Adrenal Gland Pathology

Objectives

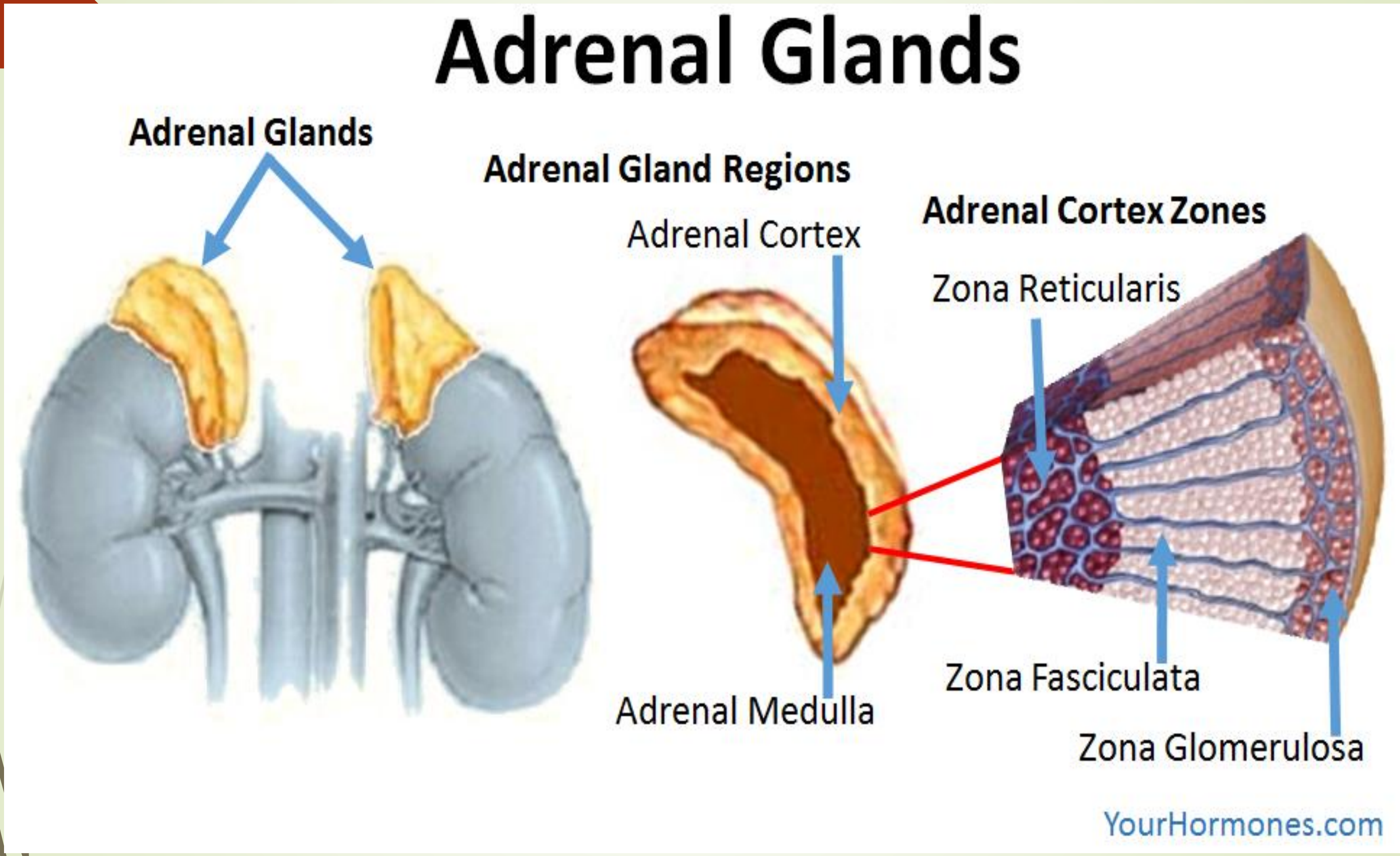
- Understand the structure and function of adrenal glands.
- Know the disorders that can cause hypo or hyper function of the adrenal cortex.
- Understand the histopathological features of both medullary (pheochromocytoma) and adrenocortical neoplasms.

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.*


Adrenal Glands
Adrenal Glands
Adrenal Gland Regions
Adrenal Cortex
Adrenal Medulla
Adrenal Cortex Zones
Zona Reticularis
Zona Fasciculata
Zona Glomerulosa
YourHormones.com

Adrenal Gland

- The adrenal cortex synthesizes three different types of steroids:

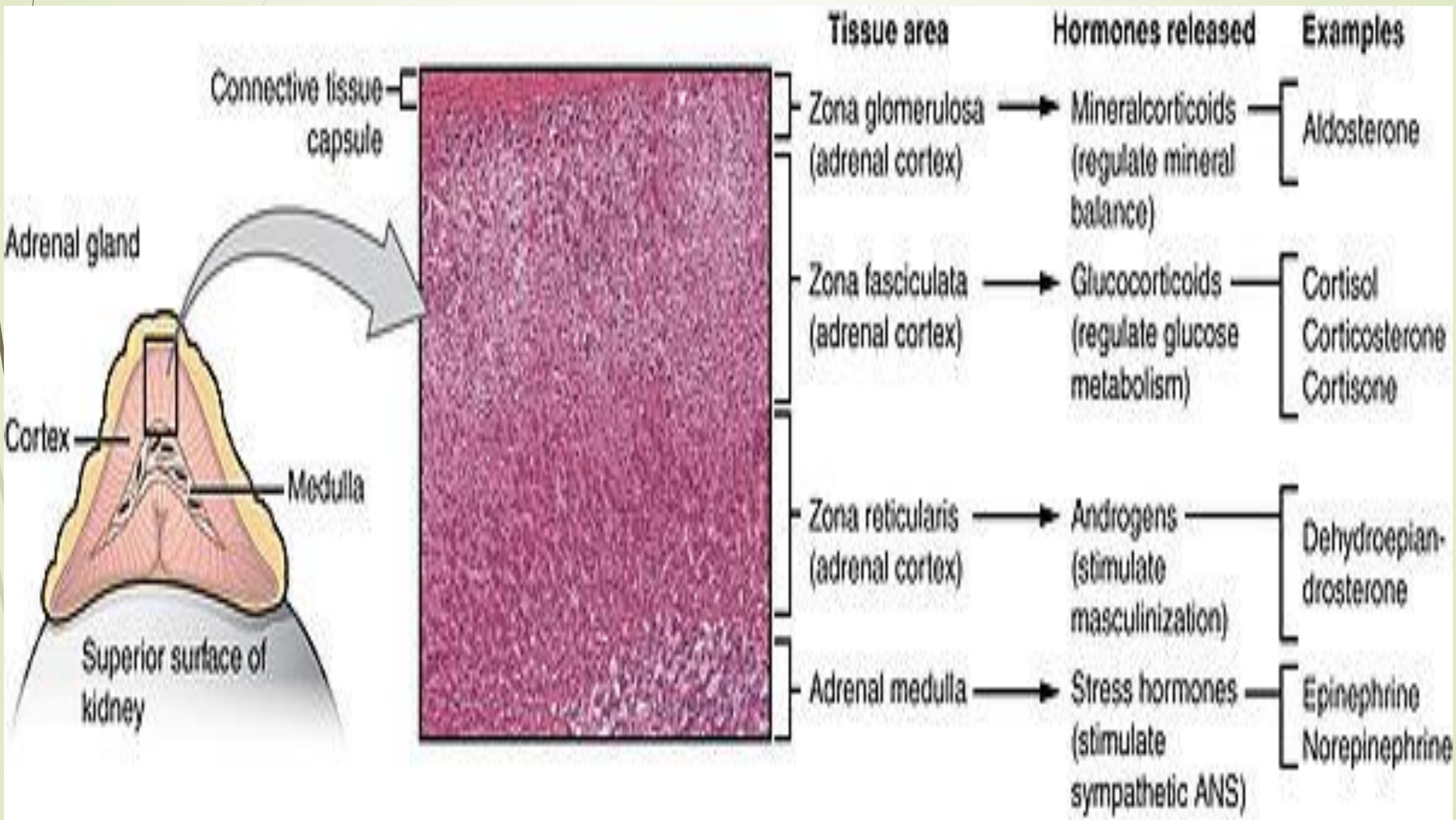
(1) Glucocorticoids (principally cortisol) zona fasciculata

