

The endocrine system consists of **two** main components:

1. **The classical endocrine organs:** pituitary, thyroid, parathyroid, adrenal, islets of langerhans in pancreas, ovary, testis and pineal gland.
2. **The diffuse endocrine system:** consists of cells scattered as single or small group of cells in various non-endocrine organs such as lung, GIT, skin.

### I. The pituitary gland and hypothalamus

The pituitary gland weighs about 600 mg. It consists of: anterior pituitary (adenohypophysis) and posterior pituitary (neurohypophysis). Anterior pituitary secretes growth hormone, prolactin, TSH, ACTH, FSH and LH. Posterior pituitary secretes oxytocin and ADH (vasopressin).

The *adenohypophysis* contains three major cell types: **acidophils**(40%), **basophils**(10%), and **chromophobes**(50%). The staining is variable, and to properly identify specific hormone secretion, immunohistochemical staining is necessary. A simplistic classification is as follows:

1. The pink acidophils secrete growth hormone (GH) and prolactin (PRL)
2. The dark purple basophils secrete corticotrophin (ACTH), thyroid stimulating hormone (TSH), and gonadotrophins: follicle stimulating hormone-luteinizing hormone (FSH and LH)
3. The pale staining chromophobes have few cytoplasmic granules, but may have secretory activity.

#### Pathology of adenohypophysis (Tumors):

**Pituitary adenoma:** most common lesion of anterior pituitary, it divided into microadenoma (<15 mm in diameter) and macroadenoma (>15 mm in diameter).

#### Effects or clinical features:

1. Endocrine effect due to hypersecretion of specific hormones.
2. Local pressure symptoms of large tumor causing compression on surrounding structure, optic chiasma, optic nerve, causing visual disturbance
3. Pressure atrophy on adjacent normal gland lead to hypopituitarism.
4. Enlargement and erosion of the floor of the sella turcica are common findings and important radiological signs.

#### Pituitary adenoma

The circumscribed mass lesion present here in the sella turcica is a pituitary adenoma. Though pituitary adenomas are benign, they can produce problems either from a mass effect (usually visual problems from pressing on the optic chiasm and/or headaches) or from production of hormones such as prolactin or ACTH.

The microadenoma of the anterior pituitary may appear in 1 to 5% of adults. These microadenomas rarely have a significant hormonal output that leads to clinical disease.

The microscopic appearance of the pituitary adenoma is shows monotonous appearance of small round cells with small round nuclei and pink to blue cytoplasm. The cells may be arranged in nests or cords and endocrine tumors also have prominent vascularity.

## Other tumors

1. **Pituitary carcinoma:** extremely rare
2. **Craniopharyngioma :**Most patients with craniopharyngioma are in the first or second decade of life. Its location is usually suprasellar, although it may occupy the sella as well
3. **Metastatic tumors:** from breast, lung, GIT. Posterior lobe is mostly affected, anterior lobe rarely involved.

A **craniopharyngioma** is derived from remnants of Rathke's pouch and forms an expanding mass arising in the sella turcica that erodes bone and infiltrates into surrounding structures. They are difficult to eradicate, even though they are composed of histologically appearing squamoid and columnar epithelium lining cystic spaces filled with oily fluid.

## Other pathology:

### Inflammatory conditions

**Circulatory disturbances (Sheehan's syndrome):** necrosis of anterior lobe due to severe post-partum hemorrhage after labour and the patient develop after that hypopituitarism.

### Hyperfunction of adenohypophysis

1. **Hypersecretion of GH:** Acromegaly and gigantism.
2. **ACTH:** Cushing's disease.
3. **Prolactin:** hyperprolactinemia

### Acromegaly and gigantism:

**Cause:** pituitary adenoma.

**Gigantism:** when hypersecretion of GH occur in children before closure of epiphysis result in proportional increase in length and thickness of bones with delayed in epiphyseal fusion. If excess of GH persists after epiphyseal closure causing feature of acromegaly.

