Diseases of the pituitary Gland

diseases of the endocrine system

can be due to

MASS EFFECT

Mass effect means an enlargement of the gland which can compress adjacent structures.

can be due to

non- neoplastic no mutation & not clonal.

hyperplasia

neoplastic all cells are mutated---> monoclonal

adenoma

- In clinical practice, 10% of intracranial neoplasms are pituitary adenomas (not rare).
- Peak.. 4th to 6th decades.
- Mostly single lesions= **solitary**
- Can be divided into micro and macro adenomas according to size.. Cutoff point: 1cm.

Can be

secretory

in this case the level of that hormone will increase
= hyperpituitarism

non-secretory

the level of pituitary hormones is unaffected = resulting in **normal hormonal levels**
- HOWEVER, if a non-secretory adenoma enlarges to the extent that it **compresses** the surrounding normal pituitary tissue, then the level of hormone secretion from the normal tissue will be **decreased**, resulting in **hypopituitarism**

Types

- **Prolactinomas**.. 20-30%.. **The most common**

These are adenomas that produce prolactin.= hyperprolactinemia
Hyperprolactinemia causes:
a. Amenorrhea (loss of menstrual cycle) and galactorrhea (milk production).
b. Loss of libido and infertility
- Prolactinomas usually are diagnosed at an earlier stage in women of reproductive age than in other persons ..
Because they are more likely to have obvious symptoms

- **Null cell adenoma**… 20%.. Non-secretory non-functional

- **ACTH cell adenoma**.. 10-15%

may be: 1.Clinically silent OR
2. May cause hypercortisolism= increased cortisol , manifested clinically as Cushing syndrome
-Large, clinically aggressive corticotroph cell adenomas may develop after surgical removal of the adrenal glands for treatment of Cushing syndrome , this condition is **Nelson syndrome.**
The reason is the metabolic demands and the loss of the feedback mechanism.
*Because ACTH is synthesized as part of a larger pro-hormone substance that includes melanocyte-stimulating hormone (MSH), hyperpigmentation may be a feature.

- **Gonadotroph cell adenoma**… 10-15%

Can be difficult to recognize because they secrete hormones inefficiently, and the secretory products usually do not cause a recognizable clinical syndrome

- **GH cell adenoma**… 5%

If a growth hormone-secreting adenoma occurs before the epiphyses closes (in children) it causes gigantism.
- gigantism: generalized increase in body size, with disproportionately long arms and legs If elevated levels of growth hormone persist, or develop after closure of the epiphyses, affected persons (adults) develop acromegaly, in which:
1. Growth is most conspicuous in soft tissues, skin, and viscera, and in the bones of the face (coarse facial features), hands, and feet
2. Enlargement of the jaw (not due to bone enlargement but for soft tissue enlargement) results in its protrusion with separation of the teeth.
3. Enlarged hands and feet (bigger shoe size) with broad, sausage-like fingers

- **Mixed GH/Prolactn adenoma**.. 5%
- **TSH cell adenoma**… 1%.. **Least common**
- **pleurihormonal**… 15% (more than one type of hormone)

carcinoma

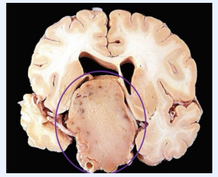
rare and usually **non-secretory.**

- are exceedingly rare, and in addition to **local extension** beyond the sella turcica, these tumors virtually always demonstrate **distant metastases**.
- As a general rule, Most endocrine carcinomas are diagnosed depending on behavior (presence of metastases) and not on histological appearance. i:e under the microscope, **adenoma and carcinoma can look similar**.. You need to know the clinical information and check if the patient has metastatic disease or infiltration (invasion) ---> this is called **behavior**, in order to call the lesion metastatic.

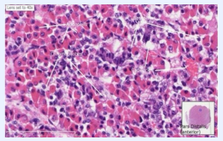
Morphology

Gross features

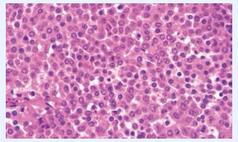
well-circumscribed, encapsulated & usually soft lesion that, if small, is confined by the sella turcica.



On microscope Monomophic: one cell type.. All cells look similar, whereas in the normal pituitary several cell types exist.



Polymorphic: chromophils & chromophobes (normal)



monotonous/monoclonal: neoplasm (mostly adenoma)

Disordered hormonal production

Hyperpituitarism **Hypopituitarism**

IMPORTANT NOTE: there is no relation between mass effect and hormonal abnormalities.
- Patients might have a mass with normal, low or high hormonal secretion.
- Also hormone overproduction is not always associated with a mass

Hyperpituitarism
- MOST COMMON CAUSE: functional **adenoma**.
- Other causes:
- **Hyperplasia** (non-neoplastic enlargement of the pituitary)
- **Carcinoma** is rarely secretory, but if they are secretory, it will become hyperpituitarism.
- Secretion of pituitary hormones by **nonpituitary tumors**. (**Ectopic** production of pituitary hormones)
- **Hypothalamic disorders.**

Hyporpituitarism

Occurs if there is a Loss of at least 75% of the anterior pituitary
Causes: anything that destroys the pituitary
a. **Congenital absence** (exceedingly rare)
b. **Hypothalamic tumors**, associated with posterior pituitary dysfunction.
C . **Nonfunctioning pituitary adenomas** .. Most common/ remember that this occurs when the adenoma compresses normal pituitary tissue and affects its function.
d. **Ischemic necrosis** of the anterior pituitary, e:g Sheehan syndrome
Sheehan syndrome, or **postpartum necrosis** of anterior pituitary, is the most common form of clinically significant ischemic necrosis of the anterior pituitary.
- During pregnancy, the anterior pituitary enlarges considerably, because of an increase in the size and number of prolactin-secreting cells and this physiologic enlargement is not accompanied by an increase in blood supply from the low-pressure portal venous system.
- The enlarged gland is thus vulnerable to ischemic injury, especially in women who experience significant hemorrhage and hypotension during the postpartum period
e. **Ablation** of the pituitary by surgery or irradiation
f. **Inflammatory lesions** such as sarcoidosis or tuberculosis
g. **Trauma and Metastatic neoplasms** involving the pituitary

End organ resistence to the effect of the hormone

the gland & its hormonal secretion is normal, also no masses are present, but the targeted organ is not responding-results are the same as the absence of the hormone (type 2 Diabetes)

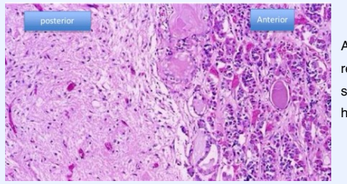
Small, bean shaped structure that lies at the base of the brain within the sella turcica, a saddle-shaped depression in the body of shenoid bone of the skull

Pituitary gland

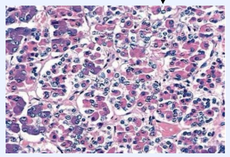
ANTERIOR LOBE **POSTERIOR LOBE**

	ANTERIOR PITUITARY	POSTERIOR PITUITARY
histology	Epithelial cells	Glial cells and neuronal axons
Embryological origin	Oral mucosa (epithelial in origin)	Neural crest (neural in origin)
Hormones secreted	TSH, PRL, ACTH, GH, FSH , LH.	ADH and oxytocin (*synthesized in hypothalamus but stored in posterior pituitary*)

Posterior: Stores hormones only.



Anterior: release & synthesize hormones.



POSTERIOR PITUITARY SYNDROMES.