(2) Mineralocorticoids (aldosterone) zona glomerulosa

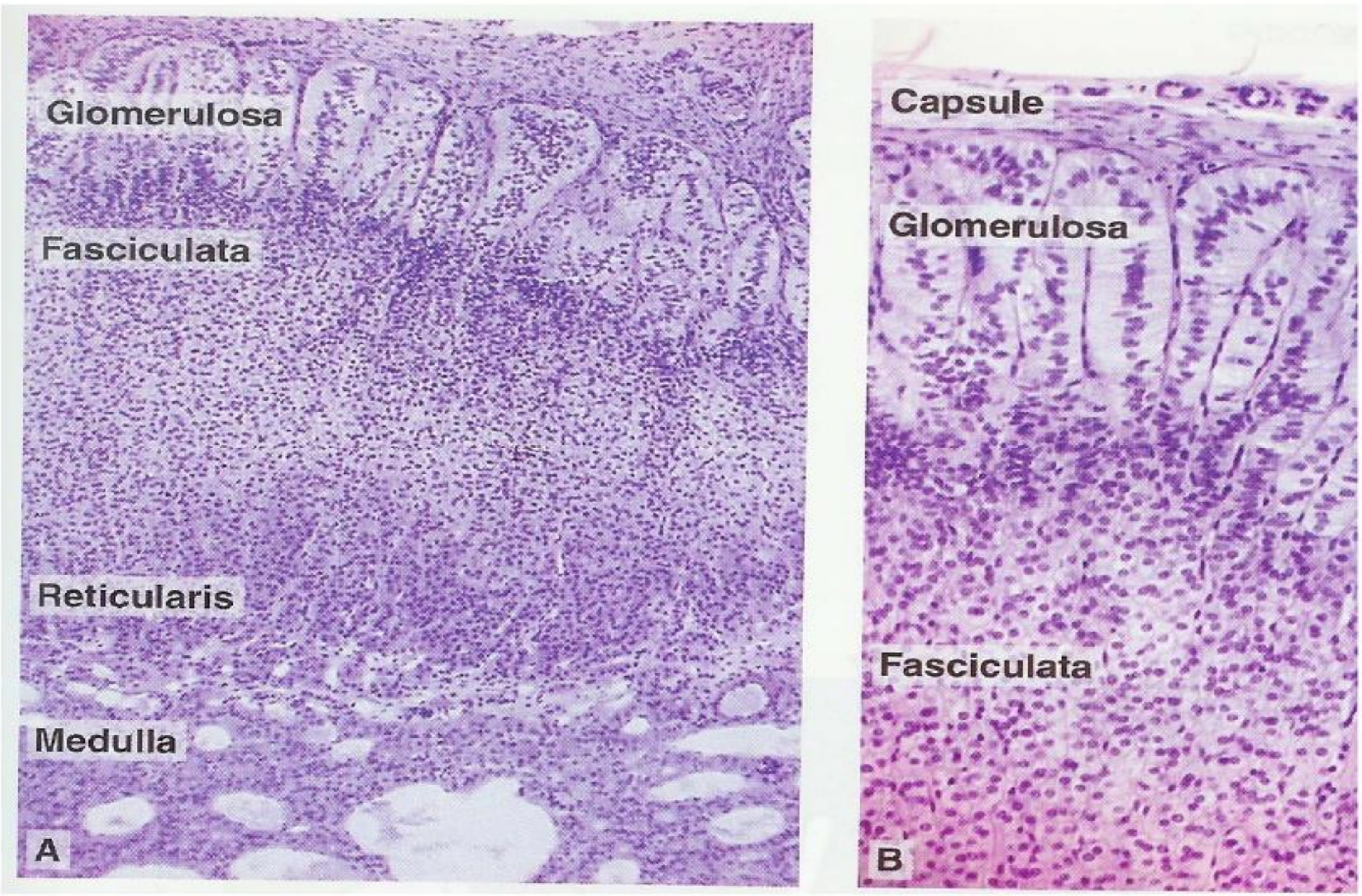
(3) Sex steroids (estrogens and androgens) zona reticularis.

- The adrenal medulla is composed of chromaffin cells, which synthesize and secrete catecholamines, mainly epinephrine.

Adrenal Gland



Adrenal Gland



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:

- (1) *Cushing syndrome, characterized* by an excess of cortisol;
- (2) *hyperaldosteronism*
- (3) *adrenogenital* or *virilizing syndromes,* caused by an excess of androgens

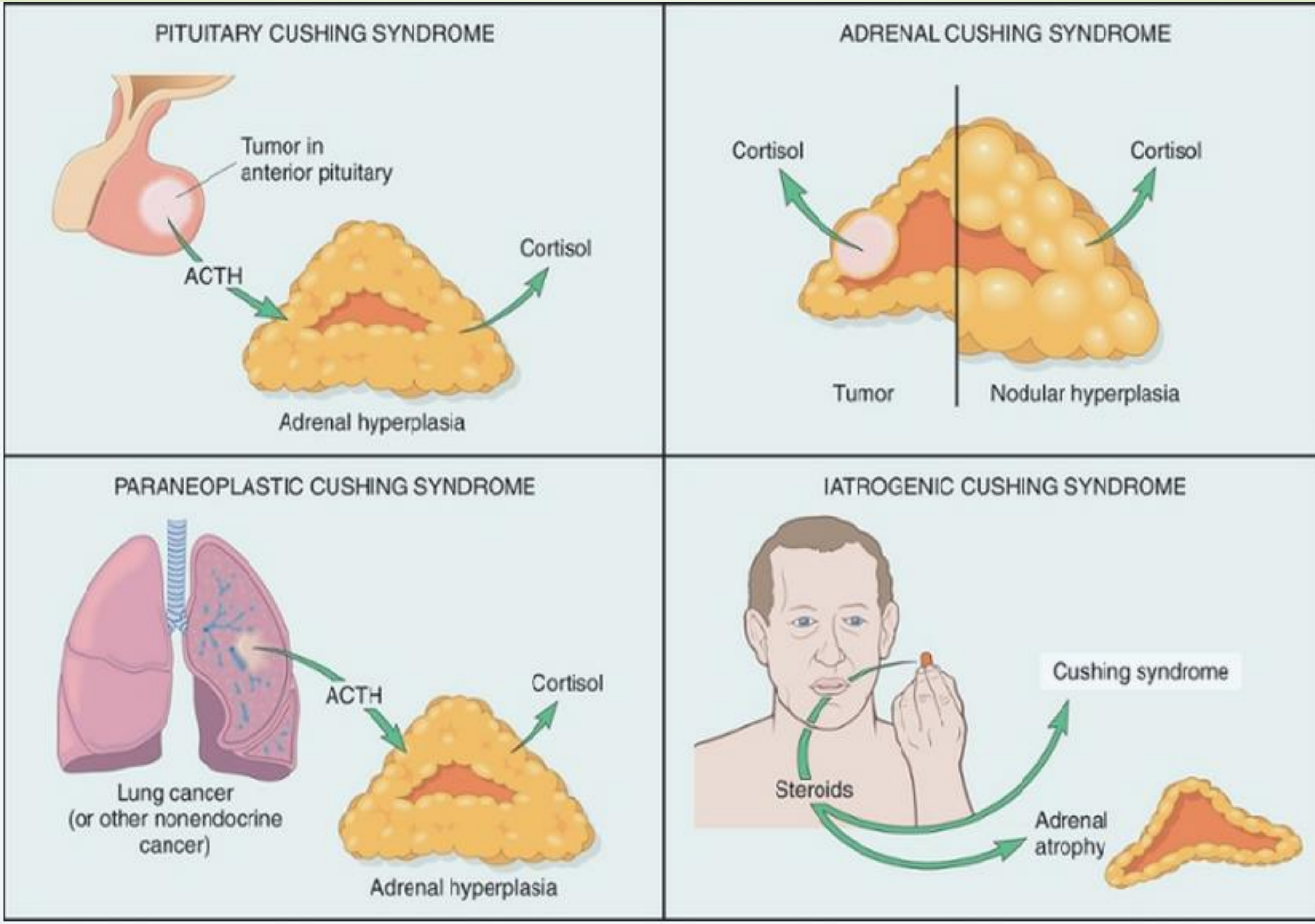
Hypercortisolism (Cushing Syndrome)

- **Broadly divided into ****exogenous*** **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:**

****** ***ACTH dependent*** **and **** ***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



PITUITARY CUSHING SYNDROME
Tumor in anterior pituitary
ACTH
Cortisol
Adrenal hyperplasia
ADRENAL CUSHING SYNDROME
Cortisol
Cortisol
Tumor
Nodular hyperplasia
PARANEOPLASTIC CUSHING SYNDROME
ACTH
Cortisol
Lung cancer (or other nonendocrine cancer)
Adrenal hyperplasia
IATROGENIC CUSHING SYNDROME
Cushing syndrome
Steroids
Adrenal atrophy

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 (“ACTHdependent” Cushing syndrome

Ectopic ACTH

- 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.

Neoplasms 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).

ADRENOCORTICAL HYPERFUNCTION, Morphology

One of the following abnormalities:

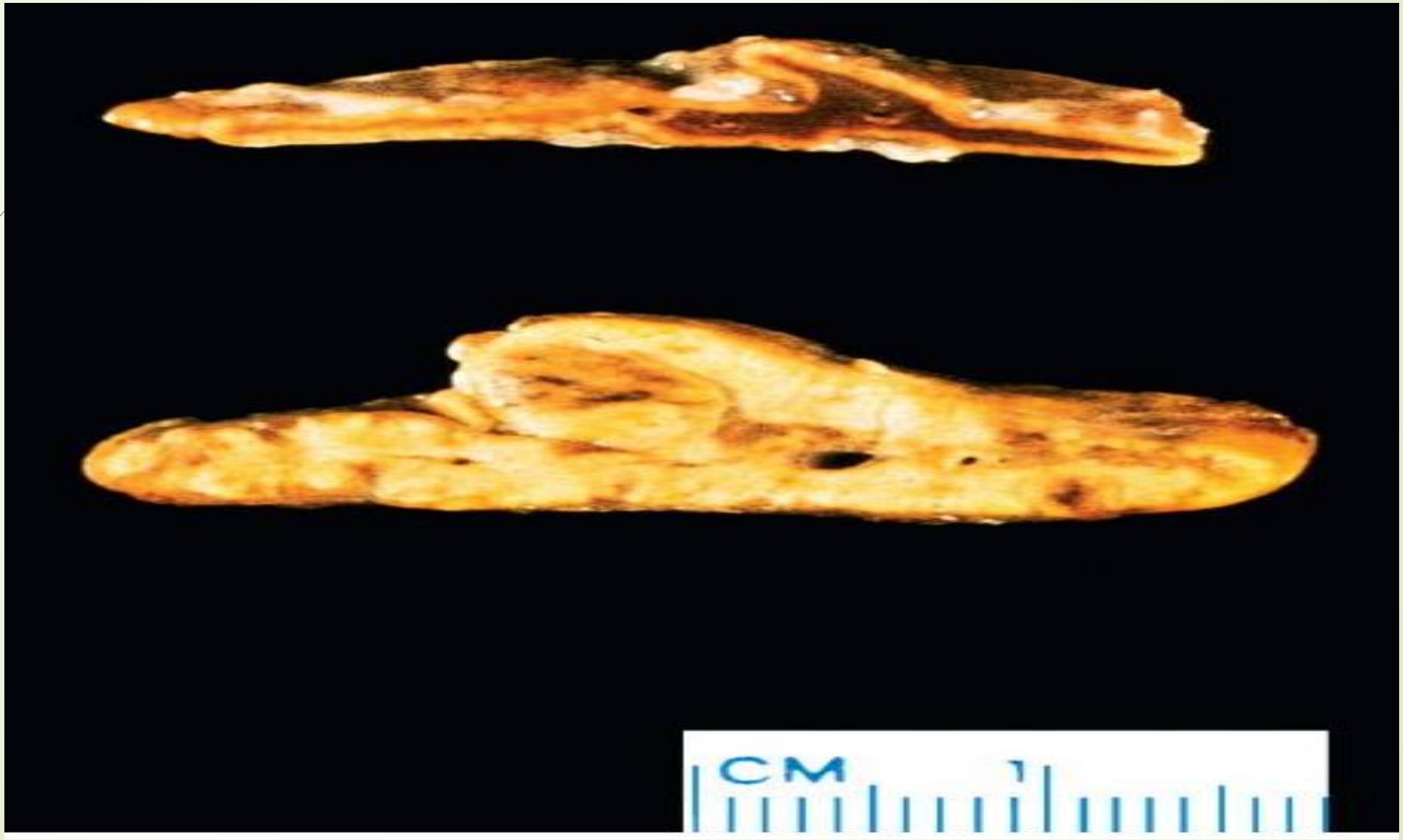
(1) **Cortical atrophy: results from exogenous glucocorticoids**

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

(3) **In primary cortical hyperplasia, the cortex is replacedby macronodules or 1- to 3-mm darkly pigmented micronodules. The pigment is believed to be lipofuscin, a wear-and-tear pigment**

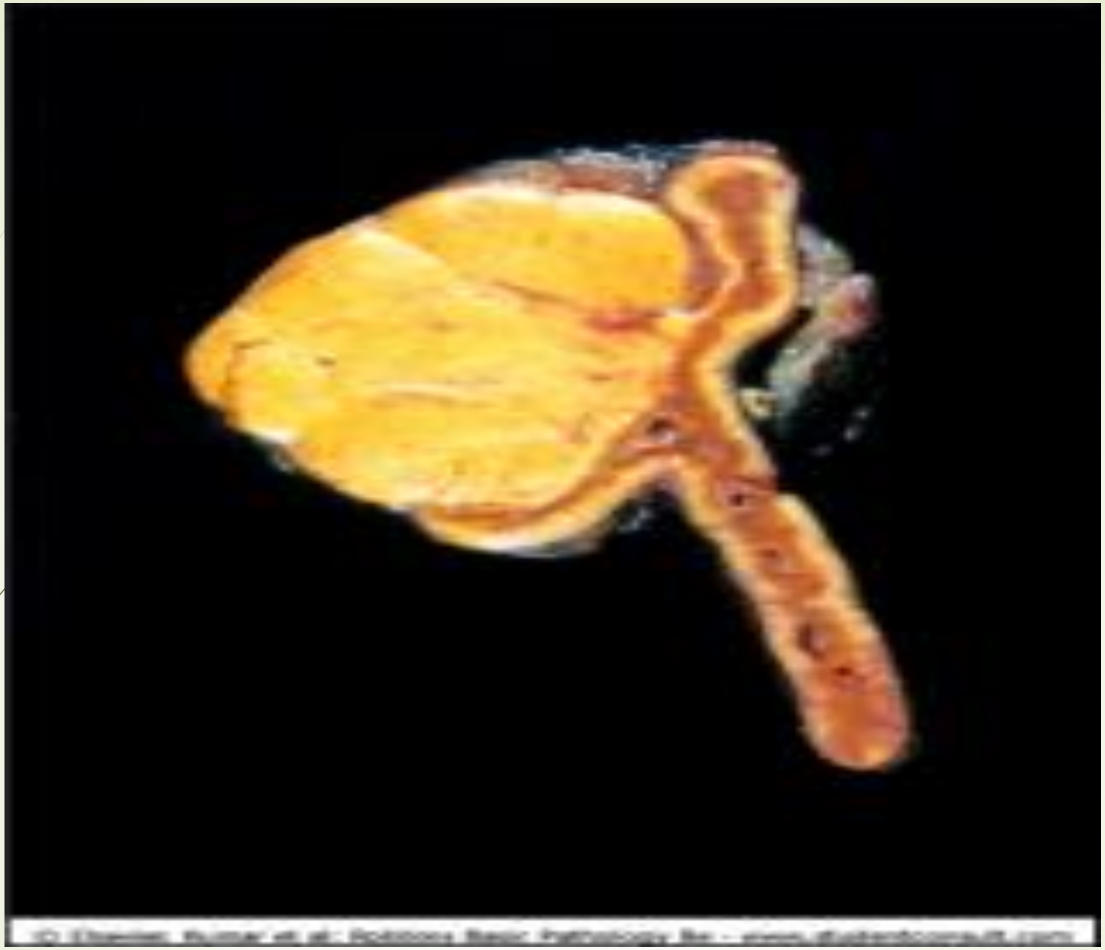
(4) **Adenoma or carcinoma**

Diffuse Cortical Hyperplasia

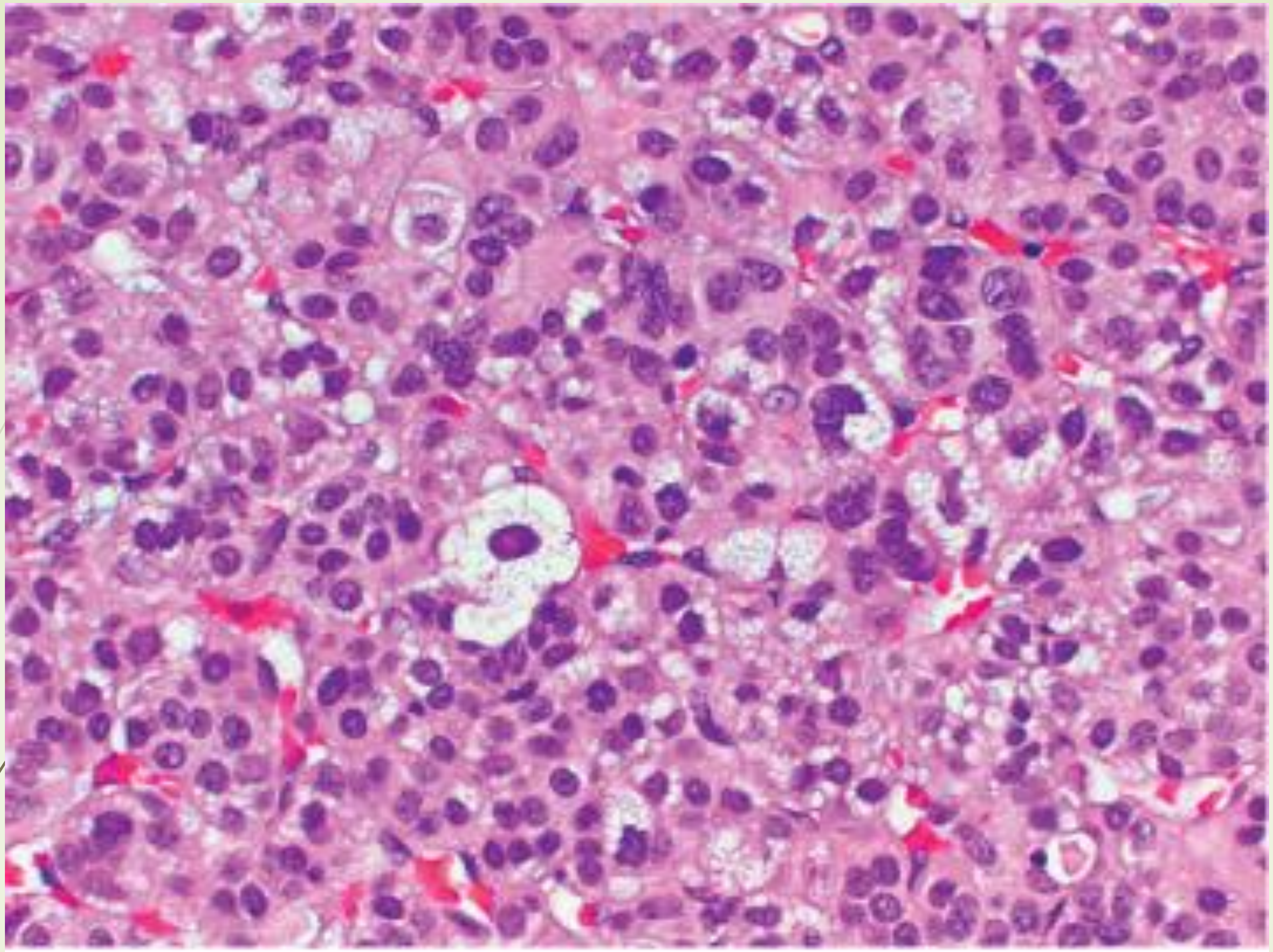


Morphology

- 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 30 g .
- On microscopic examination, they are composed of cells similar to those encountered in the normal zona fasciculata.



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

Morphology

- Carcinomas are non encapsulated masses frequently exceeding 200 to 300 g 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.

Morphology cont.

- 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

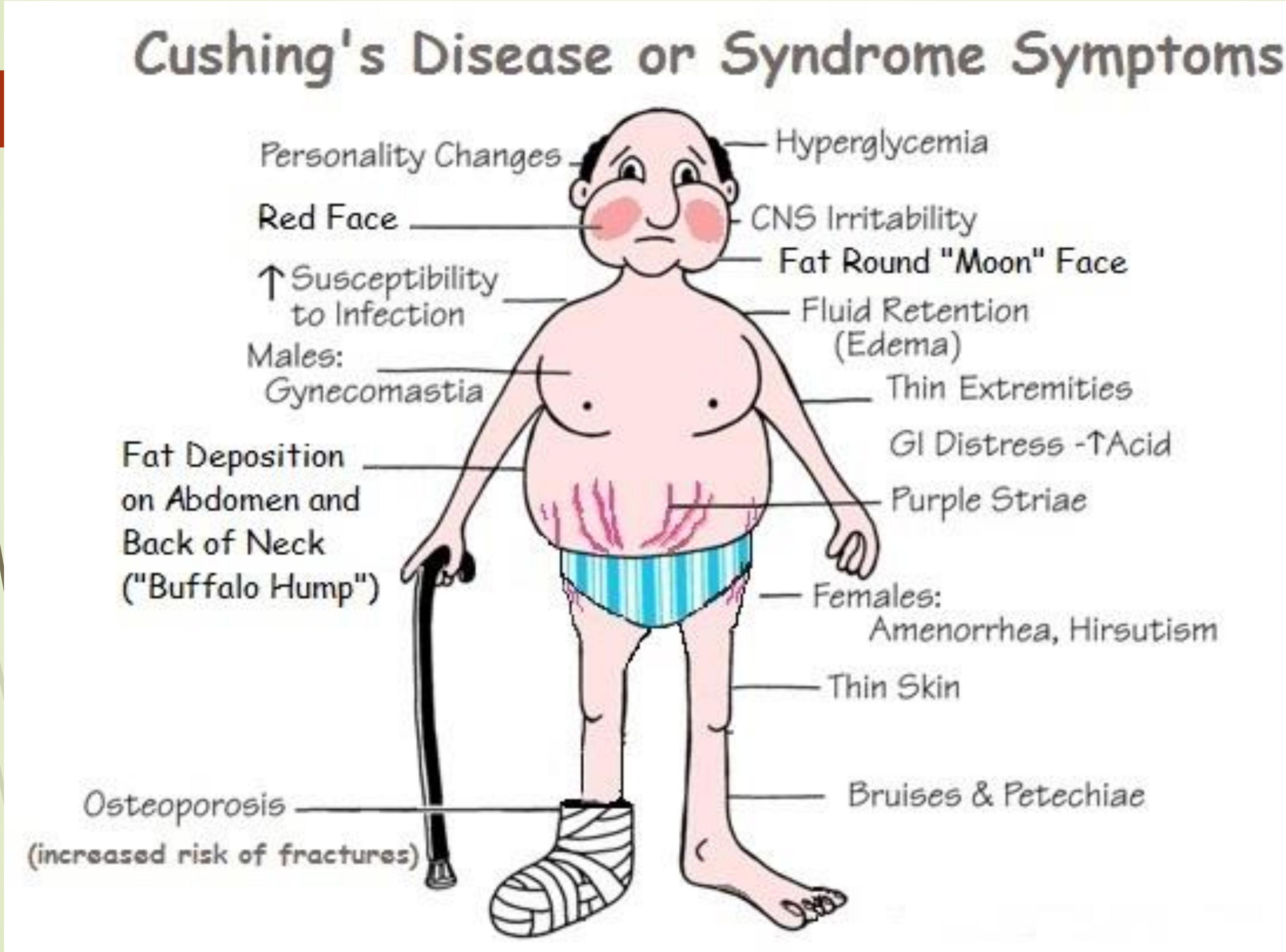
Clinical Features of Cushing Syndrome

- *Hypertension* and *weight gain.*
- Truncal obesity, "moon facies," and accumulation of fat in the posterior neck and back ("buffalo hump")
- Proximal limb weakness. (atrophy of type 2 fibers)
- Glucocorticoids induce gluconeogenesis and inhibit the uptake of glucose by cells, with resultant *hyperglycemia, glucosuria,* and *polydipsia,* mimicking diabetes mellitus.
- The skin is thin, fragile, and easily bruised; *cutaneous striae* .
- *Osteoporosis,* with consequent increased susceptibility to fractions
- Increased risk for a variety of infections.

- *Hirsutism* and *menstrual abnormalities.*

- *Mental disturbances,* including mood swings, depression, and frank psychosis.

- Extraadrenal 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's Disease or Syndrome Symptoms
Personality Changes
Red Face
↑ Susceptibility to Infection
Males: Gynecomastia
Fat Deposition on Abdomen and Back of Neck ("Buffalo Hump")
Osteoporosis
(increased risk of fractures)
Hyperglycemia
CNS Irritability
Fat Round "Moon" Face
Fluid Retention (Edema)
Thin Extremities
GI Distress -↑Acid
Purple Striae
Females: Amenorrhea, Hirsutism
Thin Skin
Bruises & Petechiae

- 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.
- 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.

ADRENOCORTICAL NEOPLASMS

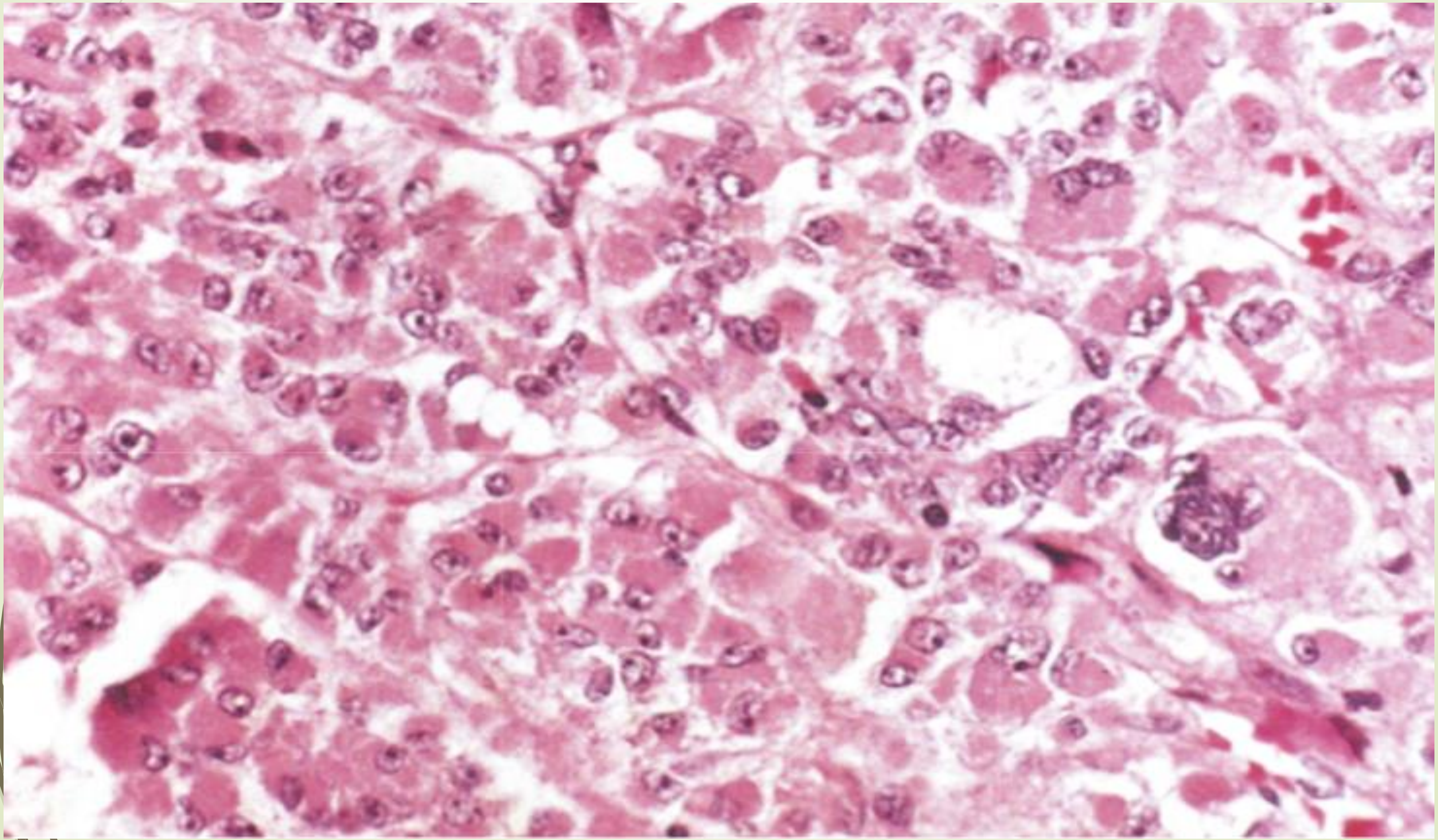
- Most cortical adenomas do not cause hyperfunction and usually are encountered as incidental findings at the time of autopsy or during abdominal imaging for an unrelated cause
- On cut surface, adenomas usually are yellow to yellow-brown, owing to the presence of lipid within the neoplastic cells . 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 carcinomas

- **Adrenocortical carcinomas** are rare neoplasms that may occur at any age, including in childhood.
- Two rare inherited causes of adrenal cortical 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, 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.

Anaplastic cells

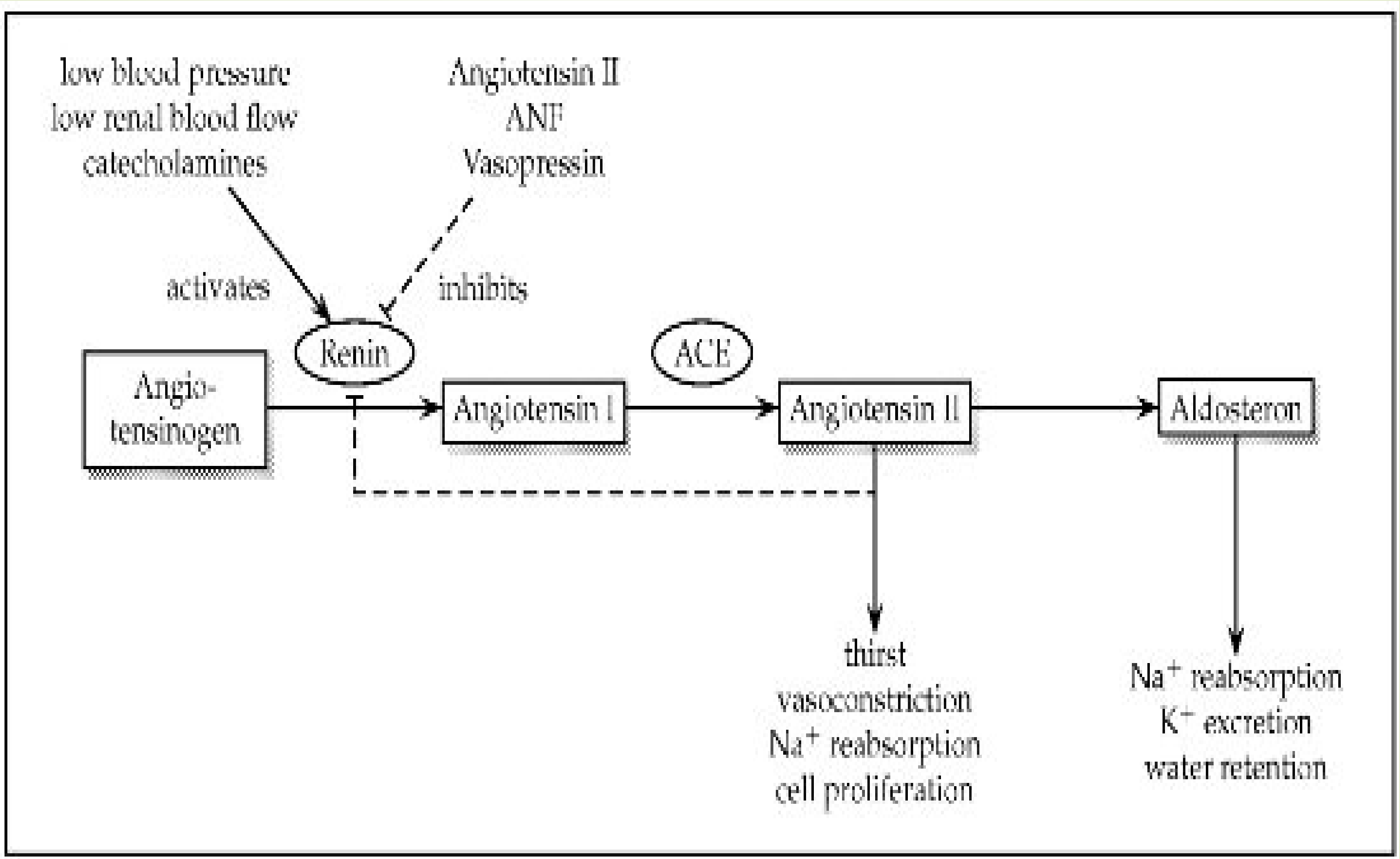


Hyperaldosteronism

Chronic excess aldosterone secretion

- *Primary aldosteronism (autonomous overproduction of aldosterone) with resultant suppression of the renin-angiotensin system and decreased plasma renin activity*
- *Secondary hyperaldosteronism, in contrast, aldosterone release occurs in response to activation of the renin-angiotensin system:*

**Decreased renal perfusion * Arterial hypovolemia * Pregnancy*


low blood pressure
low renal blood flow
catecholamines
Angiotensin II
ANF
Vasopressin
activates
inhibits
Renin
ACE
Angio-
tensinogen
Angiotensin I
Angiotensin II
Aldosteron
thirst
vasoconstriction
Na+ reabsorption
cell proliferation
Na+ reabsorption
K+ excretion
water retention

Primary aldosteronism: Causes

- ***Bilateral idiopathic hyperaldosteronism,*** characterized by bilateral nodular hyperplasia of the adrenal glands. This 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
- ***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.**
- Rarely, familial hyperaldosteronism may result from a genetic defect that leads to overactivity of the *aldosterone synthase* gene, *CYP11B2*.

Primary Hyperaldosteronism, Causes

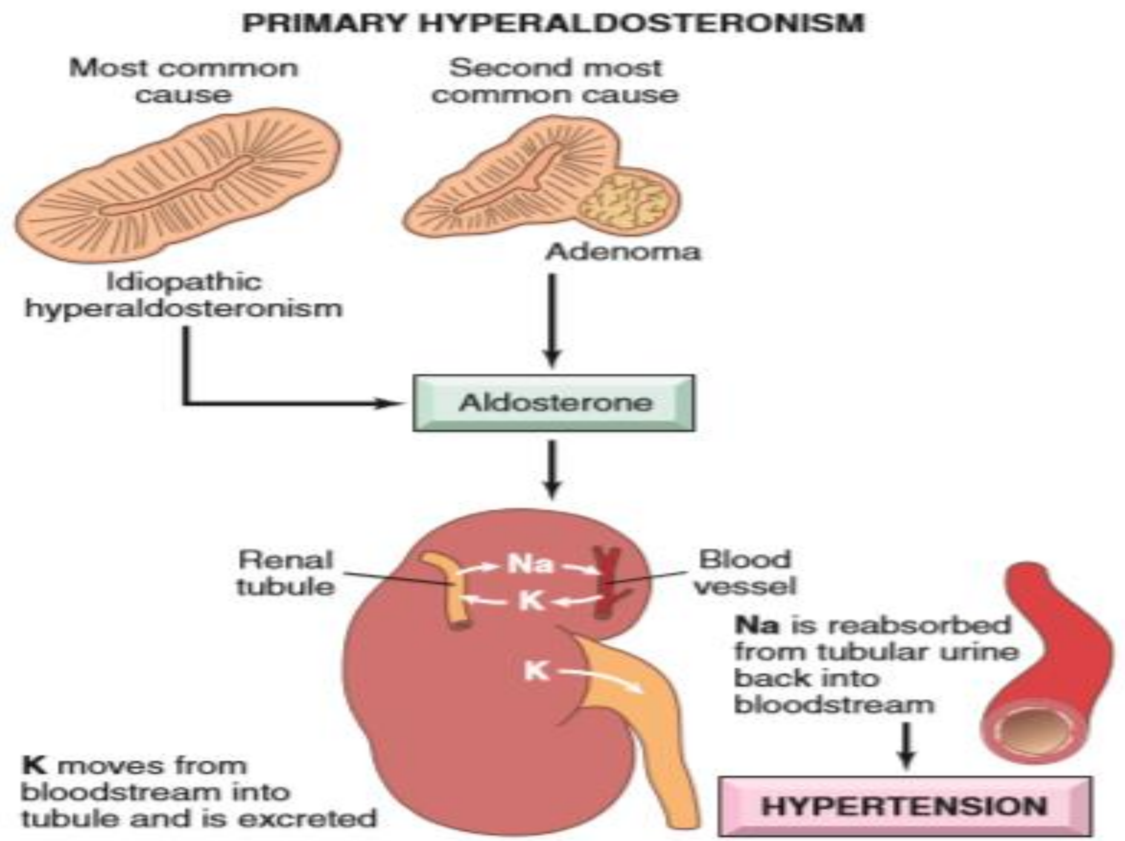


Fig. 20.39 The major causes of primary hyperaldosteronism and its principal effects on the kidney.

Hyperaldosteronism, Clinical

- ***Presents with hypertension.***
- **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 and, when present, can cause a variety of neuromuscular manifestations, including weakness, paresthesias, visual disturbances.**

Morphology

Aldosterone-producing adenomas are almost always solitary, small (<2 cm in diameter), well-circumscribed lesions. 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 anti-hypertensive 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 is 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.
- 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.

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)***

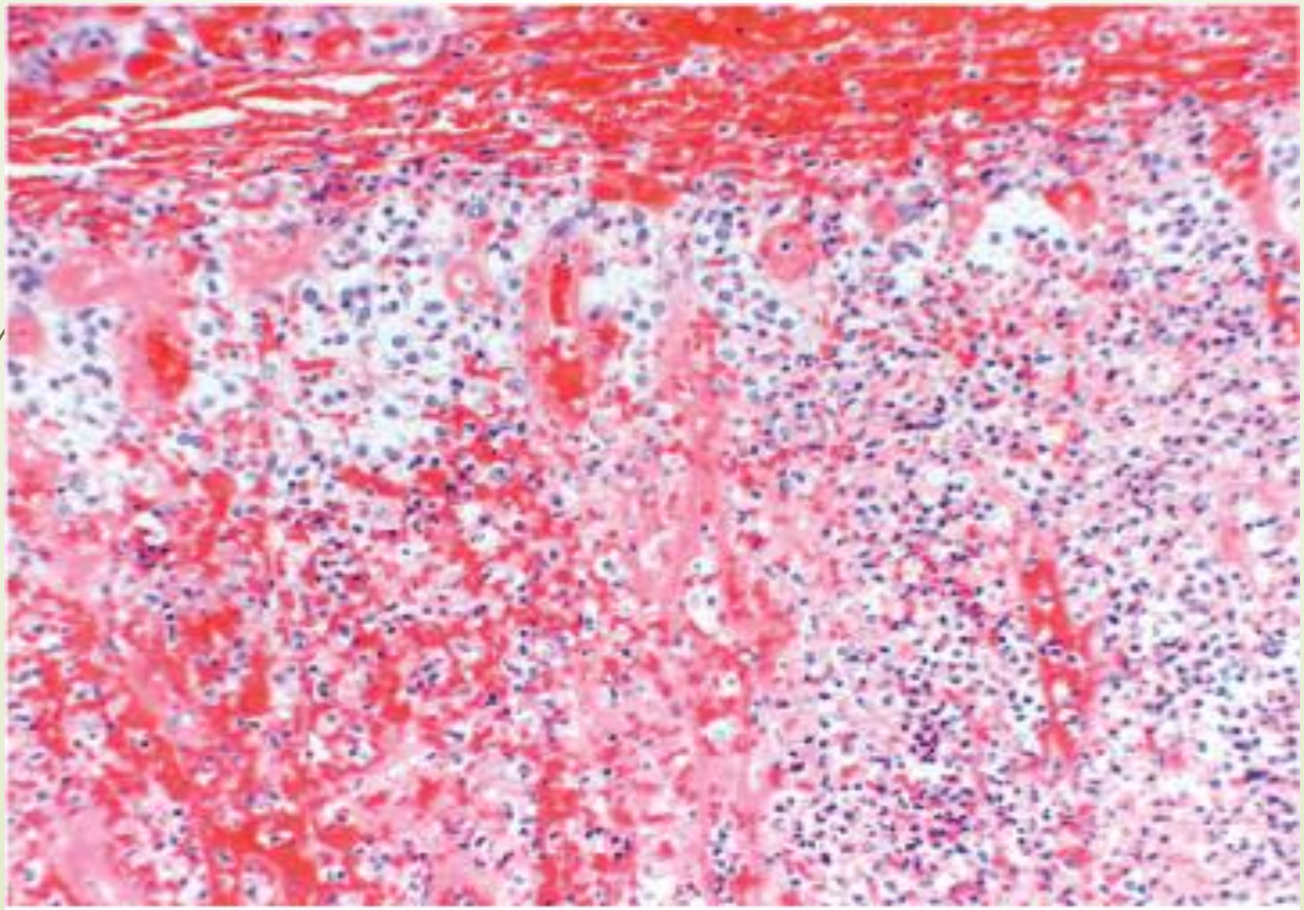
** decreased stimulation of the adrenals resulting from a deficiency of ACTH (secondary hypoadrenalism)

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. 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

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.