**Acromegaly:** occurs when hyper-secretion of GH occur after fusion of epiphysis in adult. **Clinical features:** enlargement of extremities, over-growth of bone, and soft tissue, large hand and feet, enlargement of nose and lower jaw (prognathism), cardiomegally, hypertension, D.M., osteoarthritis, kyphosis, increased sweating, 30-40% have hyper-prolactinaemia leading to galactorrhoea.

### Cushing's disease:

Hypersecretion of ACTH result in adrenal gland hyperplasia with excessive secretion of glucocorticoids by adrenals resulting in Cushing's syndrome .

### Causes of ACTH hypersecretion:

- ACTH-cell adenoma.
- ACTH-cell hyperplasia.
- Ectopic ACTH secretion

## Hyperprolactinemia:

### Causes:

- Adenoma (prolactinoma).
- Destructive lesion of hypothalamus.
- Drugs (methyldopa, phenothiazine).
- Physiological type in pregnancy.
- ❖ In **females** it results in amenorrhea, infertility, galactorrhea,
- ❖ In **men** it is usually asymptomatic, may cause loss of libido, infertility, impotence.

## Hypopituitarism:

### Causes:

- Pituitary tumor with pressure atrophy
- Sheehan's syndrome in developing countries
- Pituitary surgery or radiotherapy
- Trauma
- Inflammation (tuberculosis, sarcoidosis, syphilis)
- Autoimmune disease
- Histiocytosis X
- Craniopharyngioma
- Metastatic tumors

## Neurohypophysis:

**ADH:** reabsorption of water by renal tubules and concentration of urine.

Its *deficiency* causes diabetes insipidus: polyuria, polydipsia with diluted urine which differentiated it from psychogenic polydipsia. **Causes:** head injury, surgical trauma, destructive lesion of hypothalamus (sarcoidosis, histiocytosis-X), tumors, idiopathic.

*Excessive* secretion of ADH cause inappropriate secretion of ADH, water retention causing hyponatraemia, hypoosmolarity resulting in vomiting, muscle cramps, weakness, central edema which may lead to coma, death. **Causes:** ectopic secretion of ADH by small cell CA. of the lung, pneumonia, head injury, meningitis, subarachnoid hemorrhage and idiopathic.

## Hypothalamus:

### Tumors:

- Gliomas and germinomas.
- Gangliocytoma
- **Histologically:** this lesion is composed of a mixture of mature neurons, astrocytes, and oligodendrocytes arranged with a varying degree of organization.

## II. Thyroid gland

Normal thyroid gland is on the anterior trachea of the neck. The thyroid gland has a right lobe and a left lobe connected by a narrow isthmus. The normal weight of the thyroid is 10 to 30 grams. It cannot easily be palpated on physical examination.

Normal thyroid seen microscopically consists of follicles lined by an epithelium and filled with colloid. The normal thyroid follicle is lined by a cuboidal follicular epithelium with cells that can add or subtract colloid depending upon the degree of stimulation from TSH (thyroid stimulating hormone) released by the pituitary gland. As in all endocrine glands, the interstitium has a rich vascular supply into which hormone is secreted.

### **Congenital abnormalities:**

1. Congenital absence of thyroid (aplasia) causes cretinism.
2. Ectopic thyroid gland: lingual thyroid, along midline in neck: sublingual, suprahyoid, infrahyoid or lateral position in neck (lateral aberrant thyroid) which always represent lymph node metastasis from thyroid carcinoma (usually papillary carcinoma) rather than ectopia. Rare sites esophagus, larynx, trachea, soft tissues of the neck.
3. Thyroglossal fistula and thyroglossal cyst in midline of the neck lined by respiratory or squamous epithelium, contain thyroid tissue and lymphoid tissue in its wall.

Thyroid diseases present either as thyroid enlargement (**goiter**: diffuse or nodular) or as excess (**hyperthyroidism**) or deficiency (**hypothyroidism**) of thyroid hormones.