ADH deficiency

causes diabetes insipidus (DI) characterized by excessive urination (polyuria) - fresh water without sodium so the patient will have hypernatremia - caused by an inability of the kidney to properly resorb water from the urine
SO: patients are thirsty and have polydipsia= excessive drinking
Diabetes insipidus can result from several **causes**,
a. Head trauma, Neoplasms,
b. Inflammatory disorders and surgical procedures of the hypothalamus and pituitary
c. The condition may be idiopathic.
Note:- Diabetes insipidus from ADH deficiency is designated as central DI , to differentiate it from nephrogenic DI
In Diabetes Insipidus, fresh water is lost directly due to impaired ADH function. In Diabetes Mellitus, water is lost indirectly, dragged out with glucose in the urine (osmotic diuresis)
The clinical manifestations of DI include:
a. The excretion of large volumes of dilute urine with an inappropriately low specific gravity
b. Serum sodium and osmolality are increased as a result of excessive renal loss of free water resulting in thirst and polydipsia
- Patients who can drink water generally can compensate for urinary losses; patients who are bedridden, or are limited in their ability to obtain water may develop life threatening dehydration

Increased ADH= Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

In (SIADH) ADH excess is caused by several extracranial and intracranial disorders.
- This condition leads to resorption of excessive amounts of free water, with resultant hyponatremia.
- The most common causes of SIADH include;
a. The secretion of ectopic ADH by malignant neoplasms
b. Non-neoplastic diseases of the lung
c. local injury to the hypothalamus or neurohypophysis.
- The clinical manifestations of SIADH are dominated by hyponatremia,
cerebral edema, and resultant neurologic dysfunction

Diseases of the thyroid Gland pt.1&2

Diseases of thyroid gland

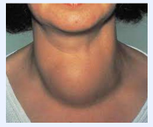
- **Inflammation** (Could cause)
  - Mass effect
  - • Hyperthyroidism (thyrotoxicosis).
  - • Hypothyroidism.
- **Goiters**
  - Mass effect
- **Graves** (Could cause)
  - Mass effect Rarely
  - • Hyperthyroidism (thyrotoxicosis).
- **Neoplasms**
  - Benign
  - Malignant

Thyroid diseases

MASS EFFECT

enlargement can be due to: inflammation, neoplasms, autoimmune diseases.

Thyroid enlargement, due to any cause is called: **goiter**.



enlarged gland doesn't necessarily mean increased hormone production.

HYPERTHYROIDISM

Causes

- Diffuse toxic hyperplasia (**Graves disease**)
- Hyperfunctioning (Toxic) **multinodular goiter**
- Hyperfunctioning (toxic) **adenoma**
- TSH-secreting **pituitary adenoma** (rare)
- **Ectopic secretion** of thyroid hormones.. So thyroid function is normal.

Clinical manifestations

- Thyroid hormones increase basal metabolic rate, increase appetite, increase breakdown of fat and glucose, increase sweating
- increase heart rate, cause hypertension
- Increase body temperature < heat intolerance >
- Constitutional symptoms : warm flushed skin, heat intolerance and excessive sweating , weight loss despite increased appetite.
- Malabsorption and diarrhoea (because of increased intestinal motility)
- Tachycardia, heart failure due to aggravation of pre-existing heart disease
- Nervousness, tremor, and irritability.
- Proximal muscle weakness (thyroid myopathy)

Thyroid storm

• Abrupt onset of severe hyperthyroidism
• This condition occurs most commonly in individuals with Graves disease, and it is a medical emergency because significant numbers of untreated patients die of **cardiac arrhythmias**
• Usually occurs in **untreated or undertreated people**

People with hyperthyroidism may develop thyroid storm after experiencing one of the following:
• trauma. • surgery. • severe emotional distress
• stroke. • diabetic ketoacidosis
• congestive heart failure. • pulmonary embolism

make sure you control their thyroid hormone levels if they have one of the above. If they undergo surgery make sure you correct their hormonal levels before the surgery

HYPOTHYROIDISM

Causes

Primary causes

- Worldwide, the most common cause of hypothyroidism is dietary deficiency of iodine.
- In most developed countries, autoimmune diseases predominate such as Hashimoto thyroiditis
- Genetic defects such as Thyroid dysgenesis or congenital biosynthetic defect (dyshormogentic goitre)

Secondary causes

- Pituitary disorder
- hypothalamic disorder

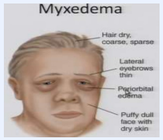
Clinical manifestations

The difference of features of hypothyroidism among these age groups is cuz thyroid hormones are vital early in life for brain and body development.

- **Cretinism** — Hypothyroidism in **infancy and early childhood**
  - Endemic cretinism — in **dietary iodine deficiency** is endemic, including mountainous areas (the Himalayas)
  - Sporadic cretinism — Caused by enzyme defects (genetics) that interfere with thyroid hormone synthesis
  - **Clinical features**
    - Impaired development of skeletal system- short stature,
    - Coarse facial features, protruding tongue, umbilical hernia.
    - Central nervous system problems , with mental retardation
- **Myxedema (Gull syndrome)** — hypothyroidism in **older children and adults.**

Clinical features

- Cold intolerance and obesity
- Generalized apathy and mental sluggishness that in the early stages of disease may mimic depression
- Broadening and coarsening of facial features
- Enlargement of the tongue, and deepening of the voice
- Bowel motility is decreased, resulting in constipation.
- Pericardial effusions are common; in later stages, the heart is enlarged, and heart failure may supervene.
- Mucopolysaccharide-rich edematous fluid accumulates in skin, subcutaneous tissue, and number of visceral sites



Diseases of thyroid gland

- **Inflammation**
- **Goiters**
  - SINGLE NODULE
    - Cold
    - Hot
  - Multinodular goiters typically are **hormonally silent** (no hyperthyroidism)
  - however, 10% of patients can manifest with thyrotoxicosis due to the development of **autonomous nodules** producing hormone independent of TSH stimulation and this condition, called toxic multinodular goiter or Plummer syndrome
  - MULTINODULAR
    - Toxic — "Plummer syndrome"
    - Non-toxic
  - DIFFUSE
    - Toxic — "graves"
    - Non-toxic
- **Graves**
- **Neoplasms**

DIFFUSE AND MULTINODULAR GOITER

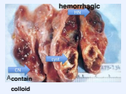
Mechanism

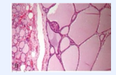
- The goiters reflect **impaired synthesis** of thyroid hormone often caused by **dietary iodine deficiency** and this leads to to a **compensatory rise in the serum TSH**, which in turn causes **hyperplasia** of the follicular cells and, ultimately, gross enlargement of the thyroid gland .

Types

- **Endemic goiter**
  Occurs in geographic areas where the soil, water, and food supply contain ***little iodine***.
  - The term endemic is used when goiters are present in **more than 10% of the population** in a given region.
  - Such conditions are common in mountainous areas of the world, including the Himalayas and the Andes but with increasing availability of iodine supplementation, the frequency and severity of endemic goiter have declined
- **Sporadic goiter**
  Less common than endemic goiter.
  - more **common in females than in males**, with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T4.
  - It may be caused by several conditions, including the:
  a. Ingestion of substances that interfere with thyroid hormone synthesis , such as excessive calcium and vegetables such as cabbage, cauliflower, sprouts, .
  b. Hereditary enzymatic defects that interfere with thyroid hormone synthesis (dyshormonogenetic goiter).
  -In most cases, the cause of sporadic goiter is not apparent.

