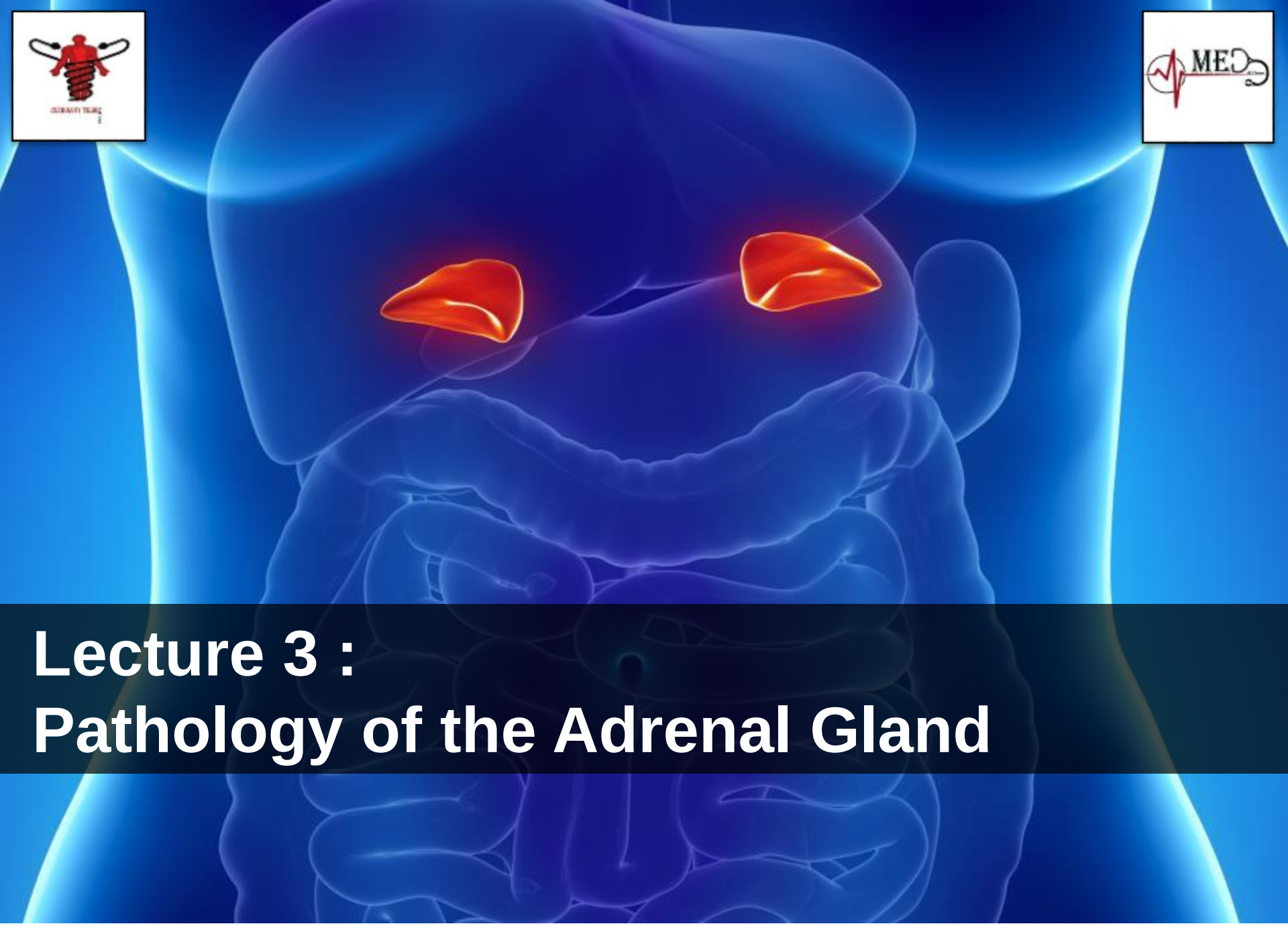
