial damage to the pituitary and surrounding sellar structures.
  - may occur spontaneously in a preexisting adenoma;
  - post-partum (Sheehan's syndrome); or in association with diabetes, hypertension, sickle cell anemia, or acute shock. The hyperplastic enlargement of the pituitary during pregnancy increases the risk for hemorrhage and infarction.
  - Apoplexy is an endocrine emergency that may result in severe hypoglycemia, hypotension, central nervous system (CNS) hemorrhage, and death. Acute symptoms may include severe headache with signs of meningeal irritation, bilateral visual changes, ophthalmoplegia, and, in severe cases, cardiovascular collapse and loss of consciousness.
  - (CT) or MRI may reveal signs of intratumoral or sellar hemorrhage, with deviation of the pituitary stalk and compression of pituitary tissue.
  - Patients with no evident visual loss or impaired consciousness can be observed and managed conservatively with high-dose glucocorticoids. Those with significant or progressive visual loss or loss of consciousness require urgent surgical decompression
  - Hypopituitarism is very common after apoplexy