MORPHOLOGY

- Gross (macroscopic) features
  Initially, the gland is **diffusely and symmetrically** enlarged (diffuse goiter) but later on it becomes **multinodular goiter.**
  Multinodular goiters cause multiloculated, asymmetrically enlarged glands. Old lesions often show fibrosis, hemorrhage, calcification
  

- Microscopic examination
  
  a. The follicular **epithelium** may be **hyperplastic** in the early stages of disease or **flattened and cuboidal** during periods of involution.
  b. **Colloid is abundant** in the latter periods (colloid goiter).
  c. With time, **recurrent episodes of hyperplasia** and **involution** produce a more irregular enlargement of thee thyroid, termed multinodular goiter and virtually all long-standing diffuse goiters convert into multinodular goiters.

Clinical Features

a. The dominant features are ***mass effects*** of the goiter
b. may cause airway **obstruction**, **dysphagia**, and **compression** of large vessels in the neck and upper thorax
c. The incidence of malignancy in long-standing multinodular goiters is low (less than 5%) but not zero and **concern for malignancy arises with goiters** that demonstrate **sudden changes in size or **associated symptoms (hoarseness)

Diseases of thyroid gland

Inflammation | Goiters | Graves | Neoplasms

Types

Chronic Lymphocytic (Hashimoto) Thyroiditis

- Is the most common cause of **hypothyroidism** in areas of the world where iodine levels are sufficient.
- It is characterized by gradual thyroid failure secondary to **autoimmune destruction** of the thyroid gland (genetic predisposition)
- It is most prevalent between the ages of 45 and 65 years and is more common in women than in men

*NOTE: ALL THYROID DISEASES ARE MORE IN WOMEN

- It can occur in children and is a major cause of non-endemic goiter in children

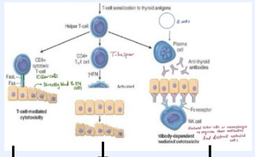
A significant **genetic component** is supported by the

a. Concordance of disease in 40% of monozygotic twins

b. the presence of circulating antithyroid antibodies in 50% of asymptomatic siblings of affected patients

PATHOGENESIS

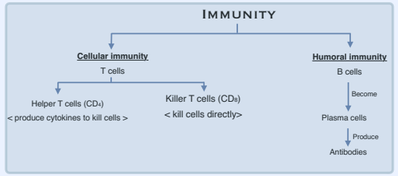
Recall



T cell mediated cytotoxicity.

Cytokine-mediated cell death: Excessive T cell activation leads to the production of inflammatory cytokines such as IFN-γ in the thyroid with resultant recruitment and activation of macrophages and damage to follicles .

Binding of anti-thyroid antibodies (antithyroglobulin, and antithyroid peroxidase antibodies), followed by antibody- dependent cell-mediated cytotoxicity



Clinically

1. **Painless diffuse thyroid enlargement** associated with some degree of hypothyroidism.
2. - In the usual clinical course, hypothyroidism develops gradually; however, it may be ***preceded by transient thyrotoxicosis*** due to disruption of thyroid follicles ,and secondary release of thyroid hormones (hashitoxicosis).

at the beginning of the disease the destruction by autoimmune antibodies might cause increased release of thyroid hormones from the destructed follicles but later there is so much destruction and no new colloid is formed, resulting in hypothyroidism

3. Patients with Hashimoto thyroiditis often :
1. Have other autoimmune diseases
2. Are at increased risk for the development of B cell **non-Hodgkin lymphomas** within the thyroid gland.

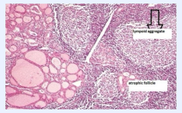
Morphology

Gross(macroscopic) features

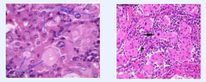
Diffuse and **symmetric** enlargement of the thyroid

Microscopic examination

- Infiltration by small lymphocytes, plasma cells, and well-developed germinal centers
- The thyroid follicles are atrophic



- Some follicles are lined by epithelial cells with abundant **eosinophilic**, cytoplasm, termed **Hürthle cells** and these Hurthle cells have numerous mitochondria



Subacute *Granulomatous* (de Quervain) Thyroiditis

- Is much less common than Hashimoto disease
- Is most common between the ages of 30 and 50 and,
- More frequently in women than in men.
- Is believed to be caused by a **viral infection** and a majority of patients have a history of an upper respiratory infection just before the onset of thyroiditis.

Clinical Features

-Acute onset characterized by neck **pain** (with swallowing)
- Fever, malaise (tiredness), and variable enlargement of the thyroid.
- Transient hyperthyroidism may occur as a result of disruption of follicles and release of excessive hormones.
- The leukocyte count is increased.
- With progression of disease and gland destruction, a transient hypothyroid phase may ensue.
- The condition typically is self-limited, with most patients returning to a euthyroid state within 6 to 8 weeks

Morphology

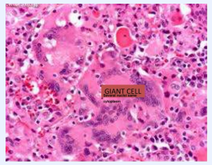
Gross (macroscopic) features

The gland has **intact capsule**, and may be unilaterally or bilaterally **enlarged**.

Microscopic examination

- Disruption of thyroid follicles, with extravasation of colloid leading to a **neutrophilic infiltrate**, which is replaced by lymphocytes, plasma cells, and macrophages.
- The extravasated colloid provokes a **granulomatous reaction** with giant cells that contain fragments of colloid.

• Granuloma: an aggregate of histiocytes, some of which fuse to form giant cells.
• Giant cell: a large cell with abundant cytoplasm and multiple nuclei.



- Healing occurs by resolution of inflammation and fibrosis.

Subacute *Lymphocytic* Thyroiditis

- Also is known as **silent or painless thyroiditis**
- And in a subset of patients the onset of disease follows - pregnancy (**postpartum thyroiditis**).
- Most likely to be **autoimmune** because circulating antithyroid antibodies are found in a majority of patients
- It mostly affects **middle-aged women**, who present with a painless neck mass or features of thyrotoxicosis

Riedel Thyroiditis

A **rare** disorder of unknown etiology,
- Characterized by **extensive fibrosis** involving the thyroid and adjacent structures simulating a thyroid neoplasm
- May be associated with idiopathic fibrosis in other parts of the body, such as the retroperitoneum
- The presence of circulating antithyroid antibodies in most patients suggests an **autoimmune etiology**

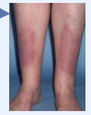
Diseases of thyroid gland

The most common cause of **endogenous hyperthyroidism** with a peak incidence in women between the ages of 20 and 40.

Inflammation | Goiters | Graves | Neoplasms

Triad of manifestations

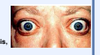
- Thyrotoxicosis, All patients
- Localized, infiltrative dermopathy (**pretibial myxedema**), minority of cases and involves the skin overlying the shins, and manifests as scaly thickening



- Infiltrative ophthalmopathy with resultant **exophthalmos** in 40% of patients

Exophthalmos is the result of increased volume of the retro-orbital connective tissues by
1. Marked infiltration of T cells with inflammatory edema
2. Accumulation of glycosaminoglycans
3. Increased numbers of adipocytes (fatty infiltration).

- These changes displace the eyeball forward, potentially intertering with the function of the extraocular muscles
- Exophthalmos may persist after successful treatment of the thyrotoxicosis, and may result in corneal injury.