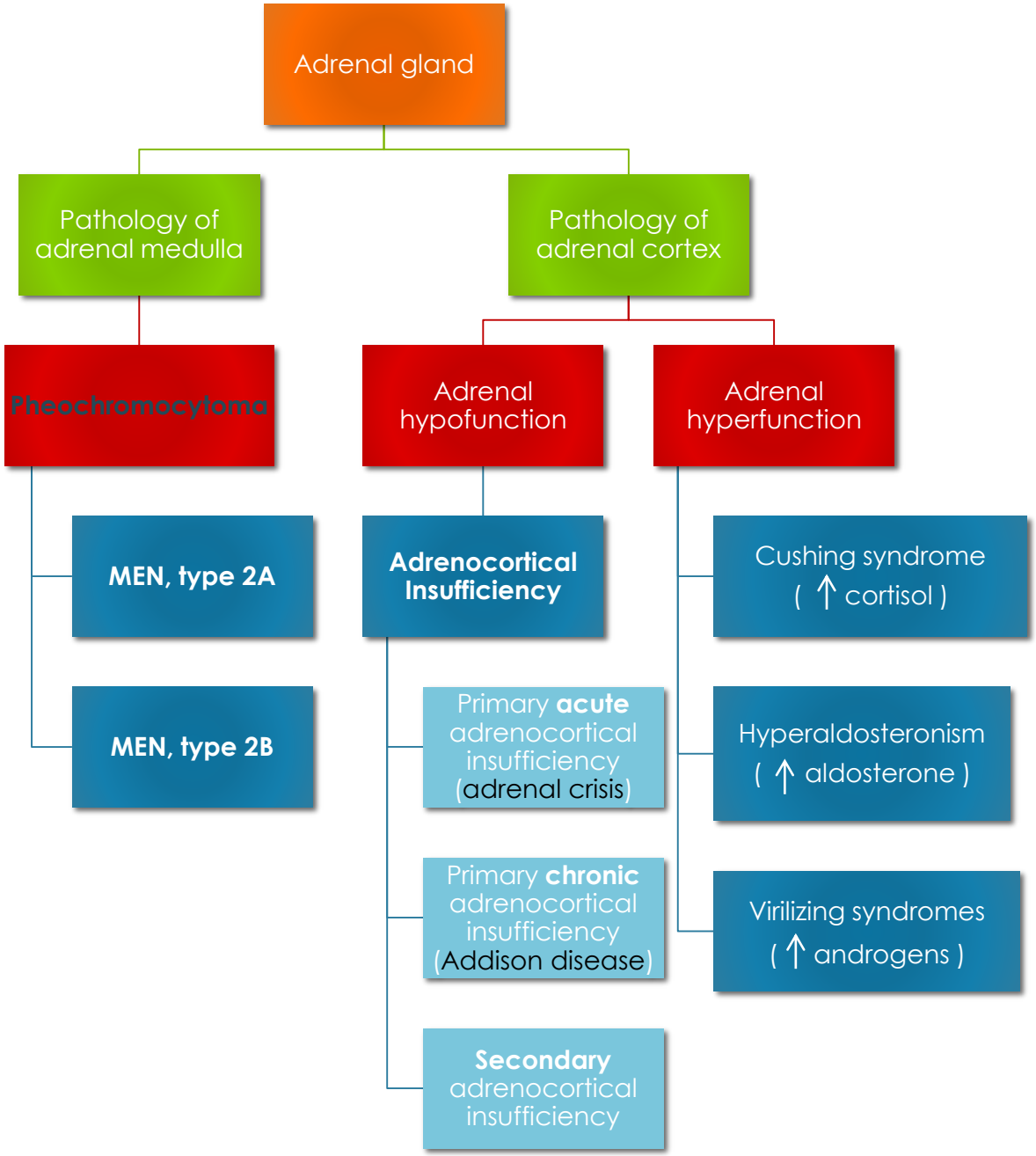