**Hyperthyroidism:** Clinically called thyrotoxicosis due to hypersecretion of thyroid hormones and presents with signs of hypermetabolism and excessive stimulation of the sympathetic system (patient present with weight loss, but increased sensitivity to circulatory adrenaline, and there is increased appetite, patient is nervous, irritable with heat intolerance, excessive sweating, fine tremor, tachycardia, atrial fibrillation, which may lead to cardiac failure, eye signs include; lid-lag and lid-retraction.

### **Causes:**

1. Grave's disease is the most common cause in 80-85% of cases.
2. Toxic nodular goiter 10% of cases.
3. Thyroid adenoma 5-10% of cases.
4. Other causes: Early Hashimoto's thyroiditis, pituitary adenoma secrete TSH, exogenous thyroid hormone and large doses of iodine give to patient with nontoxic nodular goitre

**Hypothyroidism:** Deficiency of thyroid hormones in adult is called myxoedema and in infant and early *childhood* is called *cretinism*.

**Myxedema:** dry waxy swelling of the skin of the extremities and face. Patient is lethargic, feel cold, with constipation, psychosis, skin and hair are dry, coarse facial feature due to deposition of mucopolysaccharide in dermis, and there is pain, parasthesia (involvement of nerves), voice is gruff (involvement of larynx), increased weight, increased serum cholesterol, bradycardia, pericardial effusion.

**Cretinism:** mental retardation, dwarfism, coarse facial features, a protruding tongue and umbilical hernia.

### **Causes of hypothyroidism:**

1. Autoimmune thyroiditis such as Hashimoto's thyroiditis (most common cause in adult) and primary myxoedema.
2. Congenital: aplasia or hypoplasia.
3. Iatrogenic: following thyroidectomy, radiation therapy.
4. Secondary hypothyroidism due to hypopituitarism.
5. Severe iodine deficiency (in endemic areas).
6. Dietary: goitrogens in food
7. Drugs: propylthiouracil, lithium.
8. Genetic causes; include; dysmorphogenetic goiter, due to absence of enzymes involved in synthesis of thyroid hormones.
9. Pendred's syndrome (dysmorphogenesis+deafness+mutism).

**Goiter:** is enlargement of the thyroid. It is either diffuse or nodular, nontoxic or toxic.

### **Nontoxic goiter:**

It is the commonest lesion of thyroid gland, causing enlargement of thyroid as a compensatory hyperplasia by increase TSH due to defect in the synthesis of thyroid hormones.

It is of two types:

- Endemic goiter
- Sporadic goiter

**Endemic goiter:** Occurrence of nontoxic goiter in more than 10% of population. It is always related to iodine deficiency. Usually occurs in mountainous areas and areas remote from the sea, it is due to iodine deficiency in food and water, but its incidence has decreased upon introduction of iodized salt. Morphological features are the same for sporadic and endemic goiter.

### **Nodular goiter**

Euthyroid represents the most common cause for an enlarged thyroid gland and the most common disease of the thyroid. MNG characterized by

1. Asymmetrical enlargement.
2. Multiple nodules of variable size.
3. Secondary degenerative changes: hemorrhage, fibrosis, cystic degeneration filled with fluid, and calcification can be formed.

### **Microscopic features of nontoxic goiter:**

**Early stage,** diffuse hyperplasia of follicles with scanty colloid (parenchymatous goiter), this is followed by accumulation of colloid with involution of epithelium (colloid goiter).

**Later on,** nodules formation of variable size contain colloid separated by fibrous tissue (multinodular colloid goiter) associated with degenerative changes: cystic changes, hemorrhage, fibrosis, calcification.

### **Multinodular goiter:**

Different sized follicles some are dilated and lined by flattened epithelium (indicate inactivity), filled with colloid, others lined by normal or hyperplastic epith. In some cases, one nodule prominently enlarged (dominant nodule) confused with tumor. In some cases of long standing multinodular goiter especially in elderly, show picture of hyperthyroidism (toxic nodular goiter).

### **Autoimmune thyroid diseases:**

These characterized by:

1. Presence of circulating auto antibodies to thyroid tissue.
2. Lymphocytic infiltration with destruction of thyroid tissue and formation of lymphoid follicles with germinal centers.
3. It may be associated with other autoimmune diseases such as Addison's disease, D.M., SLE, rheumatoid arthritis, pernicious anemia.