PATHOGENESIS

Genetic factors are important in the causation of Graves disease, the incidence is increased in relatives of affected patients, and the concordance rate in monozygotic twins is 60%.
- A genetic susceptibility is associated with the presence of **HLA-DR3**.
- it is characterized by a breakdown in self-tolerance to thyroid autoantigens, and is the production of **multiple autoantibodies**

Thyroid-stimulating immunoglobulin:
- An IgG antibody binds to the TSH receptor and **mimics the action of TSH**, with resultant increased hormones

Thyroid growth-stimulating immunoglobulin:
- Directed against the TSH receptor, and have been implicated in **the proliferation of follicular epithelium**

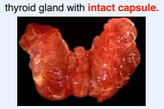
TSH-binding inhibitor immunoglobulins
- Prevent TSH from binding to its receptor on thyroid cells and in so doing may actually **inhibit thyroid cell function,** a finding explains why some patients with Graves spontaneously develop episodes of hypothyroidism.

The coexistence of stimulating and inhibiting immunoglobulins in the serum of the same patient may explain why some patients with Graves disease spontaneously develop episodes of hypothyroidism

Morphology

Gross (macroscopic) features

Diffuse Symmetrical enlargement of the thyroid gland with **intact capsule**.



Microscopic examination

a. The follicular cells in untreated cases are **tall** and crowded.

b. Lymphoid infiltrates, consisting predominantly of T cells, with few B cells and plasma cells are present throughout the interstitium; with formation of **germinal centers**

Diseases of thyroid gland

Inflammation | Goiters | Graves | Neoplasms

- They are usually **solitary** (single not multiple)
- Benign lesions in the thyroid are commoner than malignant ones.
- Carcinomas of the thyroid are uncommon, accounting for much less than 10% of solitary thyroid nodules

Solitary thyroid nodules

Could be

- Follicular **adenomas**
- A dominant nodule in **multinodular goiter**
- Simple cysts or foci of **thyroiditis**

Benign

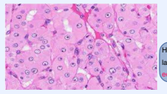
follicular adenoma and its variants

- Are **benign** neoplasms derived from follicular epithelium.
- **solitary**.
- The tumor is **demarcated and compressed** the adjacent thyroid parenchyma by a well-defined, intact capsule
- **cold** nodules on scanning but might be functional.

variants of follicular adenoma

Hurthle cell adenoma

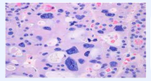
The neoplastic cells show oxyphil or Hürthle cell change) and its behavior **is not different** from those of a conventional adenoma.



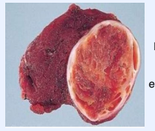
Hurthle cell adenoma, cells are large with abundant eosinophilic cytoplasm.

Atypical adenoma

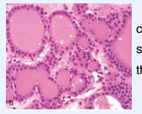
The neoplastic cells exhibit focal nuclear atypia, (endocrine atypia);and these features do not constitute evidence of malignancy



Note the large, hyperchromatic, pleomorphic cells. These are atypical and this atypia in endocrine glands doesn't necessarily mean malign.



Follicular adenoma
• Well demarcated, encapsulated nodules.



composed of follicles similar to the normal thyroid follicles.

Behavior of thyroid adenomas

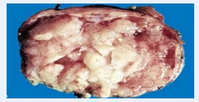
- **Carry an excellent prognosis**
- **do not recur or metastasize**
- **not forerunners to carcinomas**

malignant

- Account for about 1.5% of all cancers
- A **female predominance** has been noted among patients who develop thyroid carcinoma in the early and middle adult years
-cases manifesting in childhood and late adult life are distributed equally between men and women

Papillary carcinoma

(for more than 85% of cases)



Is the most common form

- accounts for the majority of thyroid carcinomas associated with **previous exposure to ionizing radiation**.
- May occur at any age.

Morphology

Gross

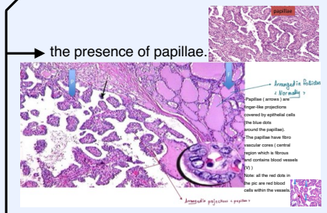
Either solitary or multifocal lesions

- Some are well circumscribed and even encapsulated
- others infiltrate the adjacent parenchyma

Microscopic features

Of tissues

the presence of papillae.

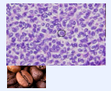


Nuclear features

optically clear nuclei, or "Orphan Annie eye" nuclei , seen on histological but not cytological preparations (formalin artefact)

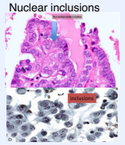
nuclei are white and empty

Grooves within nuclei: so the nucleus looks like a coffee bean

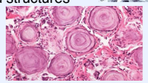


Have invaginations of the cytoplasm to the nucleus (pseudoinclusions)

Nuclear inclusions



Concentrically calcified structures (**psammoma bodies**)

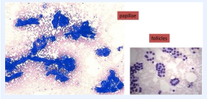


Of cells

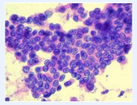
From FNA

- **Clear nuclei** are not seen in FNA because they are an **artefact due to formalin.**
- Formalin is used to fix tissues before staining them with H and E
- In cytological (**FNA**) preparations we use **alcohol** as a fixative, no formalin is used.. So no clearing artefact

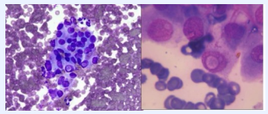
Papillae on FNA



Grooves seen on FNA



Inclusions seen on FNA



Psammoma bodies can be seen on FNA

Follicular carcinoma

(5% to 15% of cases)

- More common in women and in areas with **dietary iodine deficiency** .
- The peak incidence between the **ages of 40 and 60 years**

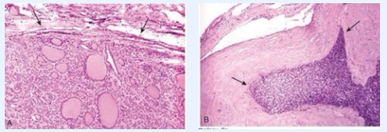
Microscopic features

- Are composed of fairly uniform cells forming small follicles,
- In other cases, follicular differentiation is less apparent
- It may be

a. widely invasive, infiltrating the thyroid parenchyma and extrathyroidal soft tissues, or

b. Minimally invasive that may be impossible to distinguish from follicular adenomas on gross examination

requires extensive histologic sampling to exclude capsular and/or vascular invasion



Anaplastic carcinoma

(< 5% of cases)

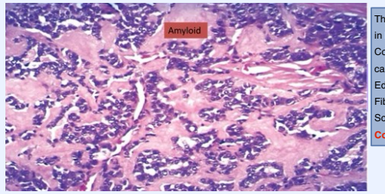
- Are undifferentiated tumors of the thyroid epithelium,
- **The mean age of 65 years.**
- They are **aggressive**, with a mortality rate of 100%.
- Approximately a quarter of patients have a past history a well-differentiated carcinoma, and a 1/4th harbor a well-differentiated tumor in the resected specimen.
- **Metastases** to distant sites are **common**, but death occurs in less than 1 year as a result of aggressive local growth which compromise of vital structures in the neck

Medullary carcinoma

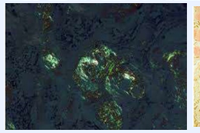
(5% of cases)

- **neuroendocrine** neoplasms. (Parafollicular cells)
- Secrete **calcitonin**, the measurement of which plays an important role in the diagnosis and postoperative follow-up evaluation of patients

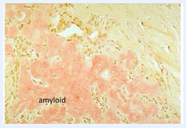
• Because medullary carcinoma secrete calcitonin; this calcitonin can accumulate and form **amyloid protein**.
• **Amyloid**: is several, **chemically different** proteins that share **similar physical characteristics**.. They can accumulate and form pink material called amyloid..