Lecture 3 :
Pathology of the Adrenal Gland

▫ Important ▫ Notes ▫ Explanation

Objectives

- ✓ Recognize the variants of hyperadrenalism.
- ✓ Recognize the variants of hypoadrenalism.
- ✓ Understand the histopathological features and molecular pathology of both medullary (pheochromocytoma) and adrenocortical neoplasms.


Adrenal gland
Pathology of adrenal medulla
Pathology of adrenal cortex
Pheochromocytoma
Adrenal hypofunction
Adrenal hyperfunction
MEN, type 2A
MEN, type 2B
Adrenocortical Insufficiency
Primary acute adrenocortical insufficiency (adrenal crisis)
Primary chronic adrenocortical insufficiency (Addison disease)
Secondary adrenocortical insufficiency
Cushing syndrome (↑ cortisol)
Hyperaldosteronism (↑ aldosterone)
Virilizing syndromes (↑ androgens)

Pathology of Adrenal Cortex (Hyperfunction)

1- Hypercortisolism (Cushing Syndrome)

- Broadly divided into exogenous (drugs for example) and endogenous causes.
- The vast majority of cases of Cushing syndrome are the result of the administration of **exogenous glucocorticoids** ("iatrogenic" Cushing syndrome)

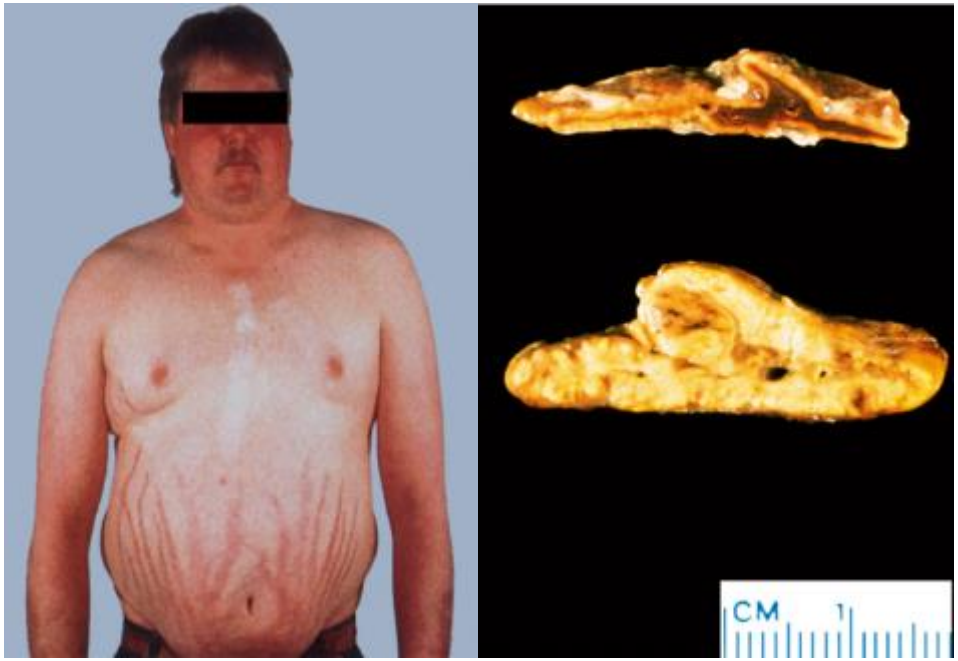
The **endogenous causes** can be divided into:

ACTH-DEPENDENT (High ACTH)	ACTH-INDEPENDENT
1. Cushing disease (pituitary adenoma, rarely CRH-dependent pituitary hyperplasia) 2. Ectopic corticotropin syndrome (ACTH-secreting pulmonary small cell carcinoma **(Paraneoplsamic Syndrome)**, bronchial carcinoid)	1. Adrenal adenoma, carcinoma 2. Macronodular hyperplasia (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin and serotonin receptors) 3. Primary pigmented nodular adrenal disease (PRKARIA and PDE11 mutations) 4. McCune-Albright syndrome (GNAS mutations)

Clinical Features of Cushing Syndrome

- Obesity or weight gain
- Facial plethora
- Rounded face (Moon face)
- Decreased libido
- Thin skin
- Decrease in linear growth in children
- Menstrual irregularity
- Hypertension
- Hirsutism
- Depression/emotional liability
- Easy bruising
- Glucose intolerance
- Weakness
- Osteopenia(↓bone matrix) or fracture
- Nephrolithiasis

More commonly seen



Diffuse hyperplasia of the adrenal(bottom)

Morphology:

One of the following abnormalities:

1. **Cortical atrophy*** : results from exogenous glucocorticoids
2. **Diffuse hyperplasia :** individuals with ACTH-dependent Cushing syndrome
3. **Macronodular** (less than 3 cm) or **micronodular** (1-3 mm) **hyperplasia**
4. **Adenoma or carcinoma** (as Solitary Mass)

* (because of the exogenous glucocorticoids, cells are at rest (not secreting) → shrunken)

2- Hyperaldosteronism (Conn's Syndrome) (Excess aldosterone secretion)

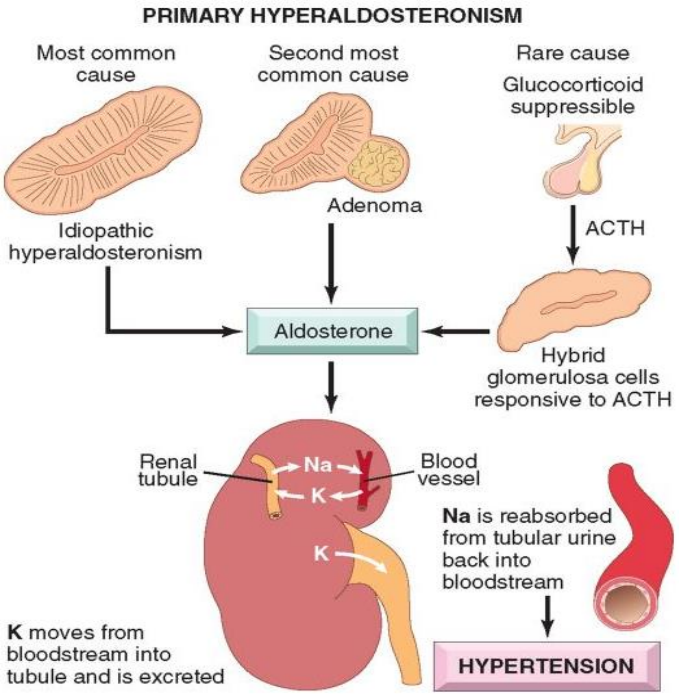
a. **Primary aldosteronism** (autonomous overproduction of aldosterone) with resultant suppression of the renin-angiotensin system and decreased plasma renin activity.

b. **Secondary hyperaldosteronism,** in contrast, aldosterone release occurs in response to activation of the renin-angiotensin system.

Causes :

Primary hyperaldosteronism is caused by :

- **Adrenocortical neoplasm**, a solitary aldosterone-producing adrenocortical adenoma (more common than carcinoma) a condition referred to as **Conn syndrome.** This syndrome occurs most frequently in adult middle life and is more common in women than in men (2:1).
- **Primary adrenocortical hyperplasia (most common)** (idiopathic hyperaldosteronism), characterized by bilateral nodular hyperplasia of the adrenal glands.



Secondary hyperaldosteronism :

- Decreased renal blood supply :

(arteriolar nephrosclerosis, renal artery stenosis).

- Arterial hypovolemia and edem :

(congestive heart failure, cirrhosis, nephrotic syndrome)

- Pregnancy :

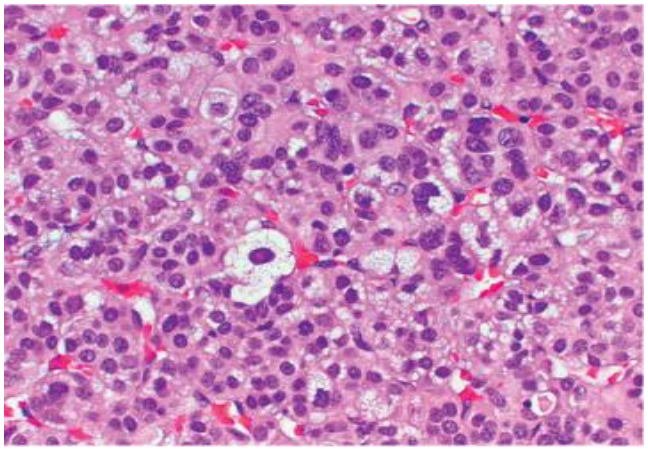
(due to estrogen-induced increases in plasma renin substrate).

Clinical Features :

- Presents with **hypertension**. With an estimated prevalence rate of 5% to 10% among nonselected hypertensive patients.
- **Primary hyperaldosteronism may be the most common cause of secondary hypertension** (i.e., **hypertension secondary to an identifiable cause).**
- Aldosterone promotes sodium reabsorption.
- **Hypokalemia** results from renal potassium wasting

Morphology:

- Solitary.
- Small (<2 cm in diameter).
- Well-circumscribed lesions in the left more than right.
- Thirties and forties.
- Women more often than in men.
- Buried within the gland and do not produce visible enlargement.
- Bright yellow on cut section.
- Cell may look like fasciculata, but still they secrete aldosterone.



Histoogically : Vacuolated cytoplasm
(because of itracytoplasmic lipid)

- Common case-scenario: female, hypertensive, left adrenal.
- Treated with spironolactone, explains the presence of spironolactone bodies in the cytoplasm.

Pathology of Adrenal Cortex (Hypofunction)

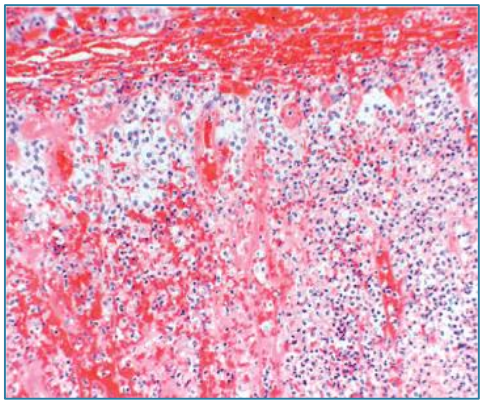
Adrenocortical Insufficiency

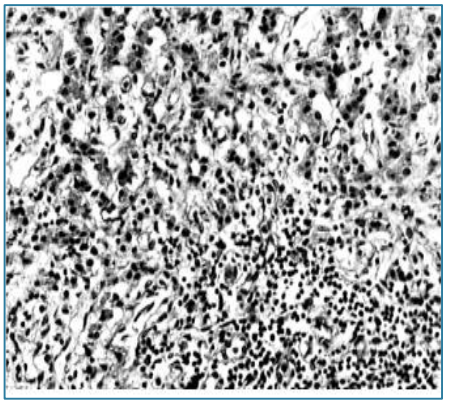
Caused by :

- Primary adrenal disease (congenital adrenal hypoplasia, Autoimmune adrenal insufficiency, infection)
  * In amyloidosis, there's infiltration suffocating the cells so they're not able to secrete anymore → insufficiency.
- Decreased stimulation of the adrenals due to a deficiency of ACTH (secondary hypoadrenalism) (related to either hypothalamic or pituitary)

Three patterns of adrenocortical insufficiency :

- Primary **acute** adrenocortical insufficiency (Adrenal crisis)
  - also in patients with sepsis (waterhouse-friderichsen syndrome) most commonly caused by Neisseria meningitidis
  - history of meningococcal infection, especially in children and old.
- Primary **chronic** adrenocortical insufficiency (Addison disease, that is an auto-immune disease in which we're losing the adrenal)
- **Secondary** adrenocortical insufficiency
- (hemorrhage & infection → loss of function), or in adrenalitis (inflammation), or due to long standing steroids.





Pathology of Adrenal Medulla

The most important diseases of medulla are neoplasms : Neuroblastoma in children and Pheochromocytoma in adults.

Pheochromocytoma

- Pheochromocytomas (chromaffin cells) secrete catecholamines.
- Some times secrete other peptide hormones so may be sometimes associated with Cushing's syndrome .
- Similar to aldosterone-secreting adenomas, give rise to surgically correctable forms of hypertension.
- 0.1% to 0.3% (fatal)
- **Majority of them are benign . Even if you see vascular or capsular invasion and even increase mitosis doesn't mean it's malignant .**
- **The only thing to say it's malignant if there is metastasis.** (To lymph node or to liver and bone).
- Hypertension is the most predominant clinical manifestation.

Rule of 10s :

- **10%** of pheochromocytomas arise in association with one of several familial syndromes MEN-2A and MEN-2B syndromes.
- **10%** of pheochromocytomas are extra-adrenal.
  Phenochromocytoma in the wall of bladder; while passing urine, there will be compression of tumer cells so there will be a shoot in hypertension → patient will feel dizzy. (important)
- **10%** of nonfamilial adrenal pheochromocytomas are bilateral; this figure may rise to 70% in cases that are associated with familial syndromes.
- **10%** of adrenal pheochromocytomas are biologically malignant
- **10%** of adrenal pheochromocytomas in childhood

Syndromes Components :

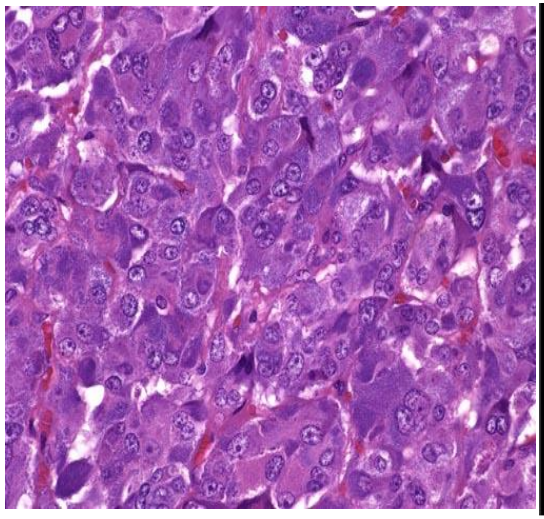
- **MEN, type 2A :** Medullary thyroid carcinomas and C-cell hyperplasia, Pheochromocytomas and adrenal medullary hyperplasia, Parathyroid hyperplasia.
- **MEN, type 2B :** Medullary thyroid carcinomas and C-cell hyperplasia, Pheochromocytomas and adrenal medullary hyperplasia, Mucosal neuromas, Marfanoid features.
- **Von Hippel-Lindau :**
  Renal, hepatic, pancreatic, and epididymal cysts, Renal cell carcinomas, Angiomatosis, Cerebellar hemangioblastomas, Pheochromocytoma.
- **Von Recklinghausen's Neurofibromatosis Type I**
  Café au lait skin spots, Schwannomas, meningiomas, gliomas, Pheochromocytoma.
- **Sturge-Weber** : Cavernous hemangiomas of fifth cranial nerve distribution.