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

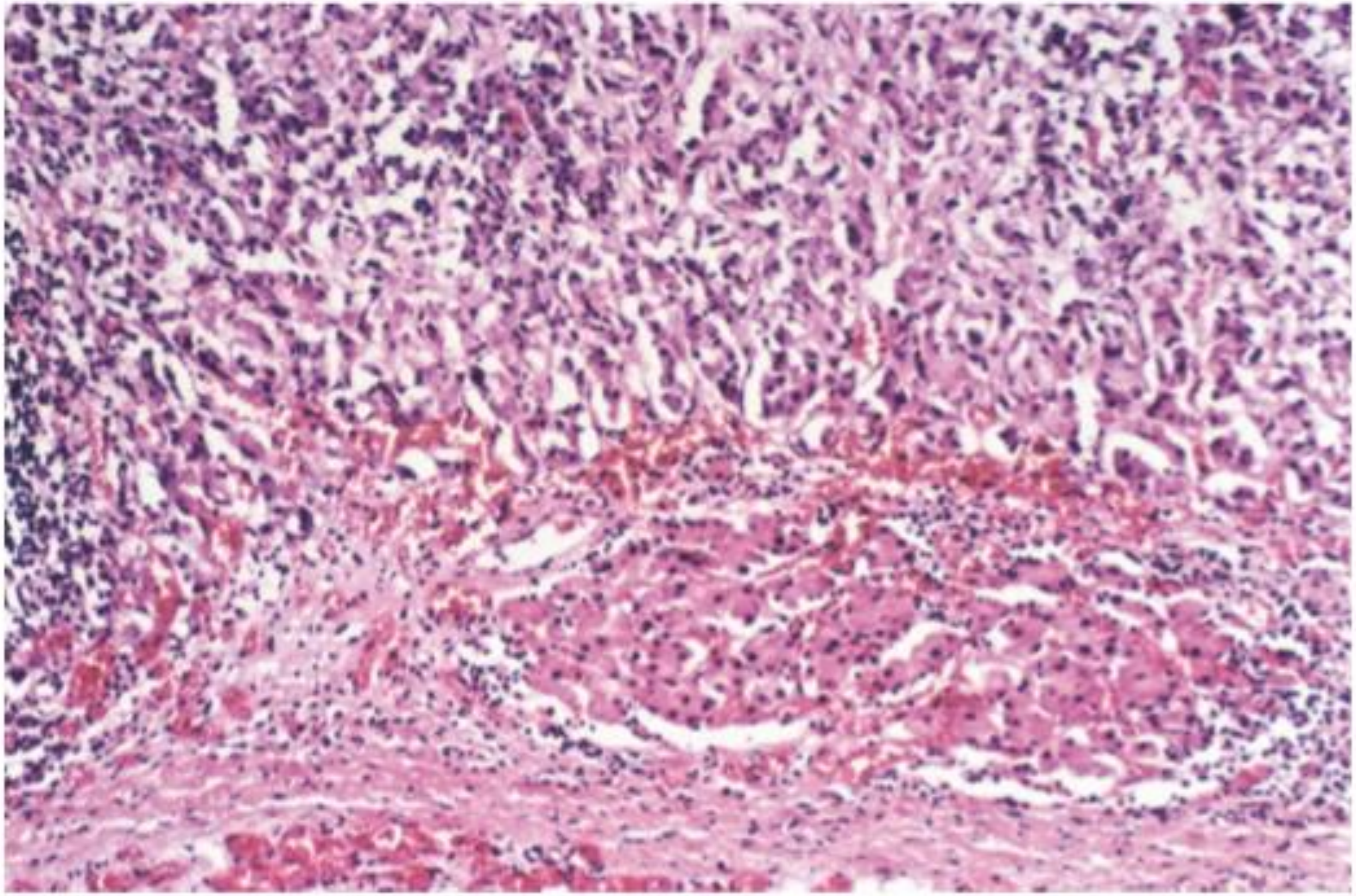


Fig. 20.41 Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is an extensive mononuclear cell infiltrate.

Clinical features

- *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.

Pheochromocytoma

- 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.

Pheochromocytoma

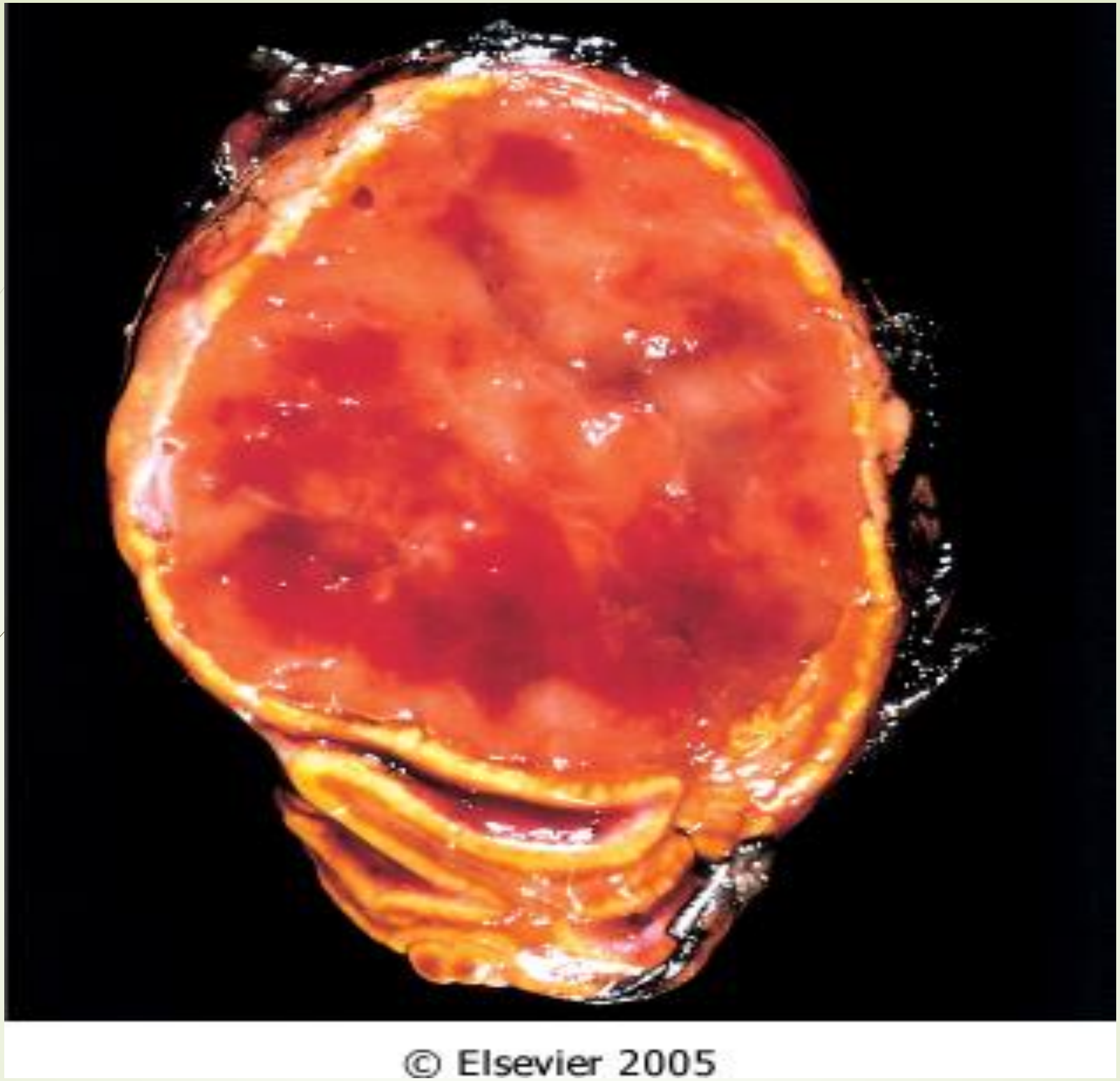
"rule of 10s":

- 10% of pheochromocytomas are extraadrenal (paragangliomas)
- 10% of adrenal pheochromocytomas are bilateral; this proportion may rise to 50% in cases that are associated with familial syndromes.
- 10% of adrenal pheochromocytomas are malignant
- 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

Pheochromocytoma Gross

- Pheochromocytomas range in size from small, circumscribed lesions confined to the adrenal to large, hemorrhagic masses weighing several kilograms.
- 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

Pheochromocytoma 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. **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.

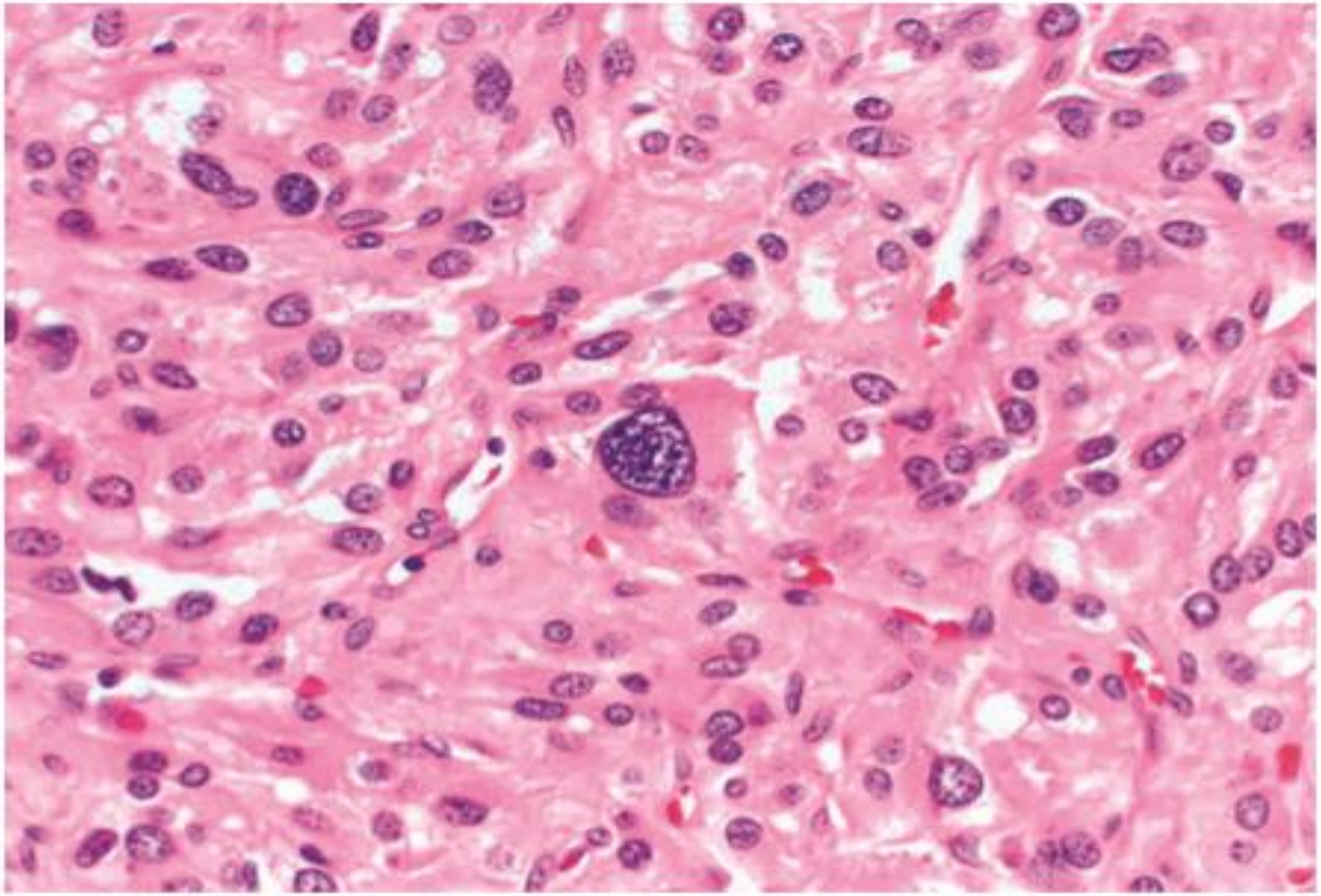
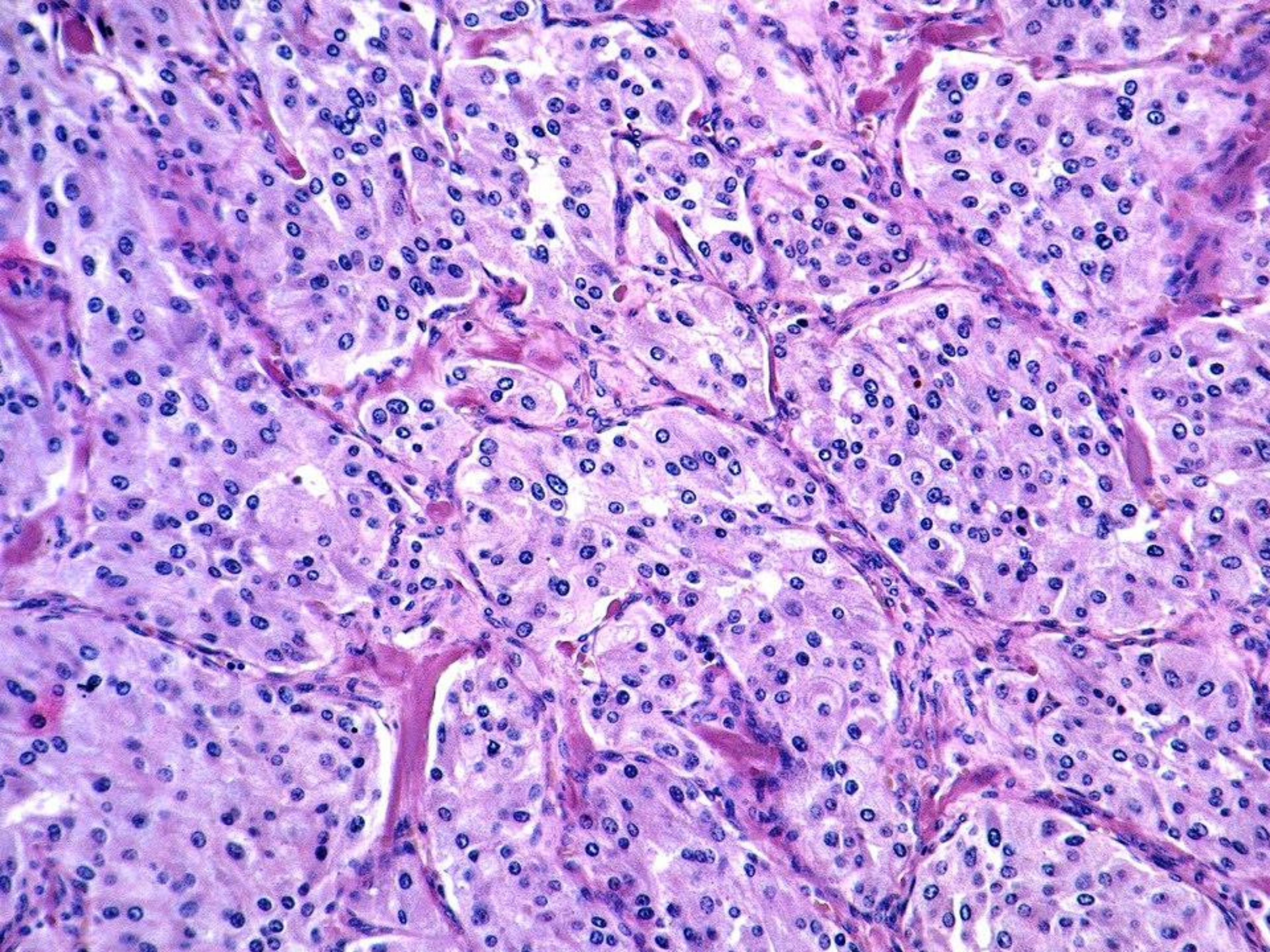


Fig. 20.45 Photomicrograph of pheochromocytoma, demonstrating characteristic nests of cells with abundant cytoplasm. Granules containing catecholamine are not visible in this preparation. It is not uncommon to find bizarre cells (such as the one in the center of this image), even in pheochromocytomas that are benign.



Clinical features

- The predominant clinical manifestation of pheochromocytoma is *hypertension*.
- 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:

- The most common cause of hypercortisolism is exogenous

administration of steroids.

- • Primary adrenocortical insufficiency can be acute (WaterhouseFriderichsen syndrome) or chronic (Addison disease).Chronic adrenal insufficiency in then Western world most often is secondary to autoimmune adrenalitis.
- Pheochromocytomas are neoplasms composed of chromaffin cells, which, like their nonneoplastic counterparts, synthesize and release catecholamines

Refrence

- Robbins Basic Pathology , 10th ed