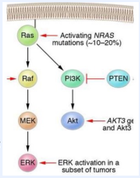
The material btw follicles seen in H&E
Could be :-
calcitonin
Edema
Fibrin
So specific stain is done here
Congo red stain



With polarized light, amyloid gives this apple green color when stained with **congo red**



Amyloid stains with Congo red stain

The difference / Type of carcinoma	papillary carcinomas	Follicular Carcinoma	Anaplastic Carcinoma	Medullary Carcinoma
Clinical Features	a. Are nonfunctional tumors manifest as **painless** masses in the neck, either within the thyroid or as metastasis in a cervical lymph node b. Are indolent lesions, with 10-year survival rates of 95%. c. The presence of isolated cervical nodal metastases does **not have influence on good prognosis of these lesions.**	- Manifest most frequently as solitary cold thyroid nodules. - Regional nodal metastases are uncommon . - As many as half of patients with widely **invasive** carcinomas succumb to their disease within 10 years, while less than 10% of patients with minimally invasive follicular carcinomas die within the same time span	_____	_____
Metastasis	**Lymphatic metastases** , In a minority of patients **hematogenous metastases** are present at the time of diagnosis, most commonly to lung.	metastasize **through the bloodstream (hematogenous dissemination)** to lungs, bone, and liver.	metastasize **through the bloodstream (hematogenous dissemination)**	**Lymphatic metastases** , In a minority of patients **hematogenous metastases** are present.
Genetic factors	Mainly 2 genes are involved: • 1. **BRAF amplification**. Remember that RAS is the most commonly mutated oncogene. RAS acts via second messeanges .. RAF is one of them BRAF (of the RAF family genes) is an oncogene in the RAS pathway. • 2. **RET /PTC gene rearrangment** resulting in a novel protein kinase. The frequency of RET rearrangements is significantly higher in papillary cancers arising after **radiation exposure** 	a. Gain-of-function point mutations of **RAS and PIK3CA,** b. Loss-of-function mutations of **PTEN**, a suppressor gene c. A **unique (2;3) translocation** presents in one third to one half of follicular carcinomas which creates a fusion gene composed of portions of PAX8, a gene that is important in thyroid development, and the peroxisome proliferator-activated receptor gene (PPARG), whose product is a nuclear receptor implicated in cell differentiation	Inactivation of **TP53**, restricted to anaplastic carcinomas and may also relate to their **aggressive behavior**	Both familial and sporadic forms demonstrate activating **RET mutations**

Diseases of the Parathyroid Glands

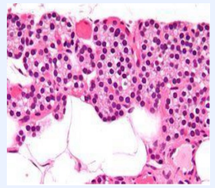
Parathyroid glands
- There are four parathyroid glands
- They are derived from the pharyngeal pouches
- (Usually) Located in close proximity to the upper and lower poles of each thyroid lobe.
- Each gland is yellow-brown in color and resemble lentil seed in size -very small -

Parathyroid glands histology

chief cells

secrete parathyroid hormone (PTH)

small nuclei and the pale, almost white cytoplasm.

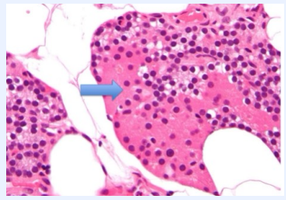


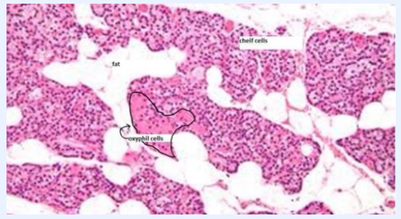
fat

The absence of fat can be a sign of abnormality, such as hyperplasia, adenoma, or carcinoma

Oxyphil cells

eosinophilic and contain mitochondria (in large numbers). Their function is unknown. Some research suggests that they can secrete PTH in some cases of hyperparathyroidism.



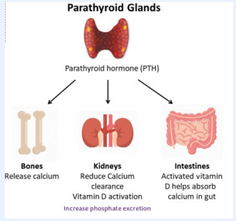


Parathyroid hormones

Regulation of PTH
- PTH regulates calcium level in blood.
- If blood calcium decreases.. Parathyroid gland secretes PTH…
- NOTE: the regulation of PTH secretion is NOT under control of the pituitary BUT is regulated by calcium levels in the blood. Unlike most endocrine glands, which function under the regulatory control of the pituitary gland.

Functions of PTH

PTH increases blood calcium by its effects on the kidneys, GIT and bone.



In kidney

Increases renal tubular reabsorption of calcium, accordingly, serum calcium concentration is increased (**direct** effect)

In GIT

Increases conversion of vitamin D to its active form. Which increases gastrointestinal absorption of calcium (the effect in GIT is **indirectly** through activation of vit D)

Increases osteoclastic activity (increases bone resorption) so releasing calcium from bone (Calcium store) to blood.

Increases phosphate excretion in urine.. So phosphate level is decreased..
So less calcium binds to phosphate..
So more free calcium in blood

Diseases of the parathyroid

Hyperparathyroidism

Primary

autonomous increase in parathyroid hormone not caused by decreased calcium (**the problem is in the parathyroid gland** or there is ectopic secretion of parathyroid hormone as a paraneoplastic syndrome) => a common disorder and important cause of hypercalcemia.

Secondary

parathyroid hormone increases due to decreased calcium level.
The most common cause is renal failure.

Tertiary

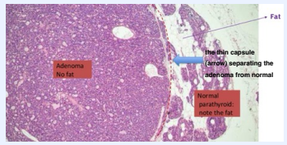
hyperparathyroidism: in some patients with secondary hyperparathyroidism, the increased parathyroid hormone production becomes autonomous and not regulated by calcium levels.

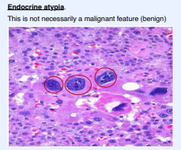
Hypoparathyroidism

Causes

Parathyroid **adenoma** (85% to 95%)

- The parathyroid gland undergoes significant enlargement.
- Most parathyroid adenomas weigh between 0.5 and 5g.
- They are encapsulated,soft and ***solitary*** which means :One gland only is usually affected and the other three are normal or atrophic
- A rim of compressed,normal,non-neoplastic, parathyroid tissue, separated by a fibrous capsule,is visible at the edge of the adenoma.
- Cells with pleomorphic nuclei may be seen(**endocrine atypia**) and must not be taken as a sign of malignancy.
- Mitotic figures arer are .
- inconspicuous adipose(fatty) tissue



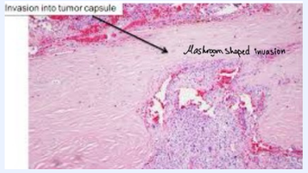


Primary parathyroid **hyperplasia**-5% to 10%.

- Multi-glandular process(more than one gland enlarged)
- The combined weight of all glands rarely exceeds1.0 g.
- Stromal fat is inconspicuous within foci of hyperplasia.