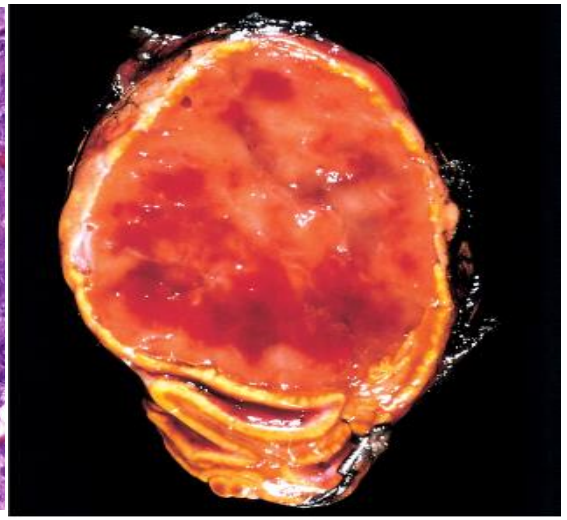
Morphology :

- Polygonal to spindle shaped

(chromaffin, chief cells)

- Small to large hemorrhagic
- Well demarcated
- Sustentacular small cells
- Together, Zellballen nests





Summary (from Robbin's basic pathology)

SUMMARY

Hypercortisolism (Cushing Syndrome)

- The most common cause of hypercortisolism is exogenous administration of steroids.
- Endogenous hypercortisolism most often is secondary to an ACTH-producing pituitary microadenoma (*Cushing disease*), followed by primary adrenal neoplasms (*ACTH-independent* hypercortisolism) and paraneoplastic ACTH production by tumors (e.g., small cell lung cancer).
- The morphologic features in the adrenal include bilateral cortical atrophy (in exogenous steroid-induced disease), bilateral diffuse or nodular hyperplasia (most common finding in endogenous Cushing syndrome), or an adrenocortical neoplasm.

SUMMARY

Adrenocortical Insufficiency (Hypoadrenalism)

- Primary adrenocortical insufficiency can be acute (Waterhouse-Friderichsen syndrome) or chronic (Addison disease).
- Chronic adrenal insufficiency in the Western world most often is secondary to autoimmune adrenalitis, which occurs in the context of one of two autoimmune polyendocrine syndromes: APS1 (caused by mutations in the *AIRE* gene) or APS2.
- Tuberculosis and infections due to opportunistic pathogens associated with the human immunodeficiency virus and tumors metastatic to the adrenals are the other important causes of chronic hypoadrenalism.
- Patients typically present with fatigue, weakness, and gastrointestinal disturbances. Primary adrenocortical insufficiency also is characterized by high ACTH levels with associated skin pigmentation.

Summary (from Robbin's basic pathology)

SUMMARY

Adrenogenital Syndromes

- The adrenal cortex can secrete excess androgens in either of two settings: adrenocortical neoplasms (usually *virilizing* carcinomas) or congenital adrenal hyperplasia (CAH).
- CAH consists of a group of autosomal recessive disorders characterized by defects in steroid biosynthesis, usually cortisol; the most common subtype is caused by deficiency of the enzyme 21-hydroxylase.
- Reduction in cortisol production causes a compensatory increase in ACTH secretion, which in turn stimulates androgen production. Androgens have virilizing effects, including masculinization in females (ambiguous genitalia, oligomenorrhea, hirsutism), precocious puberty in males, and in some instances, salt (sodium) wasting and hypotension.
- Bilateral hyperplasia of the adrenal cortex is characteristic.

Thank You!

We hope you found this helpful and informative.

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