PATHOLOGY TEAM

Leaders

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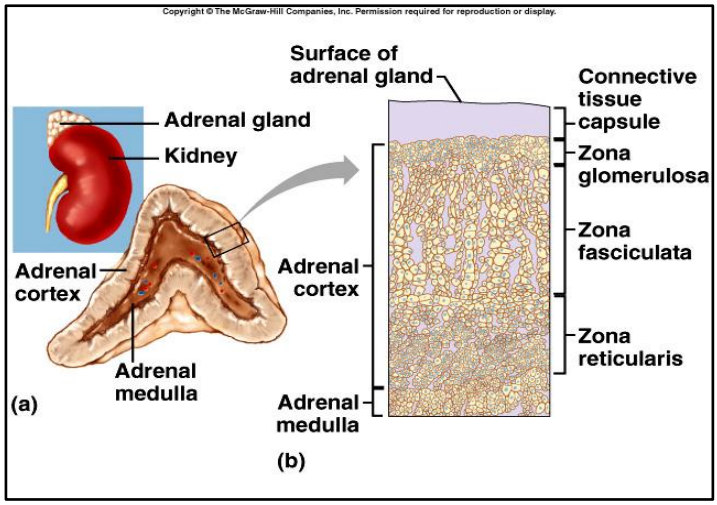
RED: Important infos. | Orange box: for the extra infos. in the comments of lecturer slids and talks | Blue box: for the infos. quoted from Robbins.

Pathology of Adrenal Gland

Adrenal Glands

- The adrenal glands: paired endocrine organs: cortex and medulla: 4 layers
- Three layers in the cortex:
- Zona glomerulosa
- Zona reticularis abuts the medulla.
- Intervening is the broad zona fasciculata (75%) of the total cortex.



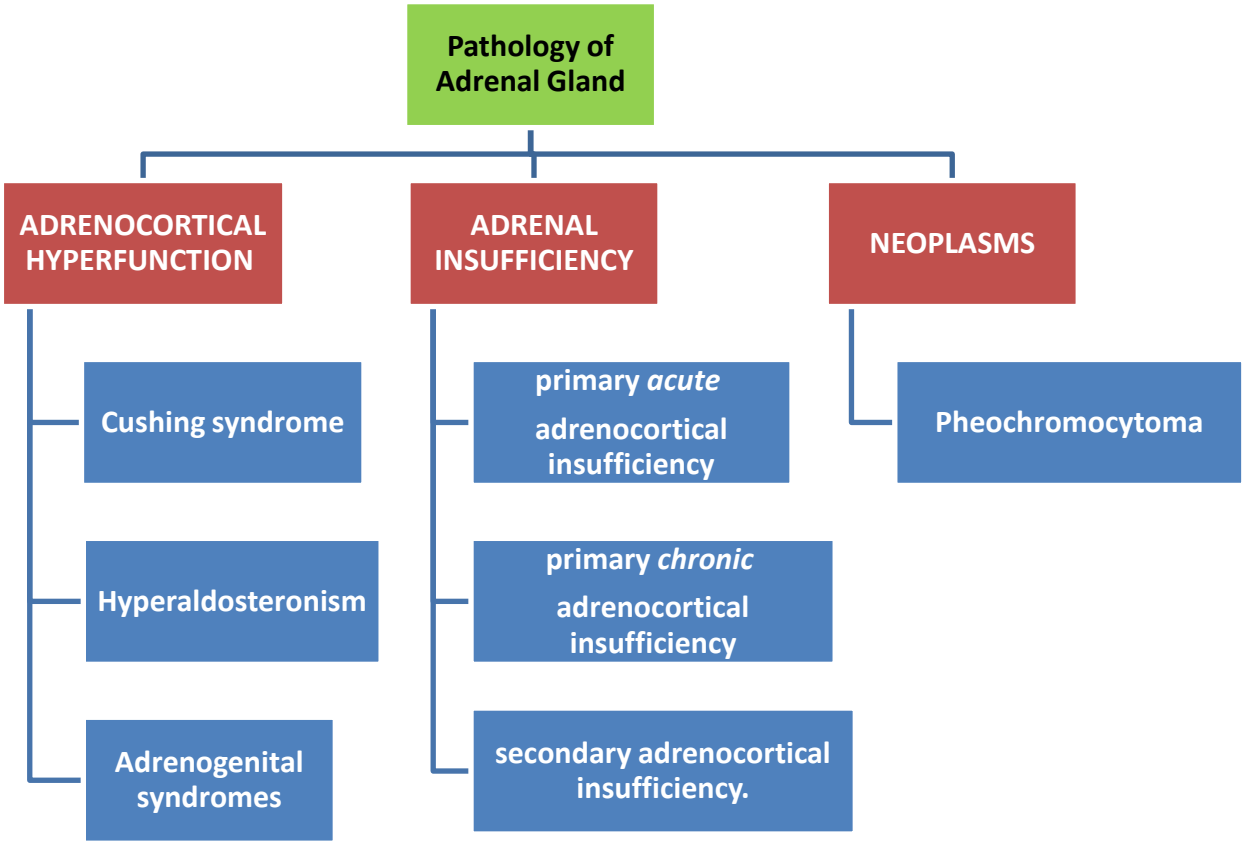
Three types of steroids:

(1) Glucocorticoids (principally cortisol) zona fasciculata

(2) Mineralocorticoids (aldosterone) zona glomerulosa

(3) Sex steroids (estrogens and androgens) zona reticularis.

- The adrenal medulla chromaffin cells- catecholamines, mainly epinephrine



ADRENOCORTICAL HYPERFUNCTION

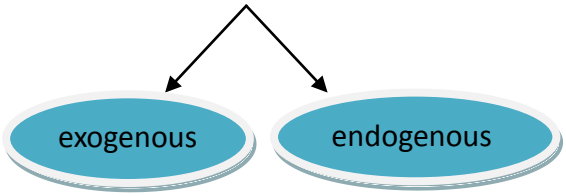
- Three basic types of corticosteroids (glucocorticoids, mineralocorticoids, and sex steroids)
- Thus Three distinctive hyperadrenal syndromes:

(1) *Cushing syndrome, characterized by increased cortisol*

(2) Hyperaldosteronism

(3) Adrenogenital or virilizing syndromes caused by an excess of androgens

(1) Cushing syndrome



- The vast majority of cases of Cushing syndrome are the result of the administration of exogenous glucocorticoids ("iatrogenic" Cushing syndrome)
- The endogenous causes can, in turn, be divided into those that are *ACTH dependent* and those that are *ACTH independent*

Cause	Relative Frequency (%)	Ratio of Females to Males
ACTH-DEPENDENT		
Cushing disease (pituitary adenoma; rarely CRH-dependent pituitary hyperplasia)	70	3.5:1.0
Ectopic corticotropin syndrome (ACTH-secreting pulmonary small-cell carcinoma, bronchial carcinoid)	10	1:1
ACTH-INDEPENDENT		
Adrenal adenoma	10	4:1
Adrenal carcinoma	5	1:1
Macronodular hyperplasia (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin and serotonin receptors)	<2	1:1
Primary pigmented nodular adrenal disease (*PRKARIA* and *PDE11* mutations)	<2	1:1
McCune-Albright syndrome (*GNAS* mutations)	<2	1:1

ADRENOCORTICAL HYPERFUNCTION, Morphology:

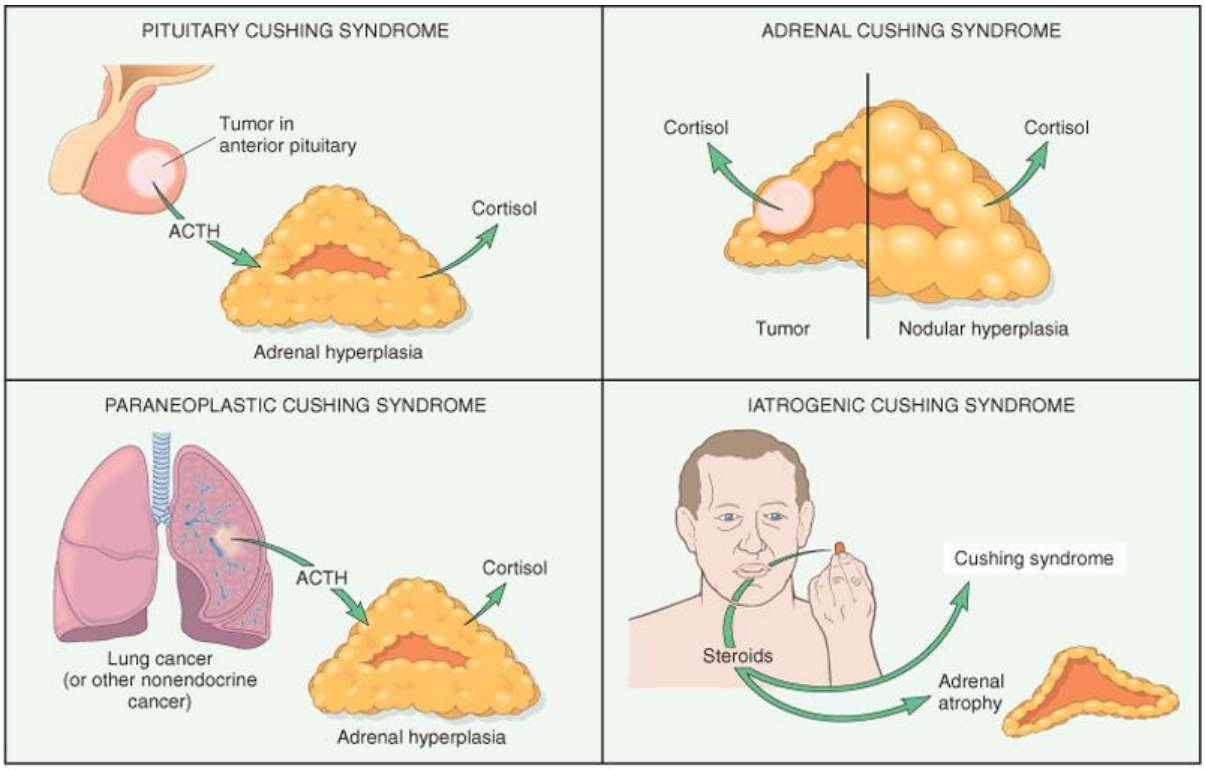
One of the following abnormalities:

(1) **Cortical atrophy**: results from exogenous glucocorticoids

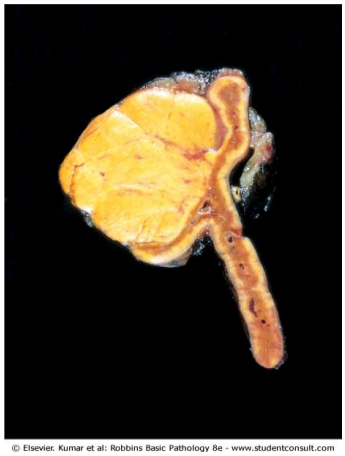
(2) **Diffuse hyperplasia**: individuals with ACTH-dependent Cushing syndrome

(3) Macronodular (less than 3cm), or micronodular(1-3mm) hyperplasia

(4) Adenoma or carcinoma



representation of the various forms of Cushing syndrome

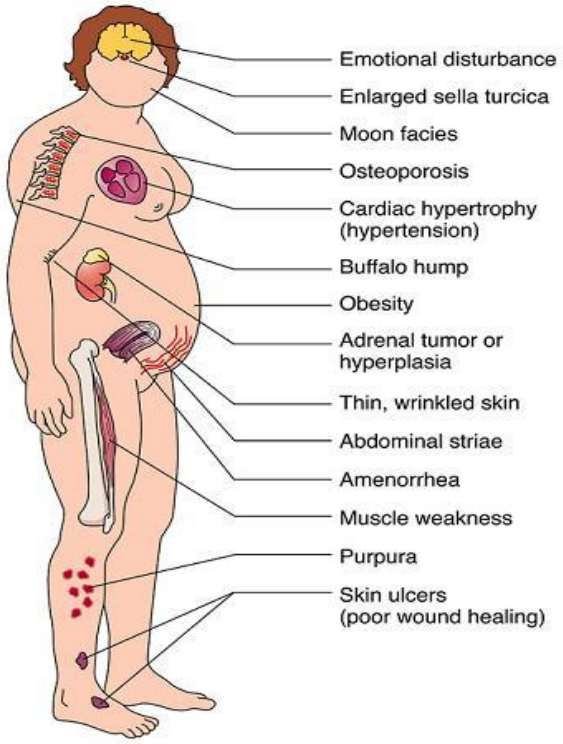


Adrenocortical adenoma

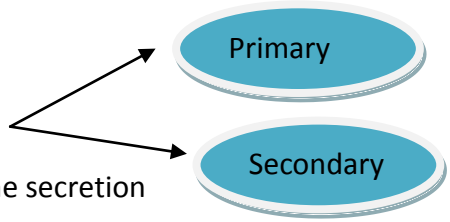
Adrenocortical hyperplasia

Clinical Features of Cushing Syndrome

Obesity or weight gain	95%[*]
Facial plethora	90%
Rounded face	90%
Decreased libido	90%
Thin skin	85%
Decrease in linear growth in children	70–80%
Menstrual irregularity	80%
Hypertension	75%
Hirsutism	75%
Depression/emotional liability	70%
Easy bruising	65%
Glucose intolerance	60%
Weakness	60%
Osteopenia or fracture	50%
Nephrolithiasis	50%



(2) Hyperaldosteronism



Definition: Excess aldosterone secretion

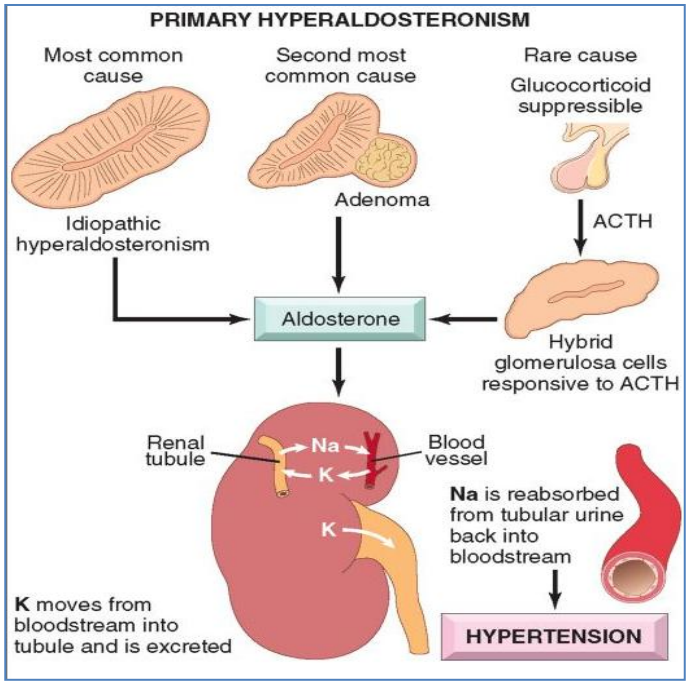
- **Primary aldosteronism** (autonomous overproduction of aldosterone) with resultant suppression of the renin-angiotensin system and decreased plasma renin activity

Causes of Primary aldosteronism:

1- **Adrenocortical neoplasm (Conn syndrome)** , either an aldosterone-producing adrenocortical adenoma (the most common cause) or, rarely, an adrenocortical carcinoma. In approximately 80% of cases, primary hyperaldosteronism is caused by a solitary aldosterone-secreting adenoma, 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). Multiple adenomas may be present in an occasional patient.

2- **Primary adrenocortical hyperplasia** (idiopathic hyperaldosteronism), characterized by bilateral nodular hyperplasia of the adrenal glands, highly reminiscent of those found in the nodular hyperplasia of Cushing syndrome. The genetic basis of idiopathic hyperaldosteronism is not clear, although it is possibly caused by an overactivity of the aldosterone synthase gene, CYP11B2.

3- Glucocorticoid-remediable hyperaldosteronism is an uncommon cause of primary hyperaldosteronism that is familial and genetic. In some families, it is caused by a chimeric gene resulting from fusion between CYP11B1 (the 11β-hydroxylase gene) and CYP11B2 (the aldosterone synthase gene). This leads to a sustained production of hybrid steroids in addition to both cortisol and aldosterone. The activation of aldosterone secretion is under the influence of ACTH and hence is suppressible by exogenous administration of dexamethasone.



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

Plasma Renin ↑ Aldosterone ↑

Causes of Secondary aldosteronism:

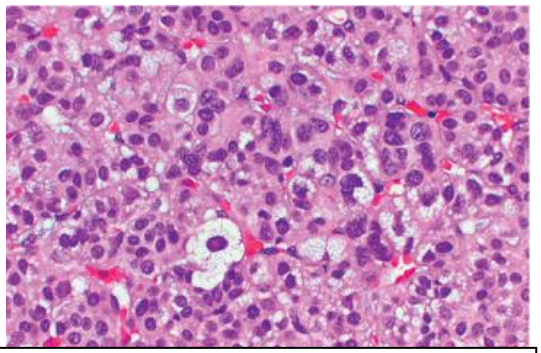
1- **Decreased renal perfusion** (arteriolar nephrosclerosis, renal artery stenosis)
2- **Arterial hypovolemia and edema** (congestive heart failure, cirrhosis, nephrotic syndrome)
3- **Pregnancy** (caused by estrogen-induced increases in plasma renin substrate)

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

Aldosterone-producing adenomas

- Solitary
- Small (<2 cm in diameter)
- well-circumscribed lesions left > 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



The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid

- composed of lipid-laden cortical cells that more closely resemble fasciculata cells than glomerulosa cells (the normal source of aldosterone).
- In general, the cells tend to be uniform in size and shape and resemble mature cortical cells; occasionally, there is some nuclear and cellular pleomorphism but no evidence of anaplasia.
- A characteristic feature of aldesterone-producing adenomas is the presence of eosinophilic, laminated cytoplasmic inclusions, known as spironolactone bodies, found after treatment with the antihypertensive drug spironolactone.
- In contrast to cortical adenomas associated with Cushing syndrome, those associated with hyperaldosteronism do not usually suppress ACTH secretion. Therefore, the adjacent adrenal cortex and that of the contralateral gland are not atrophic.

ADRENAL INSUFFICIENCY

Caused by either primary adrenal disease or decreased stimulation of the adrenals due to a deficiency of ACTH (secondary hypoadrenalism)

- **Three patterns of adrenocortical insufficiency**

(1) Primary *acute* adrenocortical insufficiency **(adrenal crisis)**

(2) Primary *chronic* adrenocortical insufficiency ***(Addison disease)*****,** and

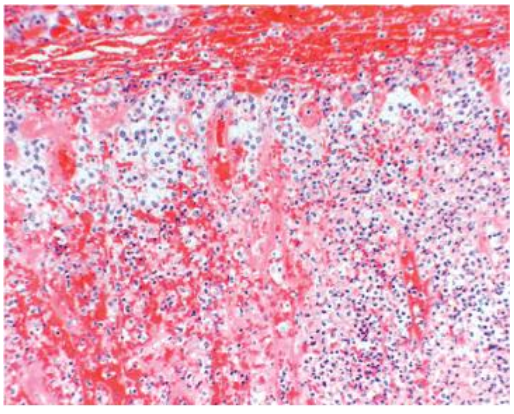
(3) Secondary adrenocortical insufficiency

Causes of Primary Adrenal insufficiency

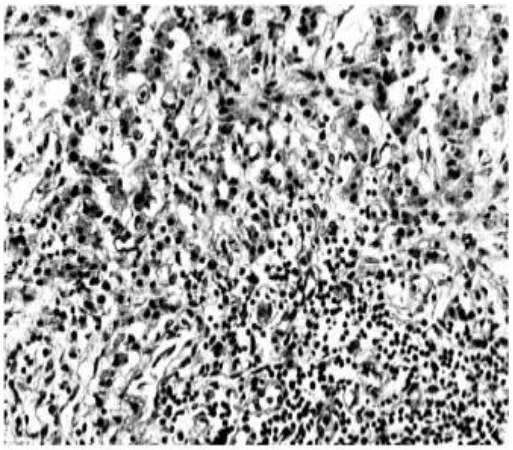
Acute	
Waterhouse-Friderichsen syndrome (associated with Neisseria meningitis sepsis) mostly, affect children	
Sudden withdrawal of long-term corticosteroid therapy	
Stress in patients with underlying chronic adrenal insufficiency	
Chronic	
MAJOR CONTRIBUTORS	**MINOR CONTRIBUTORS**
Autoimmune adrenalitis	Systemic amyloidosis
Tuberculosis	Fungal infections
Acquired immunodeficiency syndrome	Hemochromatosis
Metastatic disease	Sarcoidosis

Other Cause of primary adrenal insufficiency + Cause of secondary Adrenal insufficiency

TABLE 24-10 -- Adrenocortical Insufficiency
PRIMARY INSUFFICIENCY
Loss of Cortex
Congenital adrenal *hypo*plasia
X-linked adrenal hypoplasia (*DAX1* gene on Xp21)
"Miniature"-type adrenal hypoplasia (unknown cause)
Adrenoleukodystrophy (*ALD* gene on Xq28)
Autoimmune adrenal insufficiency
Autoimmune polyendocrinopathy syndrome type 1 (*AIRE1* gene on 21q22)
Autoimmune polyendocrinopathy syndrome type 2 (polygenic)
Isolated autoimmune adrenalitis (polygenic)
Infection
Acquired immune deficiency syndrome
Tuberculosis
Fungi
Acute hemorrhagic necrosis (*Waterhouse-Friderichsen syndrome*)
Amyloidosis, sarcoidosis, hemochromatosis
Metastatic carcinoma
Metabolic Failure in Hormone Production
Congenital adrenal *hyper*plasia (cortisol and aldosterone deficiency with virilization)
Drug- and steroid-induced inhibition of ACTH or cortical cell function
SECONDARY INSUFFICIENCY
Hypothalamic Pituitary Disease
Neoplasm, inflammation (sarcoidosis, tuberculosis, pyogens, fungi)
Hypothalamic Pituitary Suppression
Long-term steroid administration



Acute adrenal insufficiency caused by severe bilateral adrenal hemorrhage in an infant with overwhelming sepsis (Waterhouse-Friderichsen syndrome)



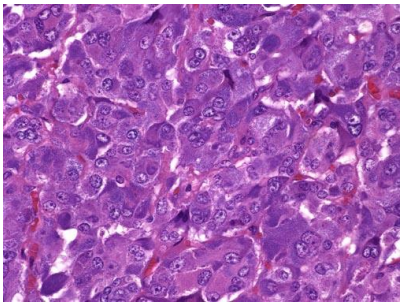
Autoimmune adrenalitis

Pheochromocytoma

- Pheochromocytomas are uncommon neoplasms composed of chromaffin cells, which synthesize and release catecholamines
- Similar to aldosterone-secreting adenomas, give rise to surgically correctable forms of hypertension.
- 0.1% to 0.3%(fatal)
- Occasionally, one of these tumors produces other, and so may be associated with Cushing syndrome peptides –Cushing etc…

"rule of 10s"

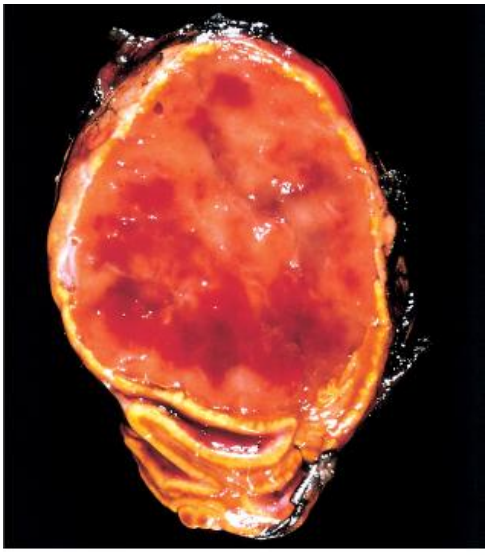
- **10%** of pheochromocytomas arise in association with one of several **familial syndromes** MEN-2A and MEN-2B syndromes.
- **10%** of pheochromocytomas are **extra-adrenal**.
- **10%** of nonfamilial adrenal pheochromocytomas are **bilateral**; this figure may rise to 70% in cases that are associated with familial syndromes.
- **10%** of adrenal pheochromocytomas are biologically **malignant**
- **10%** of adrenal pheochromocytomas in **childhood**



Pheochromocytoma, Morphology

- Small to large hemorrhagic
- Well demarcated
- **Polygonal to spindle shaped** (chromaffin, chief cells)
- Sustentacular small cells
- Together, **Zellballen nests**
-

The tumors are composed of polygonal to spindle-shaped chromaffin cells or chief cells, clustered with the sustentacular cells into small nests or alveoli (**zellballen) by a rich vascular network**, Uncommonly, the dominant cell type is a spindle or small cell; various patterns can be found in any one tumor. The cytoplasm has a finely granular appearance, best demonstrated with silver stains, owing to the appearance of granules containing catecholamines. (nuclei show **"salt and pepper" chromatin**)



Immunoreactivity for neuroendocrine markers (**chromogranin and synaptophysin) is present in the chief** cells, **while the peripheral sustentacular cells label with S-100**, a calcium-binding protein expressed by a variety of mesenchymal cell types.

the definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

MEN Type 1 "THE 3Ps"

- Primary **hyperParathyroidism**
- Endocrine tumors of the **Pancreas**
- **Pituitary** Adenoma

MEN Type 2

- **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**

von Recklinghausen Neurofibromatosis

- Café au lait skin spots**, Schwannomas, meningiomas, gliomas**

Sturge-Weber

- **Cavernous hemangiomas of fifth cranial nerve distribution**

Summary

Chusing syndrome :

- The most common cause of hypercortisolism is exogenous administration of steroids.
- Endogenous hypercortisolism is most often secondary to ACTH-producing pituitary micro-adenoma (cushing disease),followed by primary adrenal neoplasms (ACTH producing by tumors (e.g:small cell lung cancer)
- The morphologic features in 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

Adrenocortical insufficiency (hypoadrenalism)

- Primary adrenocortical insufficiency can be acute (waterhouse friderichsen syndrome) or chronic (Addison disease)
- Chronic adrenal insufficiency in the developed world is most often secondary to autoimmune adrenalitis which can be an isolated lesion or part of an autoimmune polyglandular syndrome
- T.B and opportunistic pathogens associated with human immunodeficiency virus and tumors metastatic to the adrenals are the other important cause of chronic hypoadrenalism
- Patients typically present with fatigue weakness and gastrointestinal disturbances .primary adrenocortical insufficiency is also characterized by high ACTH levels with associated skin pigmentation

Hyperaldosteronism

Primary:caused by adrenal hyperplasia or an aldosterone-secreting adrenal adenoma (conn's syndrome) resulting in hypertension hypokalemia metabolic alkalosis and low plasma rennin may be bilateral or unilateral

Secondary: kidney perception of low intravascular volume result in an overactive rennin-angiotensin system due to renal artery stenosis chronic renal failure CHF cirrhosis or nephrotic syndrome associated with high plasma renin.

Pheochromocytoma

Most common tumor of adrenal medulla in adult derived from chromaffin cells can cause episode of hypertension crisis secret epinephrine NE and dopamine associated with MEN 2A,2B neurofibromatosis

Episodic hyperadrenergic symptoms (5 P's)

Pressure – pain (headache)- perspiration- palpitations- pallor

Questions

Q1: which of the following are 2 surgically correctable forms of hypertension?

A. Pheochromocytoma and idiopathic hyperaldosteronism
B. Aldosterone-producing adenoma and Cushing syndrome
C. Pheochromocytoma and Aldosterone-producing adenoma
D. Addisons disease and virilizing syndromes

Q2: Which of the following is the most common cause of Cushing's syndrome?
A. exogenous corticosteroids
B. adrenal cortical carcinoma
C. oat cell carcinoma of the lung
D. basophilic adenoma of the pituitary

Q3: Conn's syndrome is associated primarily with an excess of:
A. glucocorticoids
B. mineralocorticoids
C. thyroid hormone
D. antidiuretic hormone

Q4: All of the following are characteristic of multiple endocrine neoplasia (MEN) syndrome, Type II (Sipple's syndrome) except:
A. medullary carcinoma of the thyroid
B. hyperparathyroidism
C. abnormal serum calcium
D. presence of peptic ulcers

Q5: The most common cause of Waterhouse-Friderichsen syndrome is:
A. severe postpartum hemorrhage
B. severe sodium depletion
C. meningococcemia
D. adenocortical adenoma

Q6: All of the following are related to hypofunctional states except:
A. Waterhouse-Friedericksen syndrome
B. myxedema
C. insulin-dependent diabetes mellitus (type 1)
D. Conn's syndrome
E. Addison's disease

Good Luck

Q1:C ,Q2:A ,Q3:B ,Q4:D ,Q5:C ,Q6:D