### **Hashimoto's thyroiditis:**

This disease due to presence of auto antibodies (antithyroglobulin, anti-microsomal antibody). Increase in HLA-DR5 and B5 suggests genetic predisposition. 1-2% led to B-cell lymphoma. Increase risk of papillary carcinoma. This end result of Hashimoto's thyroiditis is atrophy of the thyroid with symmetrical shrinkage of the gland and hypothyroidism. Initially, the thyroid is enlarged and there may be transient hyperthyroidism, followed by a euthyroid state and then hypothyroidism with eventual atrophy years later.

In Hashimoto's thyroiditis lymphoid follicles can be seen in the gland. This is an autoimmune disease and often antithyroglobulin and antimicrosomal antibodies can be detected. Other autoimmune diseases such as Addison's disease or pernicious anemia may also be present.

In Hashimoto's thyroiditis, these cells can be seen:

1. Hürthle cells: large pink cells at the center and right
2. The lymphoid follicle with germinal center is at the left.

### **Grave's disease:**

It's characterized by diffuse thyroid hyperplasia and hyperthyroidism (diffuse toxic goiter). Its incidence increase in HLA-DR3 individuals suggests genetic predisposition. It results from presence of autoantibodies to TSH receptors cause their activation and stimulate thyroid hormone secretion causing hyperthyroidism. These antibodies are called thyroid stimulating immunoglobulin (TSI: stimulate thyroxine -T4 synthesis). TGI lead to gland hyperplasia and enlargement.

A diffusely enlarged thyroid gland associated with hyperthyroidism is known as Grave's disease. The infoldings of the hyperplastic epithelium are lined by tall columnar thyroid epithelium with clear vacuoles in the colloid next to the epithelium where the increased activity of the epithelium to produce increased thyroid hormone has led to scalloping out of the colloid.

## Other autoimmune diseases

- Primary myxoedema.
- Lymphocytic thyroiditis.

## Other type of thyroiditis:

- De Quervain's thyroiditis (granulomatous, or subacute thyroiditis).
- Riedel's thyroiditis

**DeQuervian's thyroiditis:** This is subacute granulomatous thyroiditis which probably follows a viral infection and leads to a painful enlarged thyroid. This disease is usually self-limited over weeks to months and the patients return to euthyroid state. There is foreign body giant cells with destruction of thyroid follicles.

**Riedel's thyroiditis:** Very rare disease of unknown etiology, characterized by extensive replacement of thyroid tissue by dense fibrous tissue causing hardness of the gland (stony hard) with extension of fibrous tissue outside the gland cause fixation of thyroid to adjacent structures (iron collar) such as: trachea, recurrent laryngeal nerve (clinically mimic Carcinoma), some cases associated with retroperitoneal or mediastinal fibrosis

## Thyroid tumors:

1. Tumors arise from follicular epithelial cells:
  - a. **benign:** follicular adenoma (majority of thyroid tumor)
  - b. **malignant:** follicular carcinoma, papillary carcinoma and anaplastic carcinoma.
2. Tumors arise from C cells: medullary carcinoma.

## Follicular adenoma:

It is the commonest thyroid tumor mainly in females over 30 years. Adenoma usually presents with nonfunctioning (cold) nodule but may be cause hyperthyroidism (toxic adenoma) which is hot nodule on thyroid scan. The nodule is painless, if large may produce local symptoms.

**Gross:** Adenoma usually solitary encapsulated nodule (3-10 cm) and compressing surrounding thyroid tissue.

**Histopathological features:** Adenoma consists of uniform follicles contain colloid, surrounded by fibrous capsule without capsular or vascular invasion with or without nuclear pleomorphism or atypia (endocrine atypia).

Adenoma with microfollicles and little colloid called fetal adenoma, while those with macrofollicles filled with colloid called colloid adenoma. If it consists of Hürthle cells (Hürthle cell adenoma). All have the same behavior.

Follicular adenomas can appear as a solitary neoplasm that is surrounded by a thin white capsule. It is sometimes difficult to tell a well-differentiated follicular carcinoma from a follicular adenoma. Thus, patients with follicular neoplasms are treated with subtotal thyroidectomy just to be on the safe side. This adenoma is a well-differentiated neoplasm because it closely resemble normal tissue. The follicles of the adenoma contain colloid, but there is greater variability in size than normal.

## **Papillary carcinoma:**

All papillary tumors of thyroid are malignant, it is the commonest malignant tumor of the thyroid =80% of all carcinomas. Occur most often in middle aged females. It may be solitary or multifocal within the gland. It may be well circumscribed and even encapsulated, or ill defined. This tumor commonly metastasize by lymphatic rather than by blood, and lymph node metastasis in the neck present in about half of cases and the presence of cervical lymph node metastasis doesn't affect the prognosis.

**Prognosis is good;** 10 year survival is 85%. Papillary carcinoma may be very small (occult) and patient present with cervical lymph node metastasis (previously called lateral aberrant thyroid). **Histology:** tumors have papillary structures with fibrovascular core lined by cuboidal cells with characteristic nuclear features; clear or empty nuclei with ground glass or (Orphan Annie) nuclei, intranuclear pseudoinclusion and grooved nuclei.

**Psammoma bodies:** concentrically calcified structures are often present within the papillae.

Papillary carcinoma can be multifocal, because of the propensity to invade lymphatics within thyroid, and lymph node metastases are common. The larger mass is cystic and contains papillary excrescences.

In papillary carcinoma the fronds of tissue have thin fibrovascular cores. The fronds have a papillary pattern. There is no such thing as a papillary adenoma, and all papillary neoplasms of the thyroid should be considered malignant.

The cells of the neoplasm have clear nuclei. Papillary carcinomas are indolent tumors that have a long survival, even with metastases. The most favorite site of metastasis is to local lymph nodes in the neck. In fact, some papillary carcinomas may first present as nodal metastases.

## **Follicular carcinoma:**

15 % of all thyroid cancer, more common in endemic area(dietary iodine deficiency), suggesting that, in some cases,nodular goiter may predispose to ca. more in females, occurs in 5th decade(older than papillary ca), blood metastasis is more than lymphatic metastasis, especially to bone and lung. Prognosis is poorer than papillary carcinoma, 5 year survival 50%. It is of two types:

1. Microinvasive carcinoma (minimally invasive carcinoma): Encapsulated tumor and differentiated from follicular adenoma by presence of fibrous capsular invasion and/or vascular invasion. prognosis is good.
2. Widely invasive carcinoma: Widely spread of tumor within thyroid gland and outside the gland with prominent blood vessels invasion. prognosis is poor.

## **Medullary carcinoma:**

It is a neuroendocrine neoplasm, 5% of thyroid cancer, either sporadic 80% or familial 20% as part of multiple endocrine neoplasia-type IIA or B. Sporadic type is usually unilateral (solitary) and occurs in 5th-6th decade. Familial type is usually bilateral and multifocal associated with C-cell hyperplasia; occurs in young adults and even in children.

**Gross appearance:** it is solitary nodule or multiple lesions ± hemorrhage and necrosis. **Histology:** tumor consists of polygonal to spindle cells form nests, cords or even follicles with amyloid deposition in stroma.



Medullary carcinoma spread by both blood and lymphatic. **Prognosis:** familial type is more aggressive and fatal tumor especially MEN-2B. This tumor produce calcitonin and other hormones, e.g.: VIP.

Medullary carcinomas are derived from the thyroid "C" cells and, therefore, have neuroendocrine features such as secretion of calcitonin. The amyloid stroma of the medullary thyroid carcinoma has been stained with Congo red. Medullary carcinomas can be sporadic or familial. The familial kinds are associated with multiple endocrine neoplasia syndromes.

### **Anaplastic carcinoma:**

Highly malignant tumor, form<5% of thyroid carcinoma, mainly occurs in elderly women usually present with short history and grow rapidly, locally invasive and early metastasis by blood and lymphatics. Tumor is poorly differentiated with spindle and bizarre giant cells represent poorly differentiated follicular or papillary carcinoma.

There is no resemblance to normal thyroid tissue-hence the term "anaplastic" to characterize this thyroid carcinoma. Note the elongated spindle cells. This is the most aggressive thyroid cancer, and luckily the least common.

### **Etiology of thyroid carcinoma:**

1. Iodine deficiency: May determine the type of tumor but not as causative agent. Follicular carcinoma more in endemic area where iodine is deficient (nodular goiter).
2. Radiation: To head and neck in children for treatment of lymphoma or other lesions (tonsillar enlargement, acne) may increase the risk for development of thyroid carcinoma especially papillary carcinoma. (Atomic bomb in Japan, Ionizing radiation in Chernobyl also increase inc. of papillary carcinoma).
3. Chromosomal translocation, t(2;3) recently found in a proportion of follicular carcinomas.
4. RET protooncogen mutation presents in (95%) of MEN-II.
5. Inactivating mutation of TP53 in anaplastic carcinoma.

### **Lymphoma:**

Primary NLH of thyroid is B-cell lymphoma; mainly in elderly patients. 80% of cases are associated with Hashimoto's disease.(1-2% of thyroiditis....). It's usually of diffuse large cell type of follicular center cell and it's regarded as MATL-lymphoma. The cells of lymphoma infiltrate the thyroid follicles (lymphoepithelial lesion). It has poor prognosis.

### **Solitary thyroid nodule:**

Benign lesions: Adenomas or localized non neoplastic conditions (e.g., nodular hyperplasia , simple cysts, or foci of thyroiditis). Carcinomas are uncommon >1%.

Clinical criteria suggest neoplastic nodule:

1. Solitary
2. Solid
3. Nodules in young patients
4. In males
5. Cold

Definite dx. By FNAC AND HISTOLOGICAL STUDY.

### III. Parathyroid glands

They are 4 glands located on posterior surface of thyroid gland (3-4mm in size) consist of 2 types of cells: Chief cells and Oxyphil cells. It secretes PTH (parathyroid hormone) acts on bone and kidney to increase the  $\text{Ca}^{+2}$  level in blood.

#### Hyperparathyroidism:

**Primary:** excess secretion of PTH causing hypercalcemia (one of most common endocrine disorders). MEN-1, 2A

#### Causes:

1. Single parathyroid adenoma: commonest cause(80-90%), solitary and encapsulated confined to single gland (others are normal or shrunken).
2. Primary hyperplasia (10-20%): all glands are diffusely involved.
3. Parathyroid carcinoma (less than 1% of cases).

#### Clinical features

- Painful bones: due to osteoporosis or osteitis fibrosa cystica.
- Renal stones: polyuria, nephrocalcinosis.
- Abdominal pains: constipation, peptic ulcers, G.stones, pancreatitis...
- Psychic moans: depression, seizures.

#### Morphology:

**Adenoma:** soft, tan encapsulated nodule composed of uniform, polygonal chief cells with few nests of oxyphil cells), a rim of compressed parathyroid tissue separated by a fibrous capsule at the edge. Adipose tissue is inconspicuous within the adenoma. No invasion or metastases.

**Other organs:** skeletal; osteitis fibrosa cystica, brown tumor. **Renal:** UT-stones, nephrocalcinosis. Metastatic calcification in stomach, lungs, myocardium and blood vessels.

**Parathyroid adenoma:** This is the most common cause for primary hyperparathyroidism. A rim of normal parathyroid tissue admixed with adipose tissue cells are compressed to the right and lower edge of the adenoma.

Parathyroid hyperplasia: is the second most common form of primary hyperparathyroidism, with parathyroid carcinoma the least common form.