Parathyroid **carcinoma**-(1%)

- one gland affected.
- Consist of irregular masses that sometimes exceed 10 g in weight .
- The diagnosis of carcinoma based on cytologic detail is unreliable, and **invasion of tissues and metastasis are the only definitive criteria**
- Local recurrence occurs in one third of cases,
- Distant dissemination (metastasis) occurs in another third

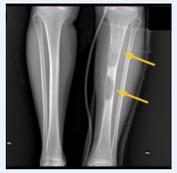


Mass lesions

Morphologic changes in other organs in hyperparathyroidism

skeletal changes

- **Increased osteoclastic activity**, resulting in erosion of bone and mobilization of calcium salts.
  - In severe cases the cortex is grossly thinned and the marrow contains increased amounts of fibrous tissue accompanied by foci of hemorrhage and cysts (**Osteitis fibrosa cystica**)



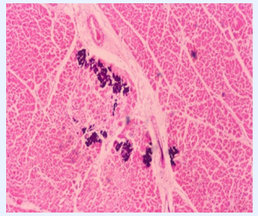
- **Brown tumors of hyperparathyroidism**
  - Aggregates of osteoclasts,, and hemorrhage

kidney changes

- **nephrolithiasis**
  Increased calcium favours formation of urinary tract **stones**
- **nephrocalcinosis**
  Calcification of the renal interstitium

metastatic calcifications

may be seen in the stomach, lungs, myocardium, and blood vessels



Diseases of the parathyroid

Hyperparathyroidism

- **Primary**

Clinical features of primary hyperparathyroidism
- Primary hyperparathyroidism is a disease of adults and is much more common in women than in men.
- The most common manifestation is an increase in serum calcium

Clinical Manifestations :
painful bones, renal stones, abdominal groans, psychic moans.
- Why the abdominal groans (abdominal pain)..reasons include: peptic ulcers, pancreatitis, Gallstones
- Painful bones: due to fractured bones(bones become weak due to osteoporosis and osteitis fibrosa cystica and this causes fractures)

- **Secondary**

caused by chronic decreases in the serum calcium level
- Renal failure is the most common cause

Chronic renal insufficiency results in:
1. **decreased phosphate excretion**, which in turn results in hyperphosphatemia. Which depresses serum calcium levels and so stimulates parathyroid gland activity
2. Reduced availability of α1-hydroxylase enzyme necessary for the synthesis of the active form of vitamin D, which in turn reduces intestinal absorption

Clinical Features
- Are dominated by those related to chronic renal failure
- Bone abnormalities (renal osteodystrophy) are less severe than those seen in primary type
- Serum calcium remains near normal because compensatory increase in PTH levels sustains serum calcium.

- **Tertiary**

In a minority of patients, parathyroid activity may become autonomous and excessive, with resultant hypercalcemia-a process sometimes termed tertiary hyperparathyroidism.

Hypoparathyroidism

Is less common than hyperparathyroidism and the major causes are:.

a. **Surgically induced hypoparathyroidism**: inadvertent removal of parathyroids during thyroidectomy.

b. **Congenital absence**: This occurs in conjunction with thymic aplasia (Di George syndrome) and cardiac defects,

c. **Autoimmune hypoparathyroidism** :This is a hereditary polyglandular deficiency syndrome

- Symptoms:
  - decreased Ca levels in blood (hypocalcemia)
  - sensitive nerves
  - uncontrollable spasms of the limbs
- Treatment
  - daily calcium and vitamin D supplements

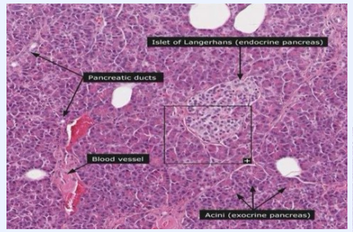
Mass lesions

- Benign
- Malignant

Endocrine Pancreas & Diabetes Mellitus

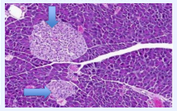
Pancreas

Exocrine pancreas
Glands and ducts that secrete enzymes, mainly for digestion



Endocrine pancreas
Islets of Langerhans (clusters of endocrine cells) that secrete hormones.

around one million Islets



Cell Types in the Pancreatic Islets

Alpha
secrete glucagon

Delta
secrete somatostatin, which supresses both insulin and glucagon.

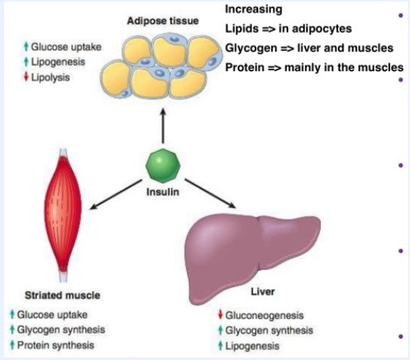
Beta
secrete insulin

The Effect of Insulin

Increase uptake of glucose by striated muscle and adipocytes.

has anabolic effect on lipid, protein and glycogen.

reduces production of glucose from liver.



Rare Causes of DM

- **Genetic defects of beta cell function**
  - o Maturity Onset Diabetes of the Young = MODY due to several mutations.
  - o Insulin gene mutations.
  - o Defects in proinsulin conversion
- **Genetic defects in insulin action: Insulin receptor mutations**
- **Gestational diabetes: During pregnancy**
- **Exocrine pancreatic defects: chronic pancreatitis, pancreatectomy, neoplasia. Etc.**
- **Endocrinopathies: Acromegaly, Cushing syndrome & pheochromocytoma**
  - A disorder in another endocrine gland can lead to secondary diabetes mellitus, as seen in Cushing's syndrome.
- **Infections: CMV, coxsackievirus B & congenital rubella.**
- **Drugs: Steroids, similar to Cushing's syndrome in the pathophysiology.**

Diabetes Mellitus (DM)

- DM IS A GROUP OF **METABOLIC DISORDERS** SHARING HYPERGLYCEMIA.
- Blood glucose levels normally are maintained in a very narrow range, usually 70 to 120 mg/dL.
- This is maintained by the balance between insulin and glucagon

Type 1 (10%)

- Is an **autoimmune** disease destructing Pancreatic B cells leading to an absolute deficiency of insulin
- Most commonly develops in childhood, manifest at puberty, and patients depend on exogenous insulin for survival; without insulin they develop complications
- The classic manifestations of the disease occur late in its course, after approximately 90% of pancreatic beta cells have been destroyed. This destruction usually progresses by the end of childhood or adolescence, which is why the disease typically presents at a young age.
- Genetic predisposition !!!

Type 2 (80-90%)

Caused by a combination of:

- **Peripheral resistance –of target tissues– to insulin action**

Is defined as the failure of target tissues to respond normally to insulin

It leads to decreased uptake of glucose in muscle & reduced glycolysis in the liver.

- **An inadequate compensatory response of insulin**

Obesity & Insulin Resistance

- Visceral obesity is common in majority of affected patients and insulin resistance is present even with simple obesity un- accompanied by hyperglycemia, indicating a fundamental abnormality of insulin signaling in states of fatty excess.
- The risk of diabetes increases as the body mass index increases, suggesting a dose-response relationship between body fat and insulin resistance

Pathogenesis

- **Autoimmune**
  - A. Defective deletion of self-reactive T cells in the thymus,
  - B. Defects in the functions of regulatory T cells
  - C. Autoantibodies against B cell antigens, including insulin and enzyme glutamic acid decarboxylase, are detected in the blood of 70% to 80% of patients
- **viral infections.**

Beta Cell Dysfunction in type 2 DM

- **Inability of beta cells to meet the increased demand on insulin due to peripheral resistance.**
- Cause**: multifactorial and overlap with those related to peripheral resistance.**
- Examples**:**
  - **FFAs cause cytokine release from the pancreatic Islets causing inflammatory damage.**
  - **Amylin, is secreted by the β- cells and its abnormal aggregation results in amyloid that replaces the islets.**

How?

