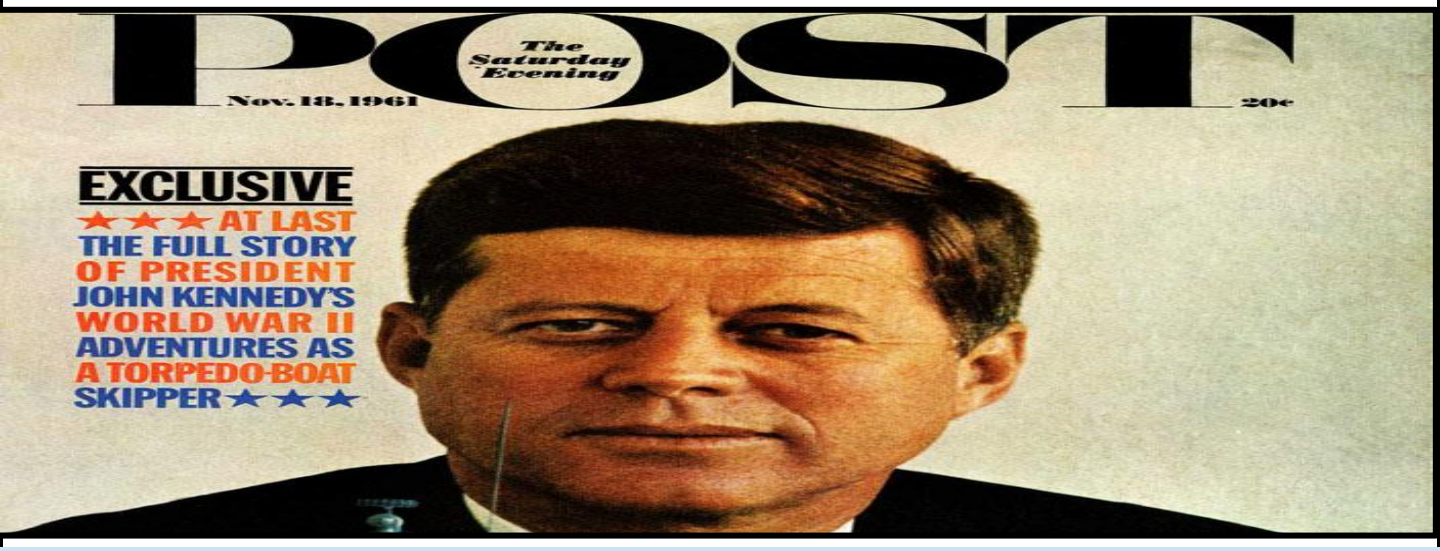
واعلموا أن مهمتكم ليست ورقة تنالونها.....
إنما مهمتكم أمة تحيونها.....

Adrenal Gland Pathology



جميع رؤساء الولايات المتحدة تقريبا يعانون من مشكلات صحية. فجورج واشنطن كان يعاني من مرض السل الرئوي. وأندرو جاكسون كان يعاني من مجموعة أمراض, وغروفر كليفلاند كان مصابا بالسرطان وقرر إجراء عملية جراحية سرية, لكيلا ينتشر الخبر بين الناس
الرئيس الأمريكي جون كينيدي لم يخلوا من هذه الأمراض خلال سنواته الجامعية اصيب بآلام الظهر المزمنة التي رافقته حتى اغتياله
ويعد جون كينيدي احد اشهر المصابين بمرض اديسون,تم تشخيص جون كينيدي بالمرض في ال30 من عمره,
لاحقا تم تشخيصه باعتلال الغدة الدرقية
Hypothyroidism
تم تفسير اصابة جون كنيدي بامراض الغدة بإصابته بمتلازمة نادرة لم تكن مكتشفة في ذلك الوقت هي
autoimmune polyendocrine syndrome type 2

الشكر موصول لجميع من عمل على هذه المحاضرة:

القادة: فايز غياث الدرسوني — شيرين العكيلي

الأعضاء: منصور العبرة — غادة الحيدري — مشاعل القحطاني
عبدالاله الدوسري Golden member — غرام جليدان — منيرة المسعد
رزان الزهراني — دانه القاضي
رناد الفرم — نورة القاضي
مها بركه — رينـاد الغريبي Golden member
بتول الرحيمي

Objectives:

- Understand the structure and function of adrenal glands.
- Know the disorders that can cause hypo or hyper function of the adrenal cortex
- Understand the histopathological features of both medullary (pheochromocytoma) and adrenocortical Neoplasms.

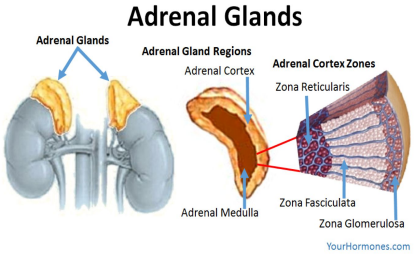
Color index:
-Text
-important
-Notes
-Extra

Adrenal gland

The adrenal glands: paired endocrine organs: **cortex and medulla: 4 layers**

Three layers in the cortex:

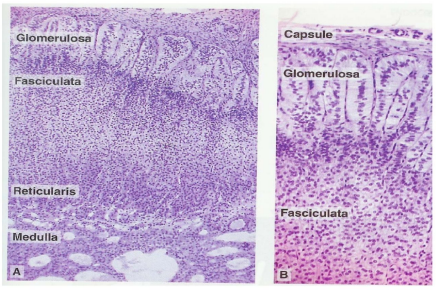
- Zona glomerulosa
- Zona reticularis abuts the medulla
- Intervening is the broad zona fasciculata (75%) of the total cortex

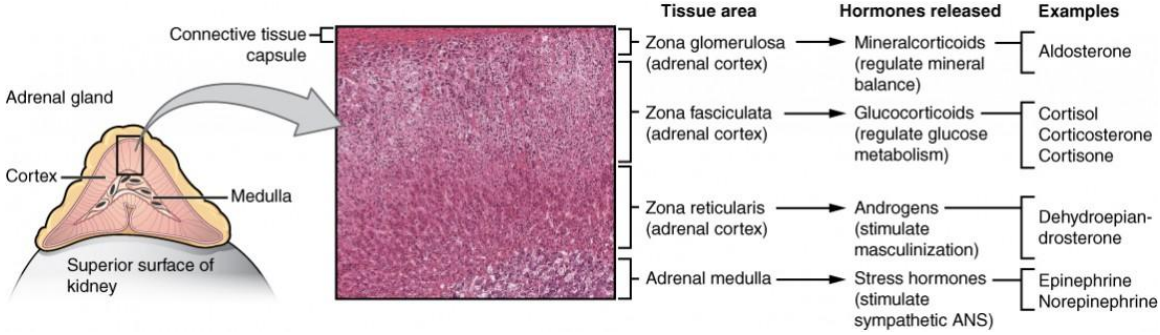


Three types of steroids:

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 <u>epinephrine.</u>

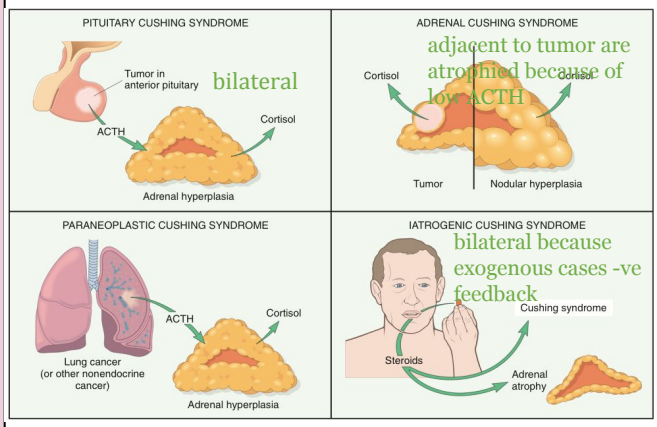




ADRENOCORTICAL HYPERFUNCTION (HYPERADRENALISM)

There are three distinctive hyperadrenal clinical syndromes, each caused by abnormal production of one or more of the hormones produced by the three layers of the cortex:

- Cushing syndrome, characterized by an excess of cortisol
- Hyperaldosteronism
  Associated with hypertension
- Adrenogenital or virilizing syndromes, caused by an excess of androgens

Disease	Character
Cushing	Broadly divided into **1- exogenous** and **2- endogenous** causes. The vast majority of cases of Cushing syndrome are the result of the administration of **exogenous** glucocorticoids ("iatrogenic" Cushing syndrome).1 mainly drug The endogenous causes can be: **ACTH dependent** and **ACTH independent** 1. Both cortices will be atrophic, no ACTH production  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 Primary hypothalamic-pituitary disease associated with hypersecretion of ACTH, also known as **Cushing disease** • Accounts for approximately 70% of cases of spontaneous, endogenous Cushing syndrome. • Four times higher among women than among men • In the vast majority of cases, the pituitary gland contains an ACTH-producing microadenoma that **does not** produce mass effects in the brain. • The adrenal glands in patients with Cushing disease show variable degrees of bilateral nodular cortical hyperplasia, secondary to the elevated levels of ACTH ("ACTH dependent" Cushing syndrome more common
Ectopic	• Secretion of ectopic ACTH by nonpituitary tumors accounts for about 10% of cases of Cushing syndrome. • In many instances the responsible tumor is a small-cell carcinoma of the lung, although other neoplasms, including carcinoids, medullary carcinomas of the thyroid, and **PanNETs**, have been associated with the syndrome. • As in the pituitary variant, the adrenal glands undergo bilateral cortical hyperplasia secondary to elevated ACTH.
Neoplasm and hyperplasia	Primary adrenal neoplasms, such as adrenal adenoma and carcinoma, and rarely, primary cortical hyperplasia, are responsible for about 15% to 20% of cases of endogenous Cushing syndrome, also designated ACTH-independent Cushing syndrome Primary cortical hyperplasia of the adrenal cortices is a rare cause of Cushing syndrome. There are two variants of this entity; the first presents as macronodules of varying sizes (typically less than 3 cm in diameter) and the second as micronodules (1–3 mm).

Adrenal hyperfunction: one of the following abnormalities:

1. Cortical atrophy: results from exogenous glucocorticoids*
2. Diffuse hyperplasia: individuals with ACTH-dependent Cushing syndrome.
3. In primary cortical hyperplasia, the cortex is replaced by macronodules (less than 3 cm) or (1-3 mm) darkly pigmented micronodules.The pigment is believed to be lipofuscin, a wear-and-tear pigment.
4. Adenoma or carcinoma.