### Secondary hyperparathyroidism

#### Causes:

1. Chronic renal failure.
2. Malabsorption syndrome.
3. Vitamin D deficiency.
4. Pregnancy and lactation

The glands are hyperplastic: diffuse or multinodular. In minority of patients parathyroid activity may become autonomous and excessive with resultant hypercalcemia termed tertiary hyperparathyroidism

## **Hypoparathyroidism:**

### **Causes:**

1. Surgical removal of glands during thyroidectomy.
2. DiGeorge syndrome: congenital aplasia of thymus and parathyroid gland lead to decrease in T-cell number and hypocalcaemia seen in infant and children.
3. Autoimmune disease.

## **IV. Adrenal (Suprarenal) glands**

They consist of cortex and medulla. Each adult adrenal gland weighs from 4 to 6 grams. Cortex: is mesoderm in origin, yellow in color, consisting of three zones:

1. **Outer:** zona glomerulosa produce aldosterone.
2. **Intermediate** zone: zona fasciculata produce glucocorticoids.
3. **Inner** zone: zona reticularis produce sex hormones mostly (androgen) and less estrogen.

Adrenal medulla: is neuroectoderm in origin, brown in color consisting of chromaffin cells, nerve fibers and sympathetic ganglion cells produces catecholamines (adrenaline and nor-adrenaline).

### **Adrenal cortical tumors:**

**1. Adrenal adenoma:** is commonly seen in postpartum examination as small encapsulated yellow nodule, Unilateral or bilateral, consists of cells similar to adrenal cortex, the majority are non-functioning tumor, some are functioning with excessive secretion of cortisol, aldosterone, and sex hormones.

The adenoma is composed of yellow firm tissue just like adrenal cortex. This neoplasm is well-circumscribed. Histologically, it is composed of well-differentiated cells resembling cortical fasciculata zone. It is benign.

**2. Cortical carcinoma:** most important sign to distinguish between benign and malignant cortical tumor is the presence of metastasis. Other signs include tumor >100gms, large non-functioning tumor and tumor secretes androgen are most likely to be malignant.

Histology: Very difficult to differentiate between benign and malignant tumor on morphology alone but presence of high mitotic activity, necrosis, capsular and vascular invasion, and marked anaplasia are more favorable signs of malignancy. Such neoplasms are usually functional (secreting corticosteroids or sex steroids). They have a poor prognosis.

It is difficult to determine malignancy in endocrine neoplasms based upon cytology alone. Thus, invasion (as seen here in a vein) and metastases are the most reliable indicators. Luckily, most endocrine neoplasms are benign adenomas.

**Adrenocortical hyperfunction:** It produces 3 main syndromes:

1. Cushing's syndrome: hypersecretion of cortisol.
2. Hyperaldosteronism: primary called Conn's syndrome.
3. Adrenogenital syndrome: excessive secretion of androgen.

## **Cushing's syndrome:**

Because of its effect on the metabolism results in many signs and symptoms. It occurs most commonly in women with central (truncal) obesity, moon face, buffalo hump, muscle wasting of limbs with weakness, osteoporosis may cause vertebral collapse, skin atrophy with bruising and striae, skin pigment(in extra-adrenal Cushing syndrome), hypertension, impaired GTT with hyperglycemia, glucosuria, wound healing delayed, menstrual disorder, hirsutism, amenorrhea, and virilization, depression, psychosis.

### **Causes:**

1. Long term therapy by corticosteroids: (iatrogenic) is the most common cause e.g.: patients with rheumatoid arthritis or nephrotic syndrome.
2. Cushing's disease: pituitary Cushing's syndrome, due to excessive secretion of ACTH by pituitary adenoma or hyperplasia.
3. Adrenal tumors and nodular hyperplasia (Adrenal): either adenoma or carcinoma, adrenal tumors are commonest cause of Cushing's syndrome in children, especially carcinoma. Increase serum level of the glucocorticoids and ACTH secretion is decrease due to feedback and this cause atrophy of contralateral adrenal gland and tissue adjacent to tumor.
4. Ectopic ACTH syndrome (paraneoplastic): secretion of ACTH by non-pituitary tumors such as: small cell carcinoma of lung, carcinoid tumor, and islet cell tumor of pancreas, both 2&4 produce bilateral adrenal hyperplasia .