- **Role of excess free fatty acids (FFAs):**

  The level of intracellular triglycerides often is markedly increased in muscle and liver tissues in obese persons because excess circulating FFAs are deposited in these organs (adipose tissue, liver & muscles)
  - Intracellular triglycerides are **potent inhibitors of insulin signaling** and result in an **acquired insulin resistance.**

- **Role of inflammation:**

  mediated by cytokines secreted in response to excess FFAs results in peripheral insulin resistance and beta cell dysfunction
  - **Excess FFAs within macrophages and beta cells can engage the inflammasome**, leading to secretion of the **IL-1β** which mediates secretion of additional cytokines from macrophages, that are released into the circulation and act on the major sites of insulin action to promote insulin resistance

- **Role of adipokines:**

  Adipose tissue release adipokines e.g., IL-1β which promotes peripheral insulin resistance

Morphology of DM: The Pancreas

Reduction in the number and size of islets, most often in type 1 particularly with rapidly advancing disease

Leukocytic infiltration of the islets seen in both type 1 and type 2 DM although it is more severe in type 1.
• In both types inflammation is often absent by the time the disease is clinically evident

Amyloid replacement of islets in long-standing type 2 diabetes, appear as deposition of pink, amorphous material beginning in capillaries between cells.

At advanced stages, the islets may undergo fibrosis.

Clinical Features of DM

- **The hyperglycemia exceeds the renal threshold for reabsorption, and glycosuria induces an osmotic diuresis and polyuria**
- **The obligatory renal water loss combined with the hyperosmolarity tends to deplete intracellular water, triggering the thirst centers of the brain and this generates intense thirst (polydipsia)**
- **Deficiency of insulin leads to catabolism of proteins and fats which tends to induce a negative energy balance, which in turn leads to increasing appetite (polyphagia)**

Complications of DM

Blood vessels

Diabetic Macrovascular Disease:

• The hallmark is accelerated atherosclerosis affecting the aorta, large and medium-sized arteries and it is more severe with early onset in diabetics than in non-diabetics.
• **Myocardial infarction** due to Coronary artery atherosclerosis is the most common cause of death in diabetics and is as common in diabetic women as in diabetic men.
• **Gangrene** of the lower extremities is 100 times more common in diabetics than in the general population

Diabetic Microvascular Diseases:

Hyaline arteriolosclerosis:

• Is the vascular lesion **associated with hypertension**, but it may also occur in diabetes.
• Is both more prevalent and more severe in diabetics than in non- diabetics, but it is not specific for diabetes and may be seen in elderly persons who do not suffer from either diabetes or hypertension.
• It takes the form of **hyaline thickening of the wall of the arterioles**, which causes narrowing of the lumen
• In diabetic patients, its severity is related **not only to the duration** of the disease but also to **the presence or absence of hypertension**

This pinkish material is hyaline, which narrows the lumen of blood vessels.

Diabetic Microangiopathy:

• Diffuse **thickening of basement membranes**, is most evident in the capillaries of the skin, skeletal muscle, retina and renal glomeruli.
• It may be seen in *renal tubules, nerves, and placenta*. That is why babies of diabetic mothers may be affected.
• It underlies **the development of diabetic nephropathy, retinopathy**, and some forms of **neuropathy**

Nephropathy

• The kidneys are prime targets of diabetes and renal failure is second only to myocardial infarction as a cause of death from this disease
• lesions encountered are:
A. Glomerular lesions, several forms of **glomerulonephritis** occur.
B. **Renal atherosclerosis and arteriolosclerosis**, both of which lead to ischemic changes in the kidneys.
C. **Pyelonephritis**: Inflammation in the interstitial tissue and involve the tubules and it has both acute and chronic forms

Ocular complications

• **Visual impairment**, and blindness, is one of the more feared consequences of long- standing DM. Which is Very dangerous
• **Retinopathy**, the most common pattern, consists of changes that are considered by many ophthalmologists to be virtually diagnostic of the disease
• Notes:
o DM currently is the fourth leading cause of acquired blindness in the United States.
o About 60% to 80% of patients develop a form of diabetic retinopathy approximately 15 to 20 years after diagnosis
o Diabetic patients also have an increased propensity for **glaucoma and cataract formation**

Neuropathy

A. The most frequent pattern of involvement is that of a **peripheral, symmetric polyneuropathy of the lower extremities** affecting motor and sensory nerves.
o Multiple nerves are affected bilaterally with similar severity.
B. Autonomic neuropathy produces **disturbances in bowel and bladder function** and sometimes sexual impotence,
C. **Mononeuropathy** (one nerve is affected) which may manifest as sudden foot drop or wrist-drop or isolated cranial nerve palsies
• The neurologic changes may be **the result of microangiopathy** (the main cause) and **increased permeability of capillaries that supply the nerves**, as well as direct axonal damage

Diseases of the Adrenal Glands

- mass effect
- hormonal abnormalities

Diseases of the adrenal gland

Hyperadrenalism

Hypercortisolism

Cortisol secretion is regulated via the hypothalamic–pituitary–adrenocortical axis,

Hyperaldosteronism

aldosterone secretion is controlled by the renin–angiotensin–aldosterone system (RAAS).

Adrenogenital syndromes

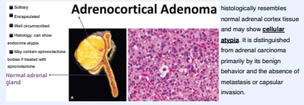
Hypoadrenalism

- Acute adrenal insufficiency
- Chronic adrenal insufficiency (Addison disease)
- Secondary adrenal insufficiency

Masses = Neoplasms

Adenoma

- Are more common in women in their 30s to 50s.
- ✓ Adrenocortical adenomas: Are yellow tumors surrounded by thin capsules, and most weigh less than 30 g
- ✓ Carcinomas tend to be non encapsulated masses , exceeding 200 to 300 g in weight



histologically resembles normal adrenal cortex tissue and may show **cellular atypia**. It is distinguished from adrenal carcinoma primarily by its benign behavior and the absence of metastasis or capsular invasion.

Carcinoma

Hypercortisolism (Cushing Syndrome)

Causes

Exogenous (Iatrogenic)

if you treat patients with glucocorticoids (iatrogenic): this is the most common cause of Cushing syndrome.

exogenous cortisol → ↓ ACTH via negative feedback → bilateral adrenal atrophy, due to a lack of stimulation of the zona fasciculata and zona reticularis by ACTH.

Endogenous causes

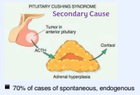
pituitary ACTH-producing **adenoma**
majority of cases

Due to

corticotroph cell **hyperplasia**

- Primary tumor
- Secondary to ACTH tumor

Hypothalamic-pituitary diseases causing hypersecretion of ACTH (Cushing disease)



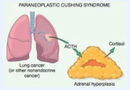
- 70% of cases of spontaneous, endogenous Cushing syndrome are due to Cushing disease.
- Occurs most frequently during young adulthood (the 20s and 30s)
- mainly affecting women

Primary adrenal hyperplasia and neoplasms

- 10% to 20% of cases of endogenous Cushing syndrome are due to primary diseases in the adrenal gland.
- This is called ACTH-independent Cushing syndrome, because of the low serum levels of ACTH
- It is **caused by adrenal adenoma or carcinoma.**
- Can also be caused by primary hyperplasia but this is very rare

Secretion of ectopic ACTH by nonpituitary tumors

mostly caused by small cell carcinoma of the lung, which will cause the adrenal gland to undergo bilateral hyperplasia due to elevated ACTH.



CLINICAL MANIFESTATIONS OF CUSHING SYNDROME

- Hypertension and weight gain
- Truncal (central) obesity, "moon facies," accumulation of fat in the posterior neck and back ("buffalo hump").

- Effect of glucose: Glucocorticoids induce gluconeogenesis with resultant **hyperglycemia**, **glucosuria**, and **polydipsia**
- The catabolic effects on proteins cause loss of collagen and resorption of bone and bone resorption results in osteoporosis and susceptibility to fractures.
- Effect on collagen: The skin is thin, fragile, and easily bruised with delayed wound healing; cutaneous striae are particularly common in the abdominal area

- Patients are at increased risk for a variety of infections.
- Hirsutism and menstrual abnormalities
- Mental disturbances, mood swings, depression, psychosis.