*The zona glomerulosa here is of normal thickness,because it functions independently of ACTH

Morphology : in adenoma here atapia is allowed and doesn't turn into carcinoma but mitosis helps us tell if it is malignant or not

Functional **adenomas** *or carcinomas* of the adrenal cortex are **not** morphologically distinct from *nonfunctioning* adrenal neoplasms.

Adrenocortical adenomas are **yellow tumors** surrounded by **thin or well-developed capsules**,and most **weigh less than 30g.**

On microscopic examination,they are composed of cells similar to those encountered in the normal zona fasciculata. distinction between them by lab only

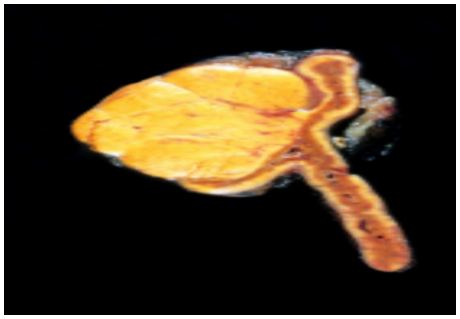
The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature.

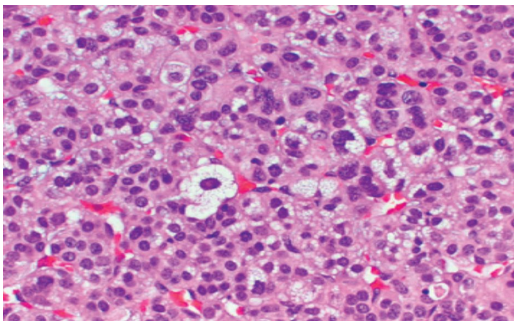
Carcinomas are non encapsulated masses frequently exceeding 200 to 300g in weight, having all of the anaplastic characteristics of cancer with functioning tumors, both benign and malignant, the adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic, as a result of suppression of endogenous ACTH by high cortisol levels. carcinoma are usually not capsulated or invades and are large.

The pituitary in Cushing syndrome shows changes that vary with different causes.The most common alteration, resulting from high levels of endogenous or exogenous glucocorticoids, is termed Crooke hyaline change. In this condition, the normal granular, basophilic cytoplasm of the ACTH producing cells in the anterior pituitary is replaced by homogeneous, lightly basophilic material.This alteration is the result of the accumulation of intermediate keratin filaments in the cytoplasm.

The adenoma is distinguished from nodular hyperplasia by its solitary solitary to differ from hyperplasia which is diffused, circumscribed nature

neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid.
There is mild nuclear pleomorphism.
Mitotic activity and necrosis are not seen.imp to remember adenomas are capsulated





Clinical features:

1. hypertension and weight gain.
2. truncal obesity, “moon face” and accumulation of fat in the posterior neck and back (“buffalo hump”)
3. proximal limb weakness. (atrophy of type 2 fibers)
4. Glucocorticoids induce gluconeogenesis and inhibit the uptake of glucose by cells, with resultant hyperglycemia, glucosuria, and polydipsia, mimicking diabetes mellitus.
5. the skin is thin, fragile, and easily bruised; cutaneous striae.
6. osteoporosis, with consequent increased susceptibility to fractures.
7. increased risk for a variety of infections.
8. hirsutism and menstrual abnormalities.
9. mental disturbances, including mood swings, depression, and frank psychosis.
10. Extra Adrenal Cushing syndrome caused by pituitary or ectopic ACTH secretion usually is associated with increased skin pigmentation secondary to melanocyte-stimulating activity in the ACTH precursor molecule.

*Cushing syndrome develops gradually, except in ectopic ACTH in Small cell carcinoma of the lung, the onset is rapid.

5: due to the catabolic effects of insulin resistance on proteins, which causes loss of collagen.
7: because cortisol suppresses the immune system. .

In pituitary and ectopic Cushing syndrome, ACTH levels are **elevated** and the urine is characterized by high levels of **excreted corticosteroids**. In contrast, ACTH levels are **low** **in Cushing syndrome secondary to adrenal tumors.**

Adrenocortical Neoplasms

While functional adenomas are most commonly associated with hyperaldosteronism and with Cushing syndrome, a virilizing neoplasm is more likely to be a carcinoma.
Virilizing neoplasm causes features of increase sex hormones like hirsutism because of adrenal tumor.
Not all adrenocortical neoplasms, however, elaborate steroid hormones. Determination of whether a cortical neoplasm is functional or not is based on clinical evaluation and measurement of the hormone or its metabolites in the laboratory. Functional and nonfunctional tumors are morphologically similar

Most cortical adenomas do not cause hyperfunction and usually are encountered as incidental findings at the time of autopsy or during abdominal imaging for an unrelated cause.
E.g. patient is doing CT scan for something else then they find that he has adrenal adenoma.

On cut surface, adenomas usually are yellow to yellow-brown, owing to the presence of lipid within the neoplastic cells . As a general rule they are small, averaging 1 to 2 cm in diameter.
On microscopic examination, adenomas are composed of cells similar to those populating the normal adrenal cortex. The nuclei tend to be small, although some degree of pleomorphism may be encountered even in benign lesions (endocrine atypia).
The cytoplasm of the neoplastic cells ranges from eosinophilic to vacuolated, depending on their lipid content; mitotic activity generally is inconspicuous.

Adrenocortical carcinoma

carcinomas metastatic to the adrenal cortex are significantly more frequent than a primary adrenocortical carcinoma.

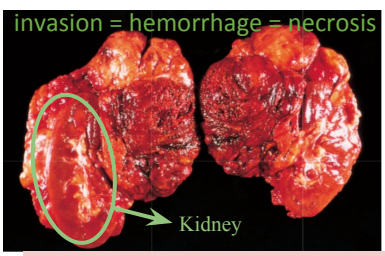
Adrenocortical carcinomas are rare neoplasms that may occur at any age, including in childhood.

Features of **Carcinoma**:
1- Exceeding **200 - 300g** in weight.
2- Capsular **invasion**.
3- **Anaplastic** features.

Two rare inherited causes of adrenocortical carcinomas are Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome.

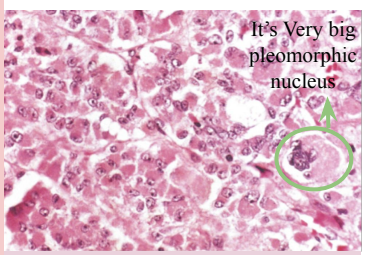
In most cases, adrenocortical carcinomas are large, invasive lesions that efface the native adrenal gland.

On cut surface, adrenocortical carcinomas typically are variegated (multicolored), poorly demarcated lesions containing areas of necrosis, hemorrhage, and cystic change.



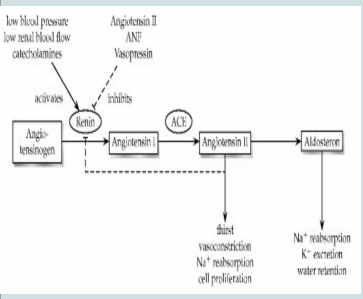
Adrenal carcinoma

The tumor dwarfs the kidney and compresses the upper pole. It is largely hemorrhagic and necrotic. There's invasion, not very well encapsulated.



Anaplastic cells

Hyperaldosteronism



Chronic excess aldosterone secretion:

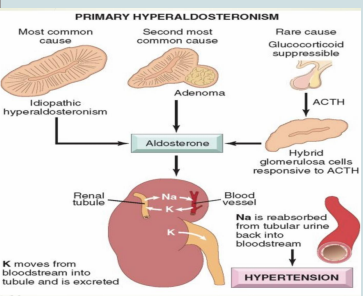
- **Primary aldosteronism** (autonomous overproduction of aldosterone) with resultant suppression of the renin-angiotensin system and **decreased plasma renin** activity.

high aldosterone > high blood volume > kidney will decrease production of renin

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

*Decreased renal perfusion *Arterial hypovolemia *Pregnancy

Causes



Mutations of KCNJ5 are also present in some cases.

Causes of primary hyperaldosteronism :-

1-Bilateral idiopathic hyperaldosteronism, characterized by bilateral nodular hyperplasia of the adrenal glands. This mechanism is the **most common underlying cause** of primary hyperaldosteronism, accounting for about 60% of cases. The pathogenesis is unclear. Some have mutations in the KCNJ5 gene, which encodes a potassium channel protein

2-Adrenocortical neoplasm, either an aldosterone-producing **adenoma** or, rarely, an adrenocortical **carcinoma**. In approximately 35% of cases, primary hyperaldosteronism is caused by a solitary aldosterone-secreting adenoma, a condition referred to as **Conn syndrome**.

3-Rarely, **familial hyperaldosteronism** may result from a genetic defect that leads to overactivity of the aldosterone synthase gene, CYP11B2.*

Clinical

Long term effects of hypertension may cause left ventricular hypertrophy.

- Presents with **hypertension**. Due to Na retention
- Primary hyperaldosteronism may be the **most common cause of secondary hypertension** (i.e., hypertension secondary to an **identifiable** "known" cause).
- Aldosterone promotes **sodium reabsorption.**
- **Hypokalemia** results from renal potassium wasting and, when present, can cause a variety of neuromuscular manifestations, including weakness, paresthesias, visual disturbances.

No K > No depolarization > neuromuscular manifestations

Morphology

Cells of aldosterone secreting adenomas, surprisingly, resemble fasciculata cells more than the glomerulosa. They look yellow on cut surface, compared with benign pheochromocytomas, which look brown.

Aldosterone-producing adenomas happens in thirties and forties, often in women. Are almost always **solitary**, **small**(< 2cm in diameter), **well-circumscribed lesions** left >right. Buried within the gland and don't produce visible enlargement. They are bright yellow on cut section and are composed of lipid-laden cortical cells.

The cells tend to be **uniform in size and shape**; occasionally there is some nuclear and cellular pleomorphism.

A **characteristic feature** of aldosterone-producing adenomas is the **presence of eosinophilic, laminated cytoplasmic inclusions**, known as Spironolactone bodies. These typically are found after treatment with the antihypertensive agent **spironolactone, which is the drug of choice in primary hyperaldosteronism.**

They do not usually suppress ACTH secretion. Therefore, the adjacent adrenal cortex and that of the contralateral gland are **not atrophic.**

Bilateral idiopathic hyperplasia:

First marked by diffuse or focal hyperplasia of cells resembling those of the normal zona glomerulosa.

Hypersecretion of sex steroids

• 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**. Remember the pathway of steroid hormones? If there is deficiency of 21-hydroxylase, the progesterone will not complete the pathway to form Aldosterone. Instead, it will shift to form 17-hydroxyprogesterone but it also can't form Cortisol. So the only pathway it can take is Androgen production.
• Reduction in cortisol production causes a compensatory increase in ACTH secretion, which in turn stimulates androgen production.Treatment of CAH is with glucocorticoids, which will also suppress ACTH and therefore the androgens production.
• Androgens have virilizing effects, including masculinization in females (ambiguous genitalia, oligomenorrhea, hirsutism), precocious puberty in males.
Cortisol deficiency places persons with CAH at risk for acute adrenal insufficiency.

Adrenocortical Insufficiency

Adrenocortical insufficiency, or hypofunction, may be caused by either

- **primary adrenal disease (primary hypoadrenalism): Acute (crisis) or chronic (Addison disease)**
- decreased stimulation of the adrenals resulting from 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)
(3) Secondary adrenocortical insufficiency

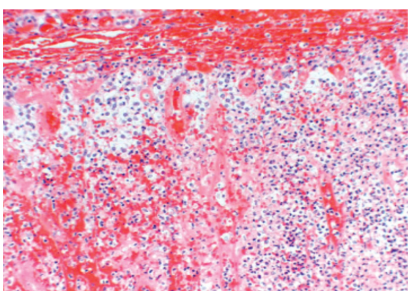
Table 20.7 Causes of Adrenal Insufficiency

Acute
Waterhouse-Friderichsen syndrome
Sudden withdrawal of long-term corticosteroid therapy
Stress in patients with underlying chronic adrenal insufficiency
Chronic
Autoimmune adrenalitis (60%–70% of cases in developed countries)—includes APS1 (*AIRE* mutations) and APS2 (polygenic)
Infections Tuberculosis Acquired immunodeficiency syndrome Fungal infections
Hemochromatosis
Sarcoidosis
Systemic amyloidosis
Metastatic disease

APS1, APS2, Autoimmune polyendocrine syndrome types 1 and 2; *AIRE*, autoimmune regulator gene.

Waterhouse-Friderichsen syndrome

Waterhouse-Friderichsen syndrome. Bilateral adrenal hemorrhage in an infant with overwhelming sepsis, resulting in **acute adrenal insufficiency**. At autopsy, the adrenals were grossly **hemorrhagic and shrunken**; in this photomicrograph, little residual cortical architecture is discernible.



Waterhouse-Friderichsen syndrome is classically associated with **Neisseria meningitidis** septicemia but can also be caused by other organisms, including Pseudomonas spp., pneumococci, and Haemophilus influenzae.
The pathogenesis of the Waterhouse-Friderichsen syndrome remains unclear but probably involves endotoxin induced vascular injury with associated **disseminated intravascular coagulation. "DIC"**

Chronic Adrenocortical Insufficiency: Addison Disease

Uncommon disorder resulting from **progressive destruction of the adrenal cortex**. More than 90% of all cases are attributable to one of four disorders:
1-Autoimmune adrenalitis (most common cause): autoimmune destruction of steroid-producing cells, and autoantibodies.
2-Infection: tuberculosis and fungal.
3- Acquired immune deficiency syndrome (AIDS).
4- Metastatic neoplasms: Carcinomas of the lung and breast are the source of a majority of metastases in the adrenals.

Clinical features

do not appear until at least 90% of the adrenal cortex has been compromised.

*hyperpigmentation is not seen in patients with secondary adrenocortical insufficiency.

•Gastrointestinal disturbances are common and include anorexia, nausea, vomiting, weight loss, and diarrhea.
•**In patients with primary adrenal disease, increased levels of ACTH** precursor hormone **stimulate melanocytes**, with resultant **hyperpigmentation** of the skin and mucosal surfaces.
• Decreased mineralocorticoid (aldosterone) activity in patients with primary adrenal insufficiency results in **potassium retention and sodium loss**, with consequent **hyperkalemia, hyponatremia, volume depletion, and hypotension.**
•**Secondary hypoadrenalism** is characterized by **deficient cortisol and androgen output** but **normal or near-normal aldosterone** synthesis.
•Hypoglycemia occasionally may occur.
•Stresses such as infections, trauma, or surgical procedures in affected patients may precipitate an acute adrenal crisis, manifested by intractable vomiting, abdominal pain, hypotension, coma, and vascular collapse. Death follows rapidly unless corticosteroids are replaced immediately.
Patients with insufficiency will take lifelong replacements, but in stressful situations as in surgery they need to increase the dose to prevent acute insufficiency

Morphology

Primary autoimmune adrenalitis is characterized by irregularly **shrunken glands**, which may be exceedingly difficult to identify within the suprarenal adipose tissue.
On histologic examination, the cortex contains only scattered residual cortical cells in a collapsed network of connective tissue.
A variable **lymphoid infiltrate** is present in the cortex and may extend into the subjacent medulla.
In **tuberculosis or fungal diseases**, the adrenal architecture may be effaced by a **granulomatous** inflammatory reaction identical to that encountered in other sites of infection.

In secondary hypoadrenalism, the adrenals are reduced to small.
When hypoadrenalism is caused by metastatic carcinoma, the adrenals are enlarged.

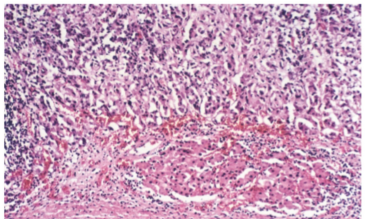


Fig. 20.41 Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is an extensive mononuclear cell infiltrate.

Pheochromocytoma

MEN 2A:
-Medullary thyroid carcinoma
-Parathyroid adenoma
-Pheochromocytoma

MEN 2B:
-Medullary Thyroid carcinoma
-Pheochromocytoma
-Mucogangliona

Von Hippel-Lindau disease

Von Recklinghausen's Neurofibromatosis Type I

•Neoplasms composed of **chromaffin cells**, which, like their nonneoplastic counterparts, synthesize and **release catecholamines.**

•Similar to aldosterone-secreting adenomas, give rise to surgically correctable forms of **hypertension**.

"Rule of 10s":

•**10%** of pheochromocytomas are **extraadrenal** (paragangliomas), common in organ of Zuckerkandl and the carotid body

•**10%** of adrenal pheochromocytomas are **bilateral**; this proportion may rise to 50% (male slides: rise to 70%) in cases that are associated with familial syndromes. MEN-2A and MEN-2B syndromes.

•**10%**of pheochromocytomas arise in association with one of several familial syndromes MEN-2A and MEN-2B syndromes.

•**10%** of adrenal pheochromocytomas are biologically **malignant**.

•**10%** of adrenal pheochromocytomas in childhood.

•**10%** of adrenal pheochromocytomas are **not associated with hypertension**.

•One "traditional" 10% rule that has since been modified pertains to familial cases.

•It is now recognized that as many as 25% of individuals with pheochromocytomas and paragangliomas harbor a germ line mutation in one of at least six known genes, including

RET, which causes type 2 MEN syndromes;
NF1, which causes type 1 neurofibromatosis;
VHL, which causes von Hippel-Lindau disease.

Gross

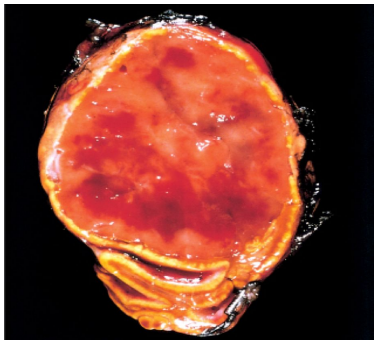
•Pheochromocytomas **range in size** from small, circumscribed lesions confined to the adrenal to large, hemorrhagic masses weighing several kilograms. We can't rely on size to differentiate between benign and malignant

On cut surface,

•Smaller pheochromocytomas are **yellow-tan**, **well-defined** lesions that compress the adjacent adrenal gland.

•Larger lesions tend to be **hemorrhagic**, necrotic, and cystic and typically efface the adrenal gland.

Pheochromocytoma.
The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage.
The comma-shaped residual adrenal gland is seen (lower portion).



Morphology

•**Polygonal to spindle-shaped** chromaffin cells and their supporting cells, compartmentalized into **small nests**, or **Zellballen,** by a rich vascular network.

•The **cytoplasm** of the neoplastic cells often has a **finely granular appearance.**

•**Electron microscopy** reveals variable numbers of **membrane-bound, electron-dense granules.**

•The nuclei of the neoplastic cells are often quite **pleomorphic.** Both **capsular and vascular invasion** may be encountered in **benign lesions**, and the mere presence of mitotic figures does not imply malignancy. so these can't be used as features to differentiate between benign and malignant

Therefore, **the definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases.** These may involve regional lymph nodes as well as more distant sites, including **liver, lung, and bone.**

Clinical

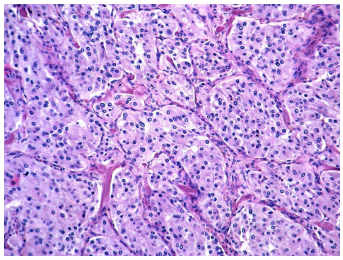
•The predominant clinical manifestation of pheochromocytoma is **hypertension**. Due to excessive epinephrine and norepinephrine "sympathetic activity"

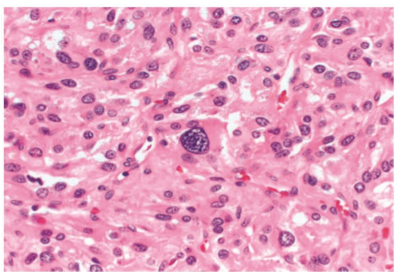
•The characteristic presentation with a **hypertensive episode** is one of abrupt elevation in blood pressure, associated with **tachycardia**, **palpitations**, **headache**, **sweating**, **tremor**, and a sense of apprehension.

•Increased risk of **myocardial ischemia, heart failure**, renal injury, and **stroke** (cerebrovascular accident).

•**Sudden cardiac death** may occur, probably **secondary to catecholamine-induced myocardial irritability** and ventricular arrhythmias.

•The laboratory diagnosis of pheochromocytoma is based on demonstration of increased urinary excretion of free catecholamines and their metabolites, such as **vanillylmandelic acid** and metanephrines.





Summary: pathoma

Adrenal glands

I. BASIC PRINCIPLES

A. Composed of three layers that each secrete distinct hormones
1. Glomerulosa produces mineralocorticoids (e.g., aldosterone).
2. Fasciculata produces glucocorticoids (e.g., cortisol).

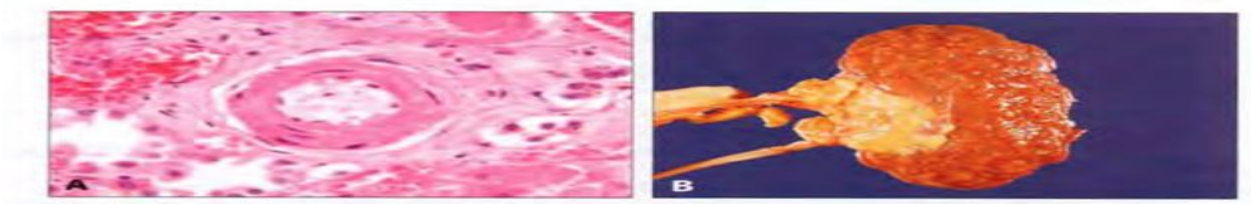


Fig. 15.13 Complications of diabetes. A, Hyaline arteriolosclerosis. B, Glomerulosclerosis.

3. Reticularis produces sex steroids (e.g., testosterone).

Hypercortisolism (cushing syndrome)

A. excess cortisol
B. clinical features
I. Muscle weakness with thin extremities-Cortisol breaks down muscle producing amino acids for gluconeogenesis.
2. Moon facies, buffalo hump, and truncal obesity-High insulin (due to high glucose) increases storage of fat.
3. Abdominal striae-due to impaired synthesis of collagen with thinning of skin
4. Hypertension
5. Osteoporosis
6. Immune suppression
C. Diagnosis is made by increased 24-hour urine cortisol levels.
D. Causes include
1. Exogenous corticosteroids-leads to bilateral adrenal atrophy; steroids suppress ACTH secretion (negative feedback).
2. Primary adrenal adenoma, hyperplasia, or carcinoma-leads to atrophy of the uninvolved adrenal gland
3. ACTH-secreting pituitary adenoma-leads to bilateral adrenal hyperplasia
4. Paraneoplastic ACTH secretion (e.g., small cell carcinoma of the lung)-leads to bilateral adrenal hyperplasia
E. High-dose dexamethasone (cortisol analog) suppresses ACTH production by a pituitary adenoma (cortisol levels decrease), but fails to suppress ectopic ACTH production by a small cell lung carcinoma (cortisol levels remain high).

III. HYPERALDOSTERONISM (CONN's SYNDROME)

A. Excess aldosterone
B. Presents as hypertension due to sodium retention, hypokalemia, and metabolic alkalosis
I. Aldosterone increases sodium absorption and secretion of potassium and hydrogen ions (distal tubules and collecting duct).
2. Increased absorption of sodium expands plasma volume leading to hypertension.
C. Primary hyperaldosteronism is most commonly due to sporadic adrenal hyperplasia; adrenal adenoma and adrenal carcinoma are less common causes.
1. Characterized by high aldosterone and low renin (high blood pressure downregulates renin via negative feedback)
D. Secondary hyperaldosteronism is seen with activation of the renin-angiotensin system (e.g., renovascular hypertension or CHF).
1. Characterized by high aldosterone and high renin

Summary: pathoma

IV. CONGENITAL ADRENAL HYPERPLASIA

A. Excess sex steroids with hyperplasia of both adrenal glands
B. Inherited 21-hydroxylase deficiency is the most common cause.
I. 21-hydroxylase is required for the production of aldosterone and corticosteroids.
2. In enzyme deficiency, steroidogenesis is predominantly shunted toward sex steroid production (which does not require 21-hydroxylase).
3. Deficiency of cortisol leads to increased ACTH secretion (lack of negative feedback), which results in bilateral adrenal hyperplasia.
C. Clinical features include
I. Salt wasting with hyponatremia, hyperkalemia, and hypovolemia due to lack of aldosterone.
2. Life-threatening hypotension due to lack of cortisol.
3. Clitoral enlargement (females) or precocious puberty (males) due to excess androgens

V. ADRENAL INSUFFICIENCY

A. Lack of adrenal hormones
B. Acute insufficiency may arise with Waterhouse-Friderichsen syndrome.
1. Characterized by hemorrhagic necrosis of the adrenal glands (Fig. 15.14), classically due to DIC in young children with N meningitidis infection
2. Lack of cortisol exacerbates hypotension, often leading to death.
C. Chronic insufficiency (Addison disease) is due to progressive destruction of the adrenal glands.
1. Common causes include autoimmune destruction (most common cause in the West), TB (most common cause in the developing world), and metastatic carcinoma (e.g., arising from lung).
2. Clinical features include hypotension, hyponatremia, hypovolemia, hyperkalemia, weakness, hyperpigmentation (increased ACTH by-products stimulate melanocytic production of pigment), vomiting, and diarrhea.

ADRENAL MEDULLA

I. BASIC PRINCIPLES

A. Composed of neural crest-derived chromaffin cells
B. Main physiologic source of catecholamines (epinephrine and norepinephrine)

II. PHEOCHROMOCYTOMA

A. Tumor of chromaffin cells (Fig. 15.15)
B. Clinical features are due to increased serum catecholamines.
1. Episodic hypertension, headache, palpitations, tachycardia, and sweating
C. Diagnosed by increased serum metanephrines and increased 24-hour urine metanephrines and vanillylmandelic acid
D. Treatment is surgical excision.
1. Catecholamines may leak into the bloodstream upon manipulation of the tumor.
2. Phenoxybenzamine (irreversible a -blocker) is administered perioperatively to prevent a hypertensive crisis.
E. Often follows the ' rule of LOs:' 10% bilateral, 10% familial, 10% malignant, and 10% located outside of the adrenal medulla (e.g., bladder wall or organ of Zuckerkand I at the inferior mesenteric artery root)
F. Associated with ME 2A and 2B, von Hippei-Lindau disease, and neurofibromatosis type 1

Fig. 15.14 Waterhouse-Friderichsen syndrome. (Courtesy of humpath.com)

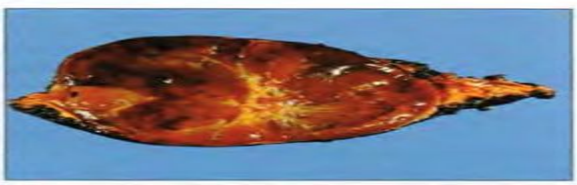


Fig. 15.15 Pheochromocytoma. (Courtesy of humpath.com)

Questions

Q1: Primary Chronic Adrenocortical Insufficiency refers to?
A- Pheochromocytoma.
B- Addison Disease.
C- Conn's Syndrome.
D- Adrenal crisis.

Answer: B

Q2: 31 years old women was diagnosed with rheumatoid arthritis the doctor prescribed her glucocorticoids. After few months she notice increasing in her body weight and increasing in facial hair. Which one of the following best describe laboratory finding in her case?
A- CRH high, ACTH high, cortisol high
B- CRH low, ACTH high, cortisol high
C- CRH low, ACTH low, cortisol high
D- CRH low, ACTH low, cortisol low

Answer: C

Q3: which one the following cause unilateral atrophy of the adrenal gland?
A- Adrenal tumor
B- Exogenous intake of glucocorticoids
C- Cushing disease
D- Ectopic Cushing syndrome

Answer: A

Q4: Which one of the following considered as clinical feature in Cushing syndrome?
A- atrophy of type 2 muscle fibers
B- hyperplasia of type 2 muscle fibers
C- atrophy of type 1 muscle fibers
D- hyperplasia of type 1 muscle fibers

Answer: A

Q5: 43 years old man presented with proximal muscle weakness, truncal obesity and rounded face that looks like the moon. After investigation they found low levels of both CRH and ACTH but high cortisol. biopsy was sent to the lap and showed vacuolated neoplastic cells with mild nuclear pleomorphism and no evidence of mitotic activity and necrosis. What is the diagnosis?
A- Cushing syndrome due to pituitary adenoma
B- Cushing syndrome due to small-cell carcinoma
C- Cushing syndrome due to adrenocortical carcinoma
D- Cushing syndrome due to adrenocortical adenoma

Answer: D

Q6: Crooke hyaline change happened in the cells of the ....., due to accumulation of .....?
A- adrenal cortex, intermediate keratin filaments
B- adrenal cortex, intermediate amyloid filaments
C- anterior pituitary, intermediate keratin filaments
D- anterior pituitary, intermediate amyloid filaments

Answer: C

Questions

Q7: Li-fraumani syndrome and beckwith-wiedemann syndrome is associated with which one of the following?
A- adrenocortical adenoma
B- adrenocortical carcinoma
C- Primary Hyperaldosteronism
D- secondary Hyperaldosteronism

Answer: B

Q8: Bilateral idiopathic hyperaldosteronism is associated with which Gene of the following?
A- CYP11B1
B- CYP11B2
C- KCNJ 15
D- KCNJ 5

Answer: D

Q9: Conn's Syndrome is associated with?
A- Excess aldosterone secretion.
B- Decrease aldosterone secretion.
C- Excess glucocorticoids secretion.
D- Decrease glucocorticoids secretion.

Answer: A

Q10: Adrenal crisis could be caused due to which one of the following?
A- Waterhouse-Friderichsen syndrome
B- Hemochromatosis
C- von hippel-lindau disease
D- MEN-2

Answer: A

Q11: Which of the following are not symptoms/ signs of Cushing's syndrome?
A- Facial Plethora
B- Fibromyalgia
C- Polyuria/ Polydipsia
D- Wasting of the skin/ muscles

Answer: B

Q12: Which one of the following is most likely to be Aldosterone-producing adenomas?
A- Well- encapsulated yellow tumor with mild nuclear pleomorphism
B- 250 gm non-encapsulated mass
C- presence of eosinophilic, laminated cytoplasmic inclusions "spironolactone bodies"
D- lymphoid infiltrate in the cortex

Answer: C

Q13: Which one of the following cause episodic hypertension?
A- Addison disease
B- pheochromocytoma
C- adrenal crisis
D- Conn syndrome

Answer: B

Q14: 29 years old male has tachycardia, tremor, high BP and sweating. The laboratory examination shows increase in urinary VMA and metanephrines. Which of the following is most likely to be associated with this condition??
A- MEN-1
B- Neurofibromatosis type 2
C- Von Hippel-lindau disease
D- Waterhouse-Friderichsen syndrome

Answer: C

Q15: The presence of which one of the following differentiate between malignant and benign pheochromocytoma?
A- presence of metastases
B- nuclei pleomorphism
C- vascular invasion
D- presence of mitotic figures

Answer: A