**Hyperaldosteronism:** primary or secondary

### **Primary hyperaldosteronism (Conn's syndrome):**

#### **Causes:**

1. Adenoma of zona glomerulosa 80% of cases.
2. Bilateral hyperplasia of zona glomerulosa 15% of cases.
3. Carcinoma (rare).

**Secondary hyperaldosteronism:** excessive stimulation of renin-angiotensin system stimulates aldosterone secretion.

#### **Causes:**

1. Renal disease with renal ischemia.
2. Heart failure with edema.
3. Liver cirrhosis.
4. Renin secreting tumor (rare).

To differentiate secondary from primary type both plasma level of aldosterone and renin are high in secondary type.

## **Adrenogenital syndrome:**

### **Causes:**

1. Adrenal tumors: tumors with excessive secretion of androgen cause virilism in females (hirsutism and clitoris enlargement) and in males cause precocious puberty. These tumors are mostly carcinoma.
2. Congenital adrenal hyperplasia: it is rare inborn error of metabolism, AR condition, enzyme deficiency involved in synthesis of glucocorticoids this results in plasma reduction of cortisol, hypersecretion of ACTH this in turn causes bilateral adrenal hyperplasia with excess production of androgen commonest type is 21-hydroxylase deficiency causes virilism in female and in male leads to precocious puberty also there is decrease in synthesis of aldosterone.

**Adrenocortical hypofunction:** either acute or chronic

### **Acute adrenocortical insufficiency:**

May occur in septicemia particularly in children with meningococcal septicemia (Waterhouse-Friedrichsen syndrome) less commonly with other infections. Presentation with hypotensive shock, high level K, low level Na and glucose, hypotension, collapse and death, also patients have high fever and skin rashes. Adrenal gland shows hemorrhage with extensive necrosis of cortex.

### **Other causes:**

1. Chronic adrenal insufficiency may be complicated by acute failure (Addisonian crisis) due to increased demand of cortisone as in infection or trauma.
2. Sudden withdrawal of corticosteroid TRT from patient with long term therapy (tapering of therapy by corticosteroid is mandatory in those patients).

The patient with Waterhouse-Friderichsen syndrome has sepsis with DIC and marked purpura. The adrenals are black-red from extensive hemorrhage in a patient with meningococemia. This produces the Waterhouse-Friderichsen syndrome. There is marked hemorrhagic necrosis with acute adrenal insufficiency.

## **Chronic adrenocortical insufficiency (Addison's disease):**

### **Causes:**

1. Autoimmune adrenalitis: commonest cause (75%), atrophy of adrenal cortex with lymphocyte infiltration, medulla is normal may be associated with autoimmune disease of thyroid, DM and pernicious anemia.
2. Tuberculosis: second most common cause. Adrenal enlarged with caseation and calcification medulla destroyed. Other infection: AIDS, histoplasmosis.
3. Amyloidosis.
4. Metastatic tumor: especially lung and breast carcinomas.
5. Sarcoidosis.

Addison's disease (chronic) adrenocortical insufficiency. Here are Congo red stained deposits of amyloid in the adrenal cortex. Amyloid may collect in adrenal as well as other organs.

**Adrenal medulla:**

**Pheochromocytoma:** Tumor of adrenal medulla secretes catecholamines causing paroxysmal hypertension, palpitation, severe head ache, sweating, hyperglycemia, occur in young adults, it has rule of 10:

- 10% bilateral.
- 10% non-functioning.
- 10% in children.
- 10% malignant.
- 10% familial (MEN-2).

Patients with pheochromocytoma have episodic hypertension. The tumor is grey-tan compared to the yellow cortex stretched around it.

**Neuroblastoma:** small round cell tumor of children arises from primitive cells of sympathetic system. Commonly seen in children below 5 years old, common site is adrenal medulla, other sites are posterior mediastinum, retroperitoneum. It is highly malignant tumor with lymph node metastasis and blood metastasis to the bone.

**Others:** Neurofibroma, ganglioneuroma, and myelolipoma.

**NOTE:** to see the slides and images, see the presentation.