Types of hyperplasia of adrenal gland

Primary hyperplasia , ACTH-independent المشكلة بال gland نفسها

- usually **unilateral** but may occasionally be bilateral.
- In primary cortical hyperplasia, the cortex is replaced almost entirely by **macronodules** or 1- to 3-mm **micronodules**.

Secondary hyperplasia due to ACTH production (ACTH is the cause, not adrenal gland)

- **Diffuse hyperplasia** is found in patients with ACTH- dependent Cushing syndrome .
- **Both glands** are enlarged, either subtly or markedly, each weighing up to 30 g.
- The yellow color of diffusely hyperplastic glands derives from the presence of lipid-rich cells, which appear vacuolated under the microscope

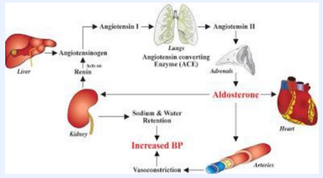
Diseases of the adrenal gland

Hyperadrenalism

- Hypercortisolism
- Hyperaldosteronism
- Adrenogenital syndromes

Hypoadrenalism

Masses = Neoplasm

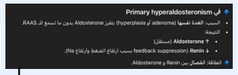


The renin–angiotensin–aldosterone system (RAAS) is a hormone system that is involved in the regulation of the plasma sodium concentration and arterial blood pressure.

Hyperaldosteronism

Primary hyperaldosteronism

autonomous overproduction of aldosterone (tumor for example) with secondary suppression of renin- angiotensin system and decreased plasma renin activity



Causes

- **Bilateral idiopathic hyperaldosteronism**
  bilateral nodular hyperplasia of adrenals
  - the most common underlying cause (60% of cases)
- **Adrenocortical neoplasm**
  adenoma (the most common cause) or, rarely, an adrenocortical carcinoma.
  - In approximately 35% of cases, the cause is a solitary aldosterone-secreting Aldosterone-producing adrenocortical adenoma referred to as **Conn syndrome**
- **Rarely, familial hyperaldosteronism may result from a genetic defect that leads to overactivity of the aldosterone synthase gene, CYP11B2.**

Secondary hyperaldosteronism

Secondary to activation of renin-angiotensin system characterized by increased levels of plasma renin

Causes

- **Decreased renal perfusion(renal artery stenosis)**
- **Arterial hypovolemia and edema e.g heart failure**
- **Pregnancy (caused by estrogen-induced increases in plasma renin substrate**

CLINICAL MANIFESTATIONS OF HYPERALDOSTERONISM

- **hypertension**
  Hyperaldosteronism may be the most common cause of secondary hypertension
- **Hypokalemia**

Diseases of the adrenal gland

Hyperadrenalism

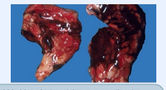
Hypoadrenalism

Acute adrenal insufficiency

Acute Adrenocortical Insufficiency

- **Crisis in patients with chronic adrenocortical insufficiency precipitated by stress**
  Acute on top of chronic
- **In patients maintained on exogenous corticosteroids .. Sudden withdrawal, or stress**
- **Massive adrenal hemorrhage.**

May destroy enough of the adrenal cortex to cause acute adrenocortical insufficiency.
- This condition may occur:
1. In patients maintained on **anticoagulant therapy**
2. Patients suffering from **sepsis**: a condition known as the Waterhouse-Friderichsen syndrome
- Sepsis due to ***bacterial infection (mostly)***: Neisseria meningitidis, Pseudomonas spp., and Haemophilus influenzae.
- Underlying cause??? unclear but probably involves endotoxin-induced vascular injury



Loss of 80–90% of adrenal tissue, exceeding the normal functional reserve, as in massive adrenal hemorrhage, results in adrenal insufficiency.

Chronic adrenal insufficiency (Addison disease)

Primary chronic adrenocortical insufficiency (Addison disease)

Uncommon disorder resulting from gradual progressive destruction of the adrenal cortex.

Causes

- ***Autoimmune adrenalitis.***
  - 60% to 70% of Addison disease cases and is the most common cause of primary adrenal insufficiency in developed countries.
  - There is **autoimmune destruction** of steroid-producing cells, and **autoantibodies to several key steroidogenic enzymes** have been detected in affected patients
- ***Infections***
  Infections (**slowly infections**): *Tuberculosis and Fungal infections*
  - Tuberculous adrenalitis, which once accounted for as many as 90% of cases of Addison disease, has become less common with the advent of anti-tuberculosis therapy
  - **Disseminated infections** caused by Histoplasma capsulatum and Coccidioides immitis also may result in chronic adrenocortical insufficiency.
  - Patients with **AIDS** are at risk for the development of adrenal insufficiency from several infectious (cytomegalovirus and TB) and noninfectious (Kaposi sarcoma, affects blood vessels and is related to herpesvirus-8).
- ***Metastatic tumors***
  Carcinomas of the lung and breast are the most common primary sources.

Secondary adrenal insufficiency

Hypothalamic- pituitary diseases (Hypopituitarism) including

- **Metastasis**
- **Infection**
- **Infarction**
- **Irradiation**

Clinical features of adrenal insufficiency

Clinical manifestations of adrenocortical insufficiency do not appear until ***at least 90% of the adrenal cortex*** has been compromised.

- progressive weakness and easy fatigability
- Gastrointestinal disturbances are common and include anorexia, nausea, vomiting, weight loss, and diarrhea
- hyperpigmentation is not seen in patients with secondary adrenocortical insufficiency because there is no increase in ACTH (POMC → MSH + ACTH).
- Decreased aldosterone in **primary hypoadrenalism** results in potassium retention and sodium loss , with consequent-hyperkalemia, hyponatremia, volume depletion, and hypotension

Masses = Neoplasms

Adrenal medulla

- Chromaffin cells… derived from the neural crest.
- Secrete catecholamines.

Most important disease: neoplasms (most of them are adenomas)

Pheochromocytoma

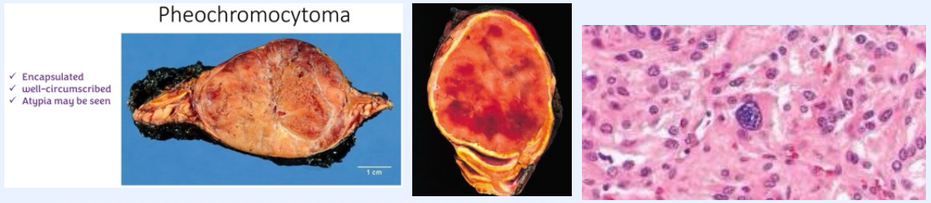
- give rise to a surgically correctable form of **hypertension**.
- Pheochromocytomas usually subscribe to "rule of 10s":

a. 10% of pheochromocytomas are extraadrenal, called paragangliomas,

b. 10% of adrenal pheochromocytomas are bilateral; this proportion may rise to 50% in cases that are associated with familial syndromes.

c. 10% of adrenal pheochromocytomas are malignant,The definitive diagnosis of malignancy (10%) in pheochromocytomas is based exclusively on the presence of **metastases**.

d. 10% familial.. Now we think up to 25% might be familial.



- The predominant clinical manifestation is **Hypertension** (considered a cause of secondary hypertension especially in young people in their 20-30s)
- Sudden cardiac death may occur, probably secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias