Adrenal Gland

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.

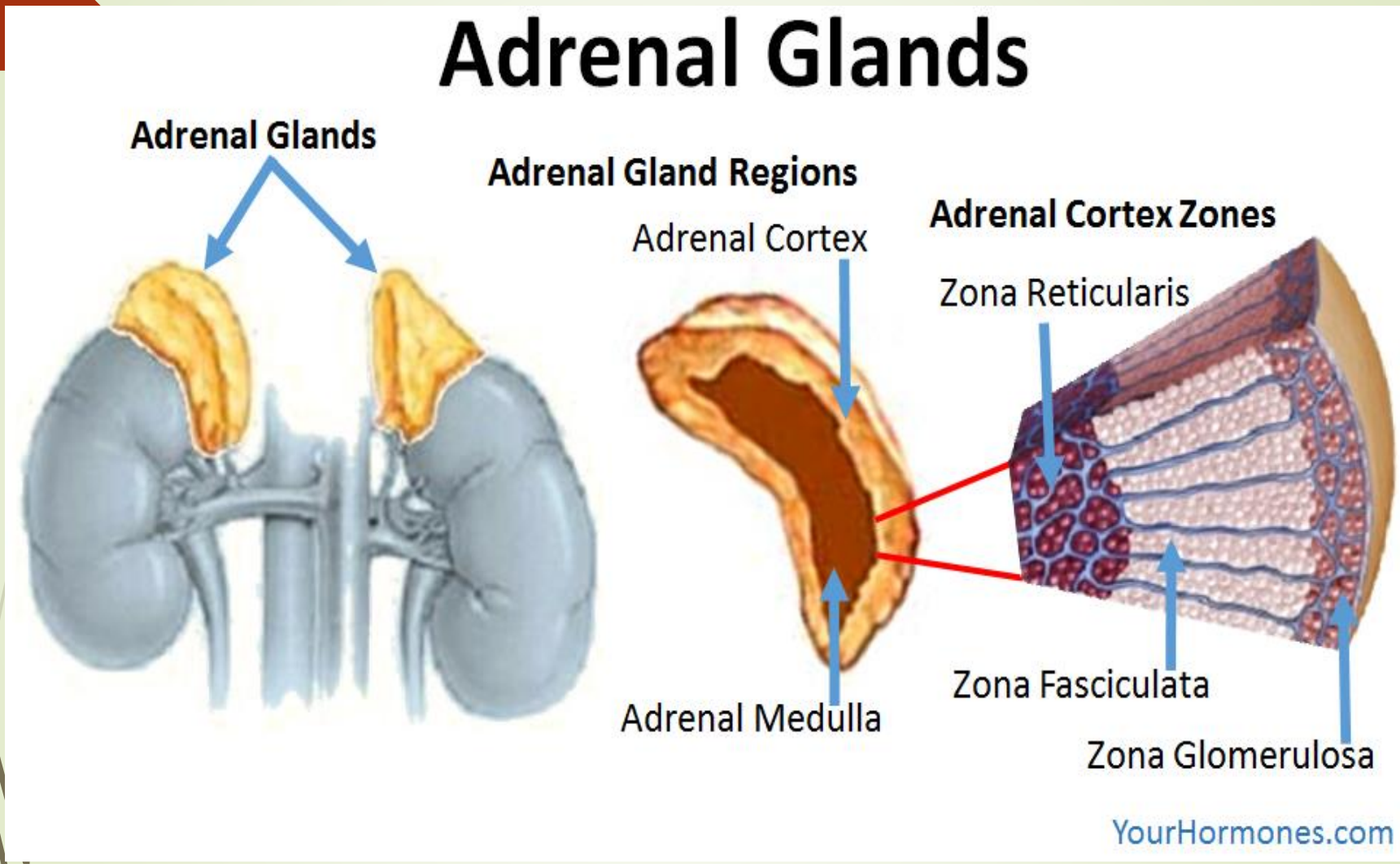
Adrenal Glands

- 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 Gland

Three types of steroids:

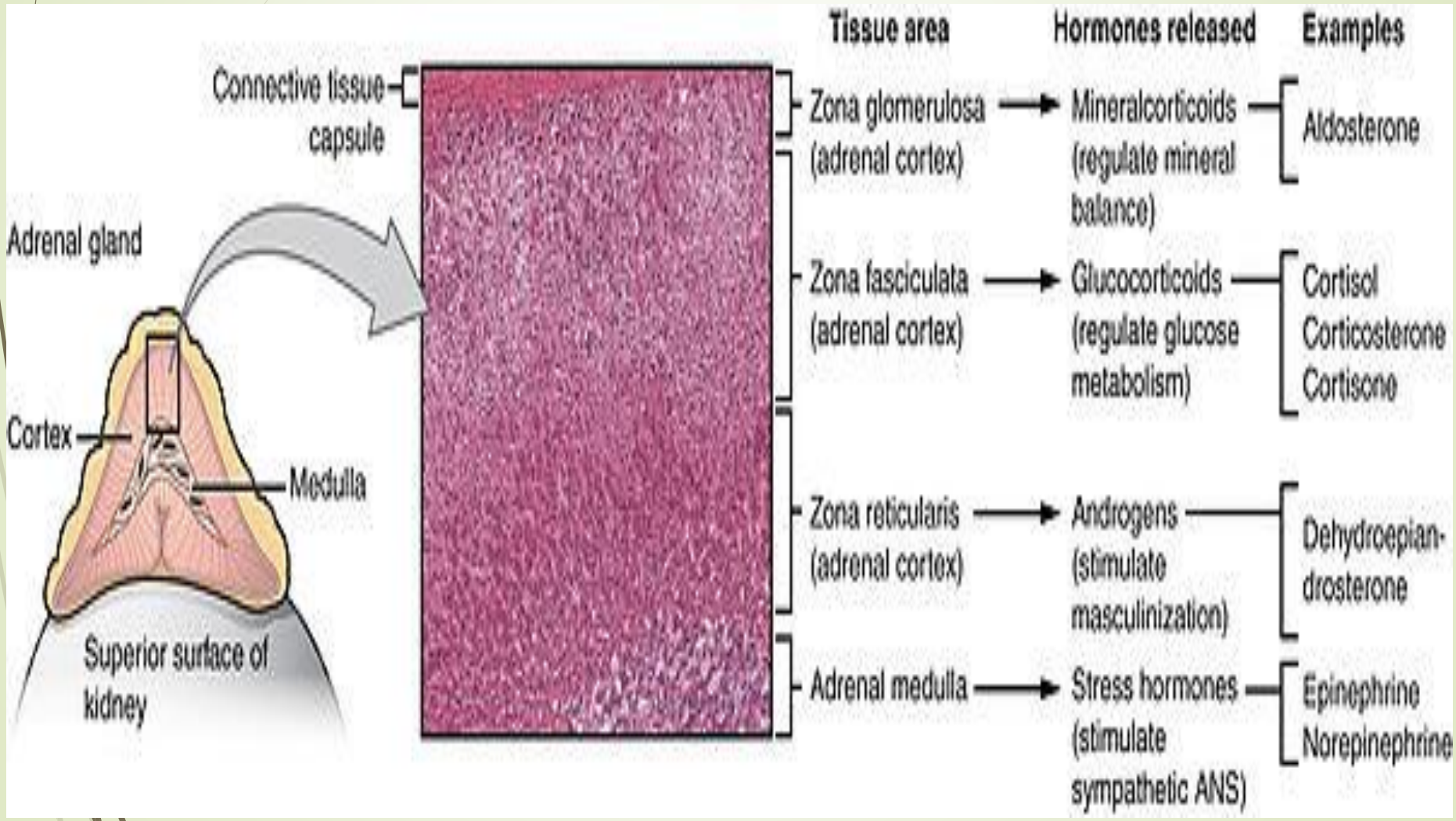
(1) Glucocorticoids (principally cortisol) zona fasciculata

(2) Mineralocorticoids (aldosterone) zona glomerulosa

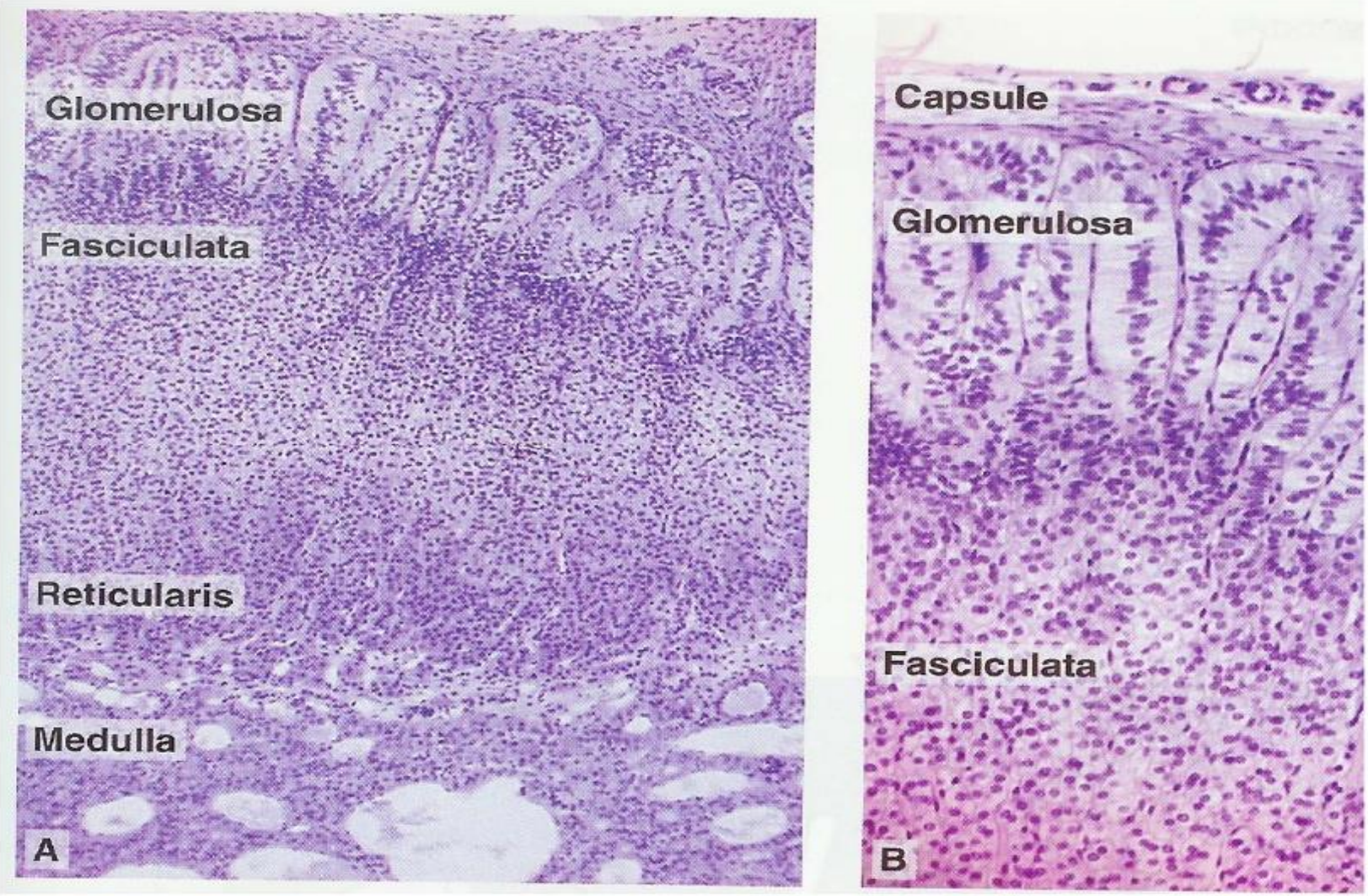
(3) Sex steroids (estrogens and androgens) zona reticularis.

- *The adrenal medulla chromaffin cells- catecholamines, mainly epinephrine*

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

ADRENOCORTICAL HYPERFUNCTION, Morphology

One of the following abnormalities:

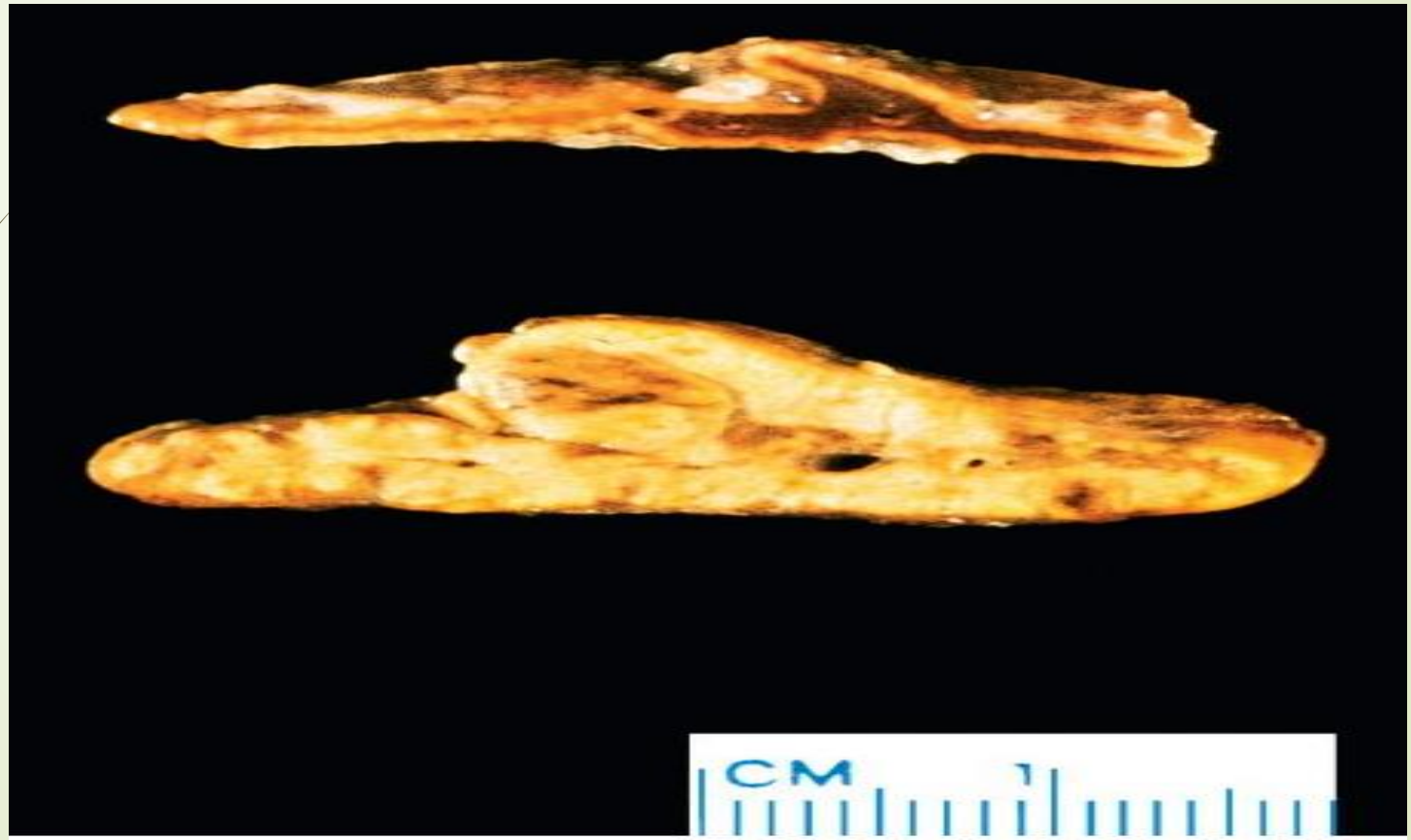
(1) Cortical atrophy: results from exogenous glucocorticoids

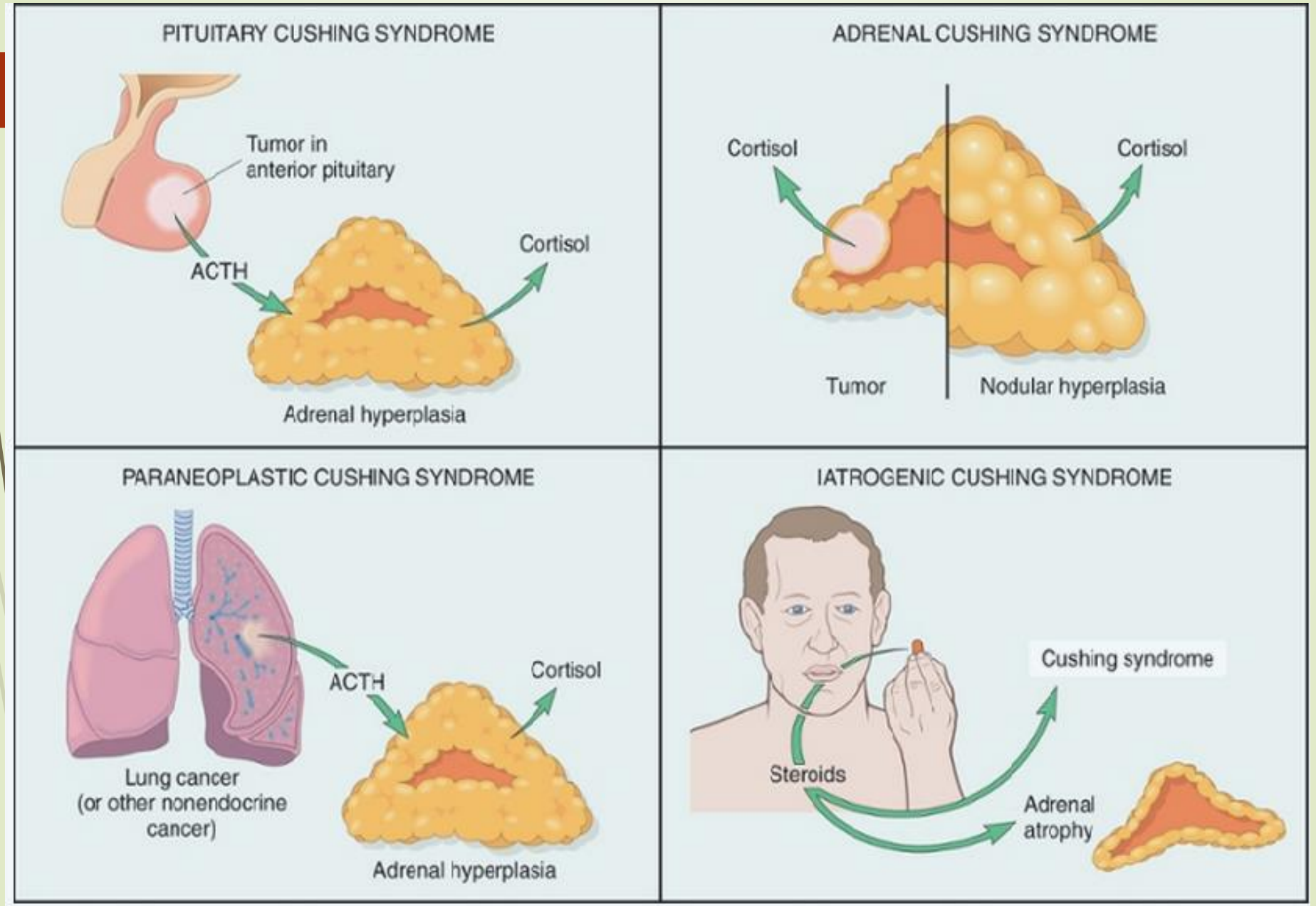
(2) Diffuse hyperplasia: individuals with ACTH-dependent Cushing syndrome

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

(4) Adenoma or carcinoma

Diffuse Cortical Hyperplasia




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

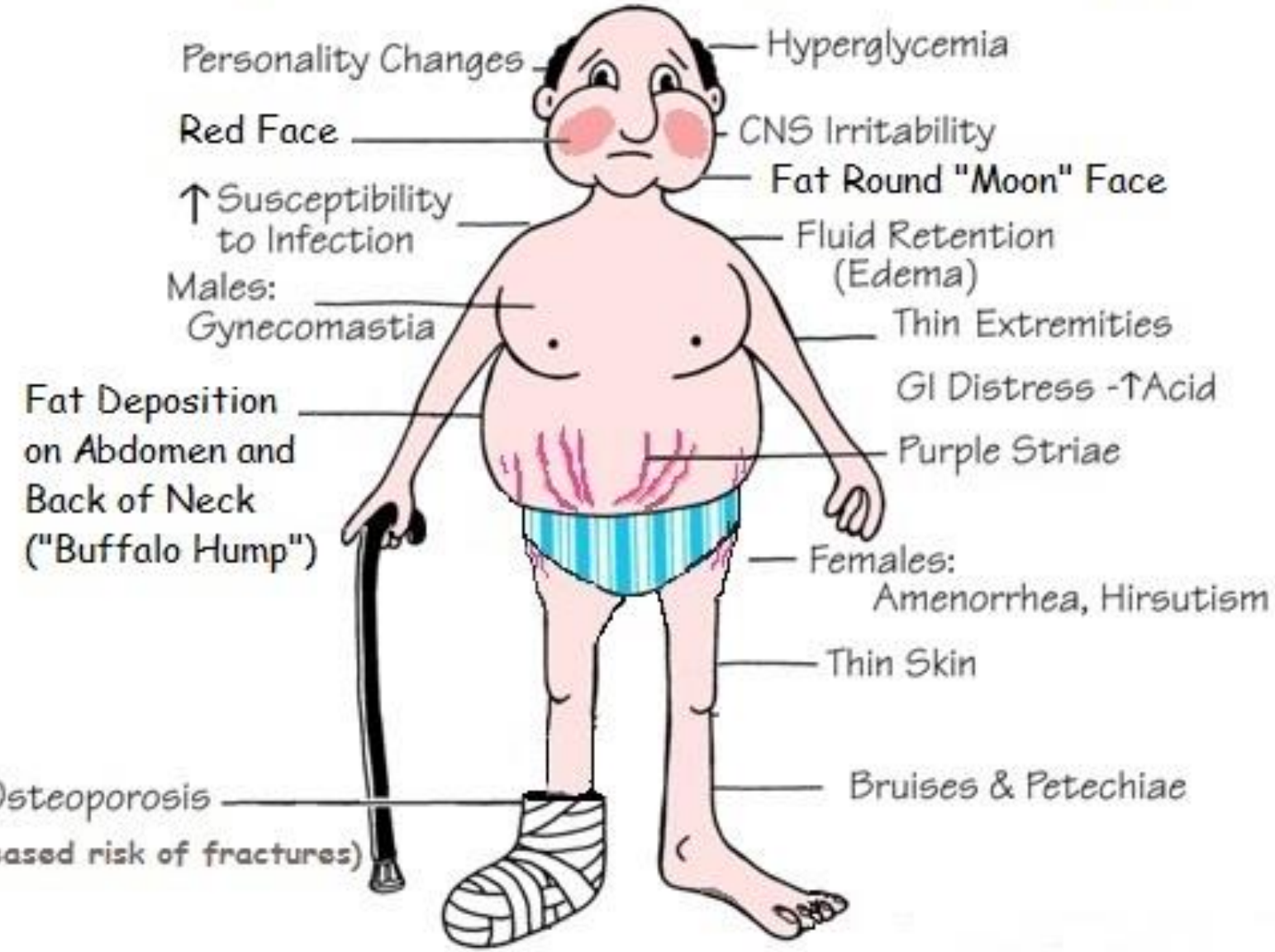
Clinical Features of Cushing Syndrome

- ***Hypertension*** **and** ***weight gain.***
- **Truncal obesity, “moon facies,” and accumulation of fat in the posterior neck and back (“buffalo hump”)**
- **Proximal limb weakness.**
- **Glucocorticoids induce gluconeogenesis and inhibit the uptake of glucose by cells, with resultant** ***hyperglycemia, glucosuria,*** **and** ***polydipsia,*** **mimicking diabetes mellitus.**
- **Skin is thin, fragile, and easily bruised;** ***cutaneous striae*** **.**

Clinical Features of Cushing Syndrome, continue…

- ***Osteoporosis,*** **with consequent increased susceptibility to fractures.**
- **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.**

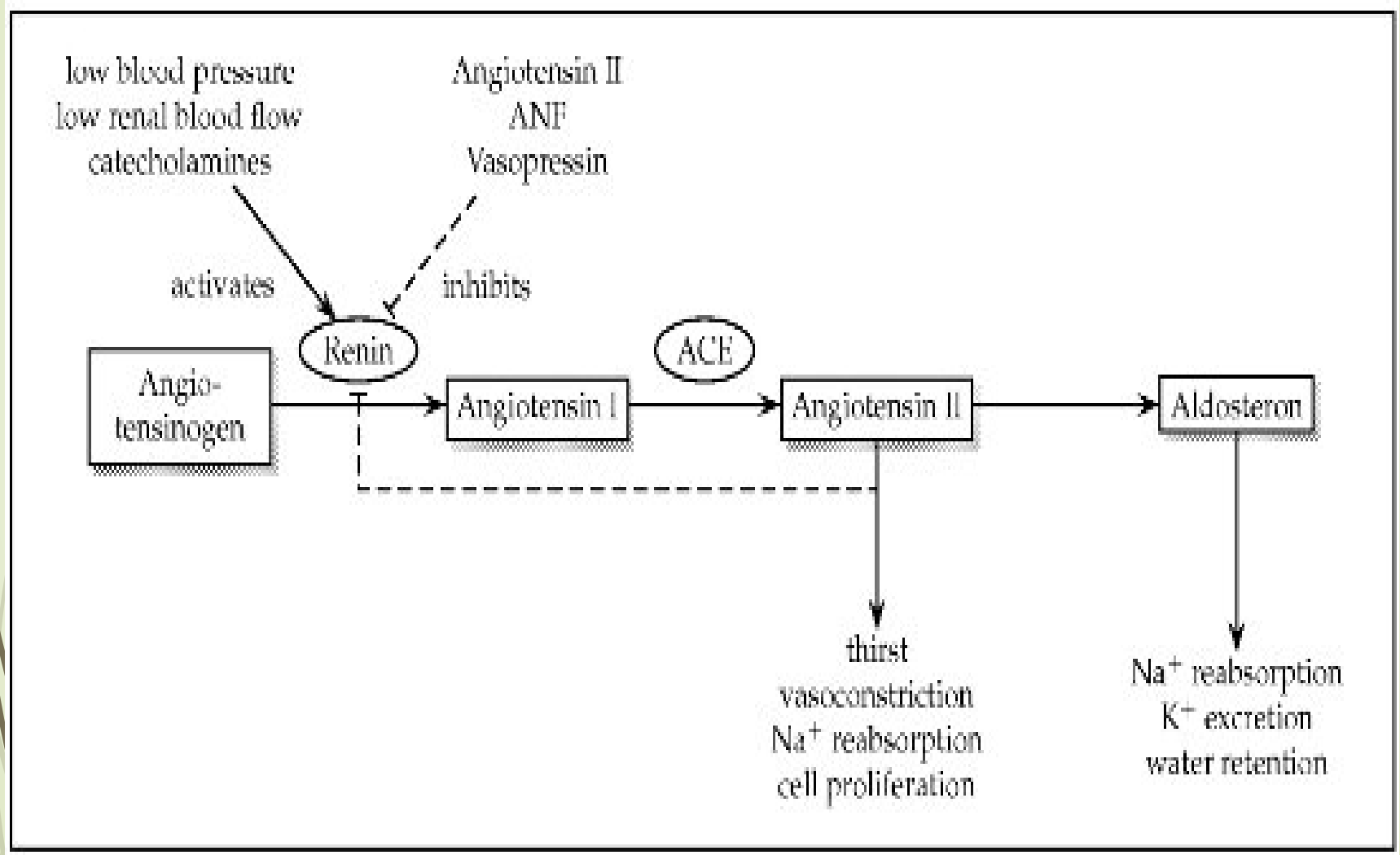
Cushing's Disease or Syndrome Symptoms



Hyperaldosteronism

Excess aldosterone secretion

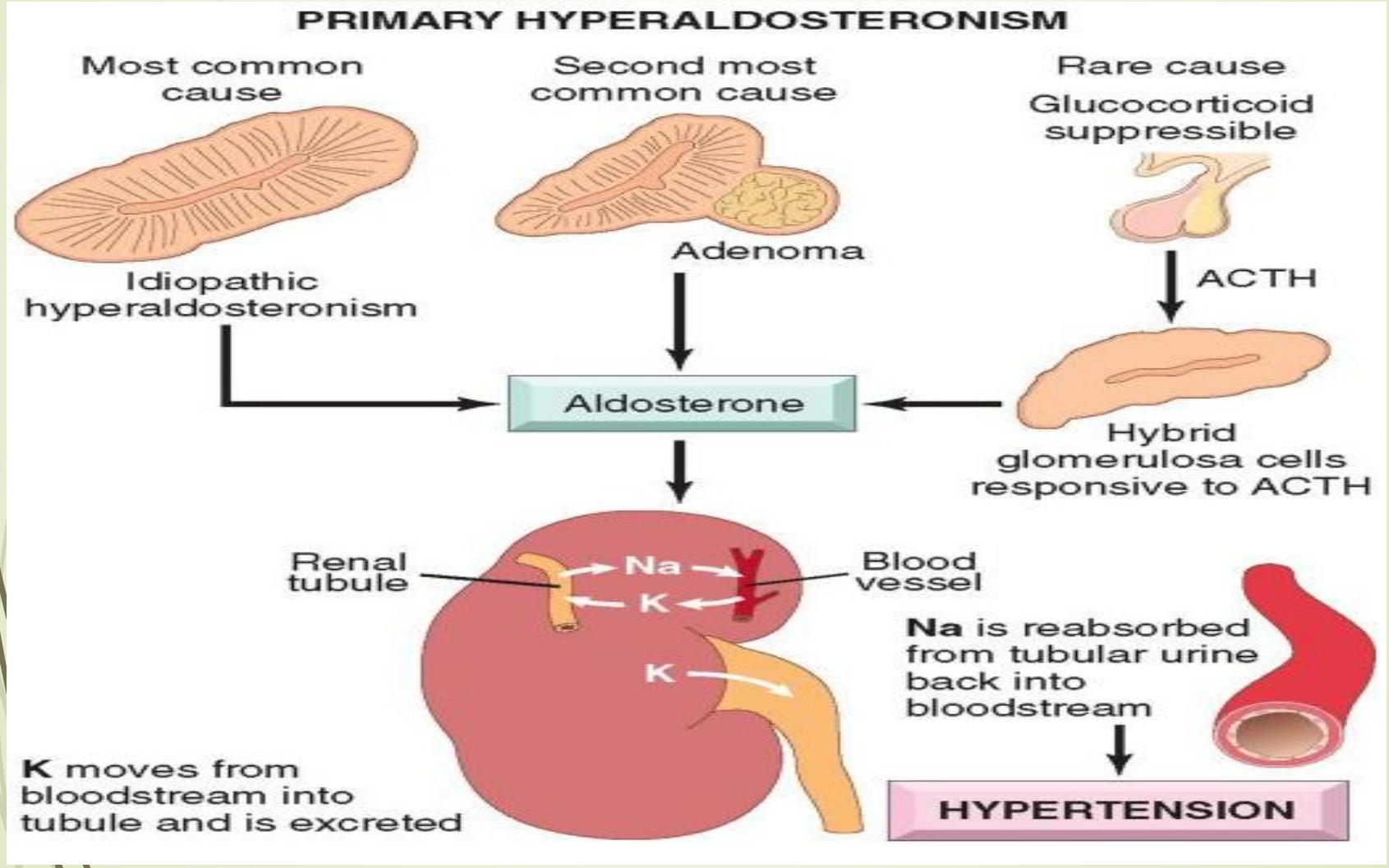
- ***Primary aldosteronism (autonomous overproduction of aldosterone) with resultant suppression of the renin-angiotensin system and decreased plasma renin activity***
- ***Secondary hyperaldosteronism, in contrast, aldosterone release occurs in response to activation of the renin-angiotensin system***


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 mechanism is the most common underlying cause of primary hyperaldosteronism, accounting for about 60% of cases. The pathogenesis is unclear.
- ***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

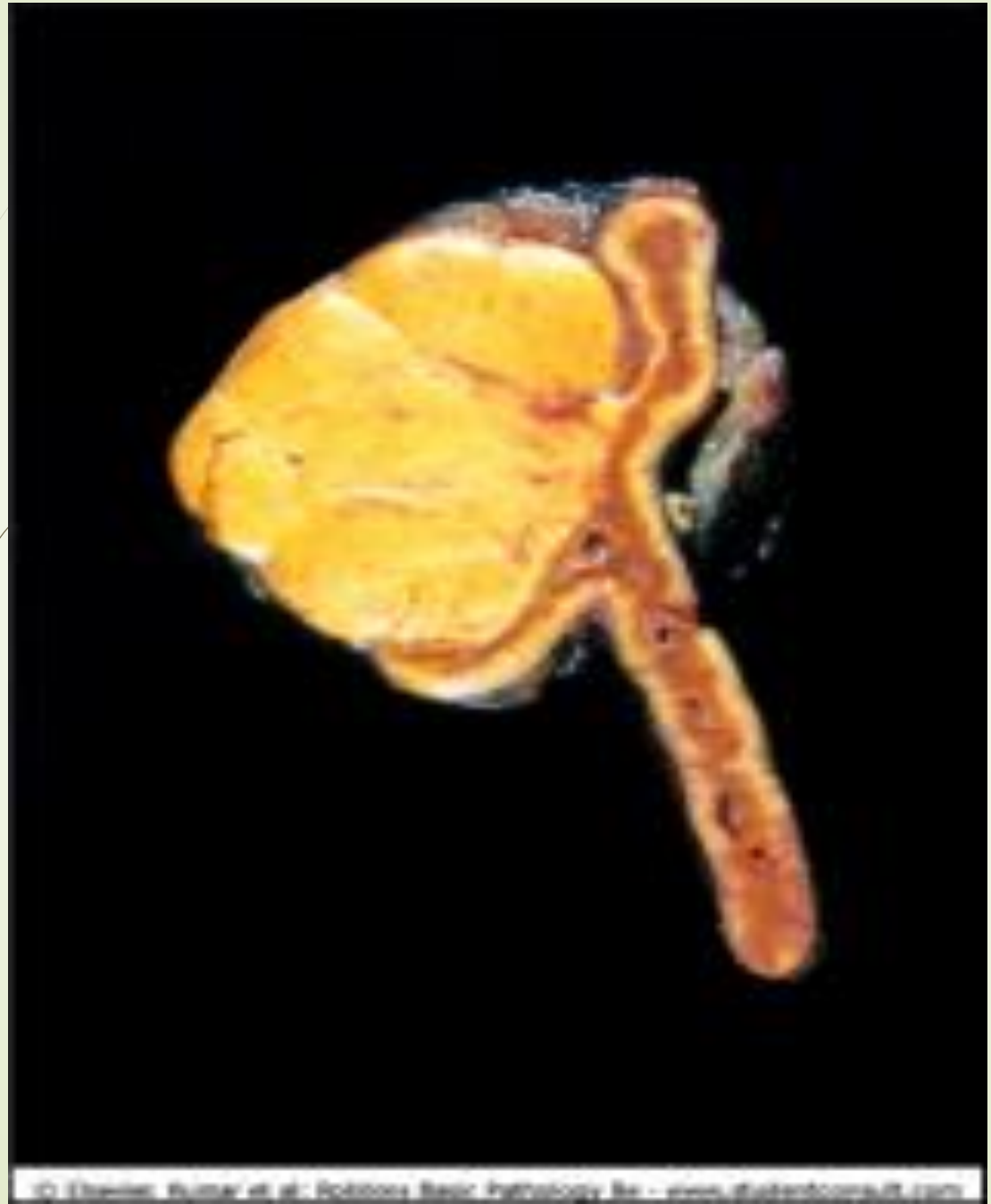


Hyperaldosteronism, Clinical

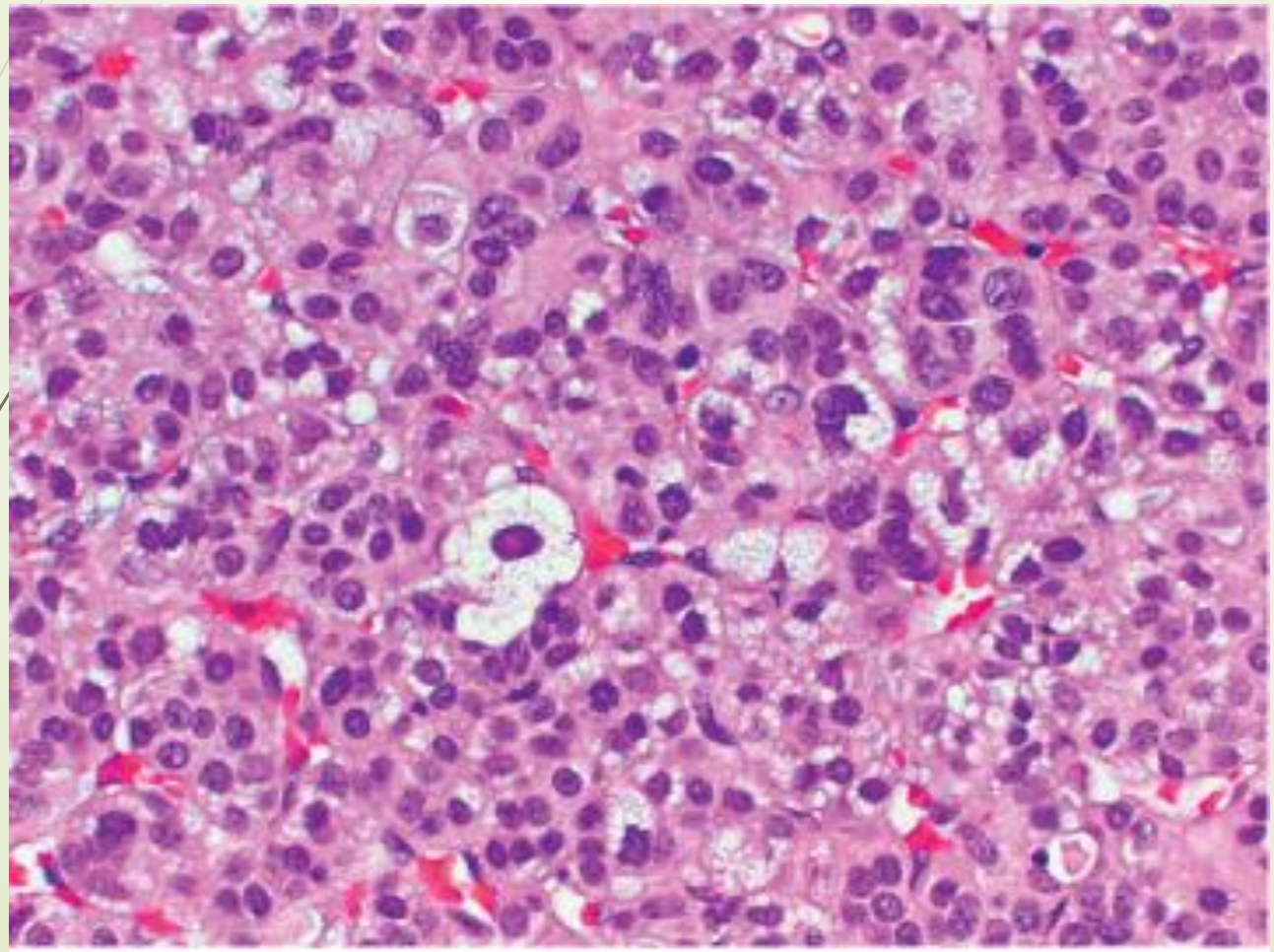
- ***Presents with hypertension.***
- **Primary hyperaldosteronism may be the most common cause of secondary hypertension (i.e., hypertension secondary to an identifiable cause).**
- **Aldosterone promotes sodium reabsorption.**
- ***Hypokalemia* results from renal potassium wasting and, when present,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

Aldosterone-producing adenomas , Morphology

- **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**



Aldosterone-producing adenomas



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.

Adrenocortical Insufficiency

Adrenocortical insufficiency, or hypofunction, may be caused by either

primary adrenal disease (primary hypoadrenalism)

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

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

Adrenocortical Insufficiency

- **Three patterns of adrenocortical insufficiency**

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

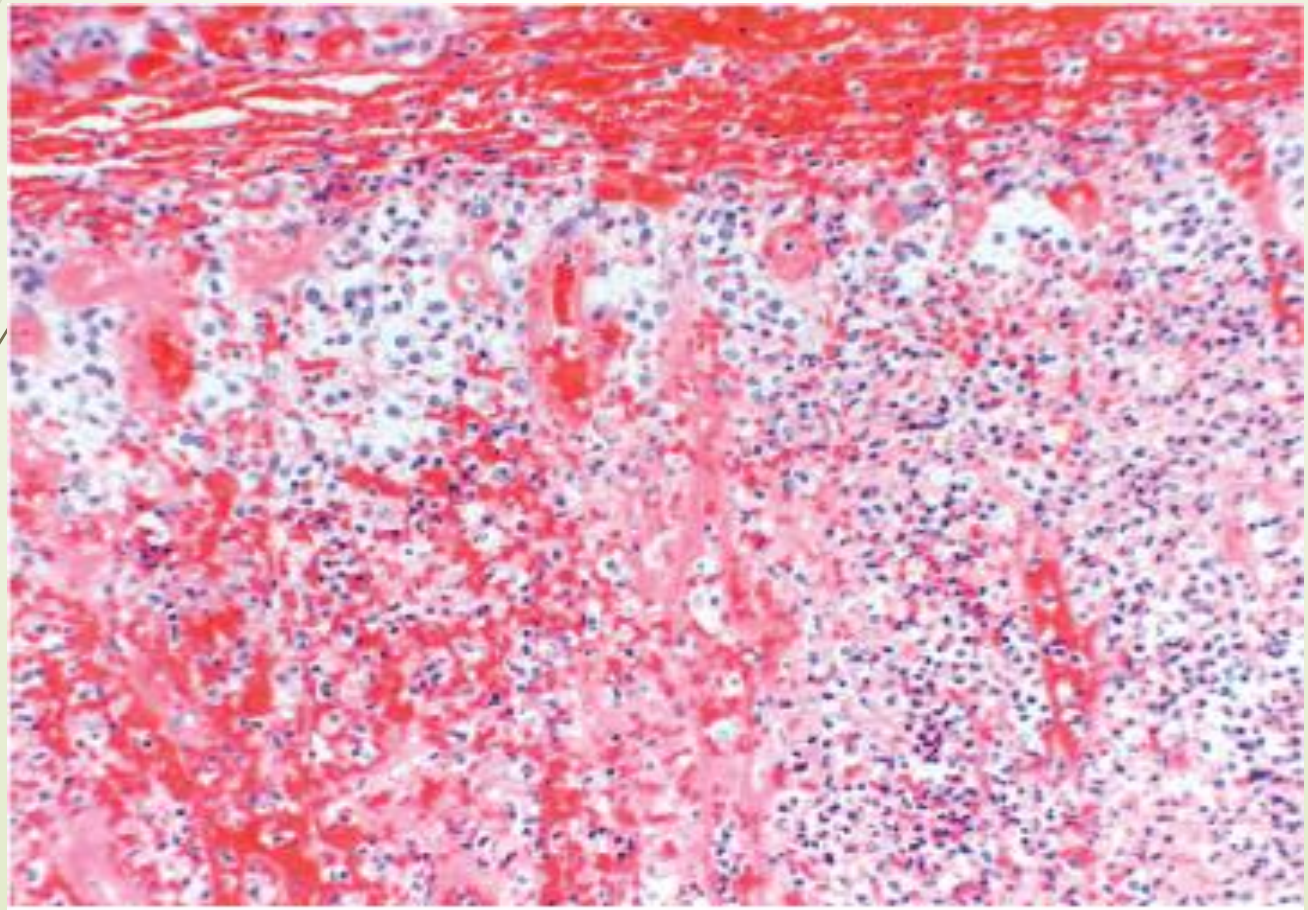
(2) Primary *chronic* adrenocortical insufficiency *(Addison disease)*

(3) Secondary adrenocortical insufficiency

Acute Adrenocortical Insufficiency

Acute
Waterhouse-Friderichsen syndrome
Sudden withdrawal of long-term corticosteroid therapy
Stress in patients with underlying chronic adrenal insufficiency

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

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

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*, whereas 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.**

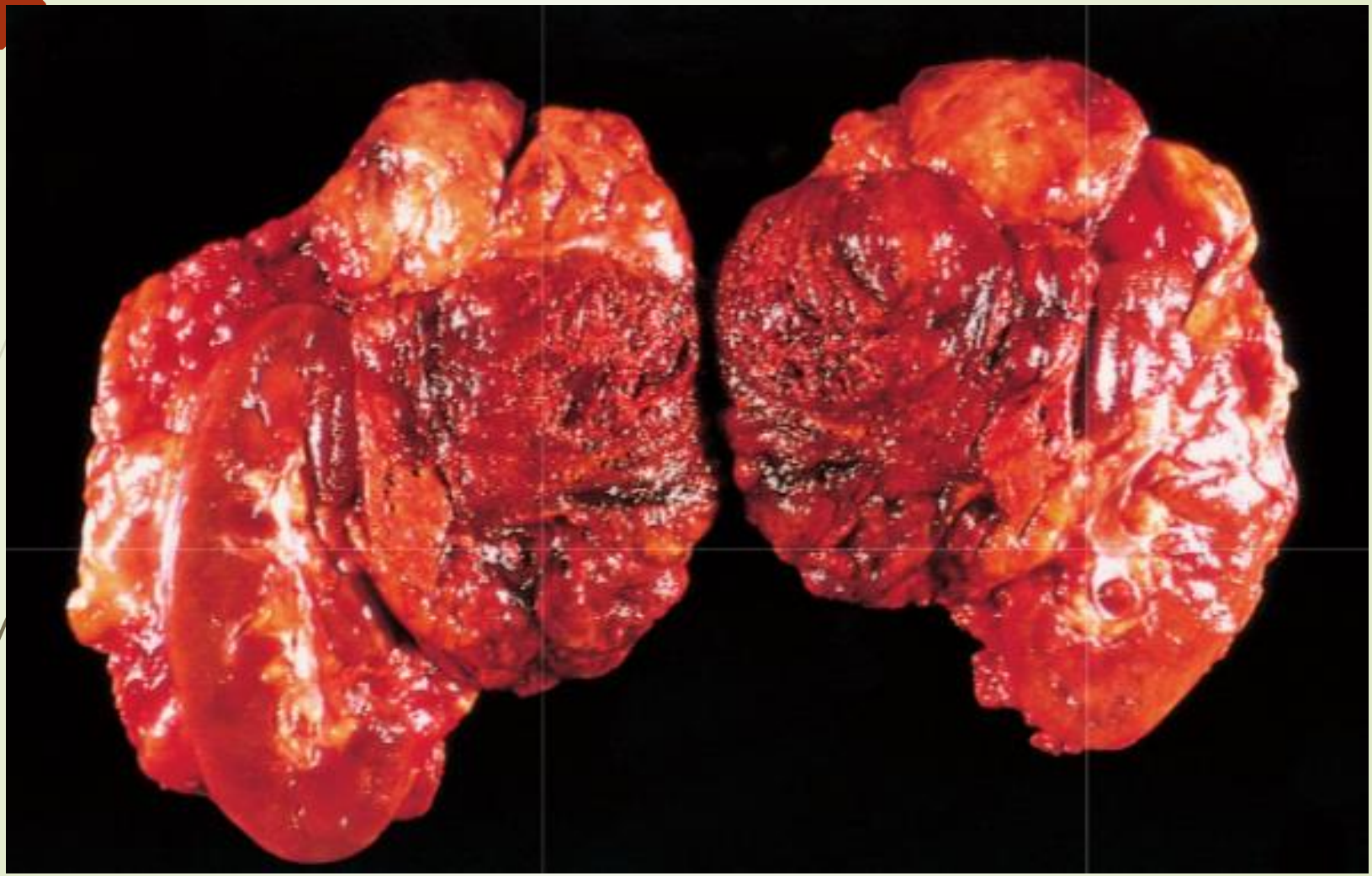
ADRENOCORTICAL NEOPLASMS

- 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.

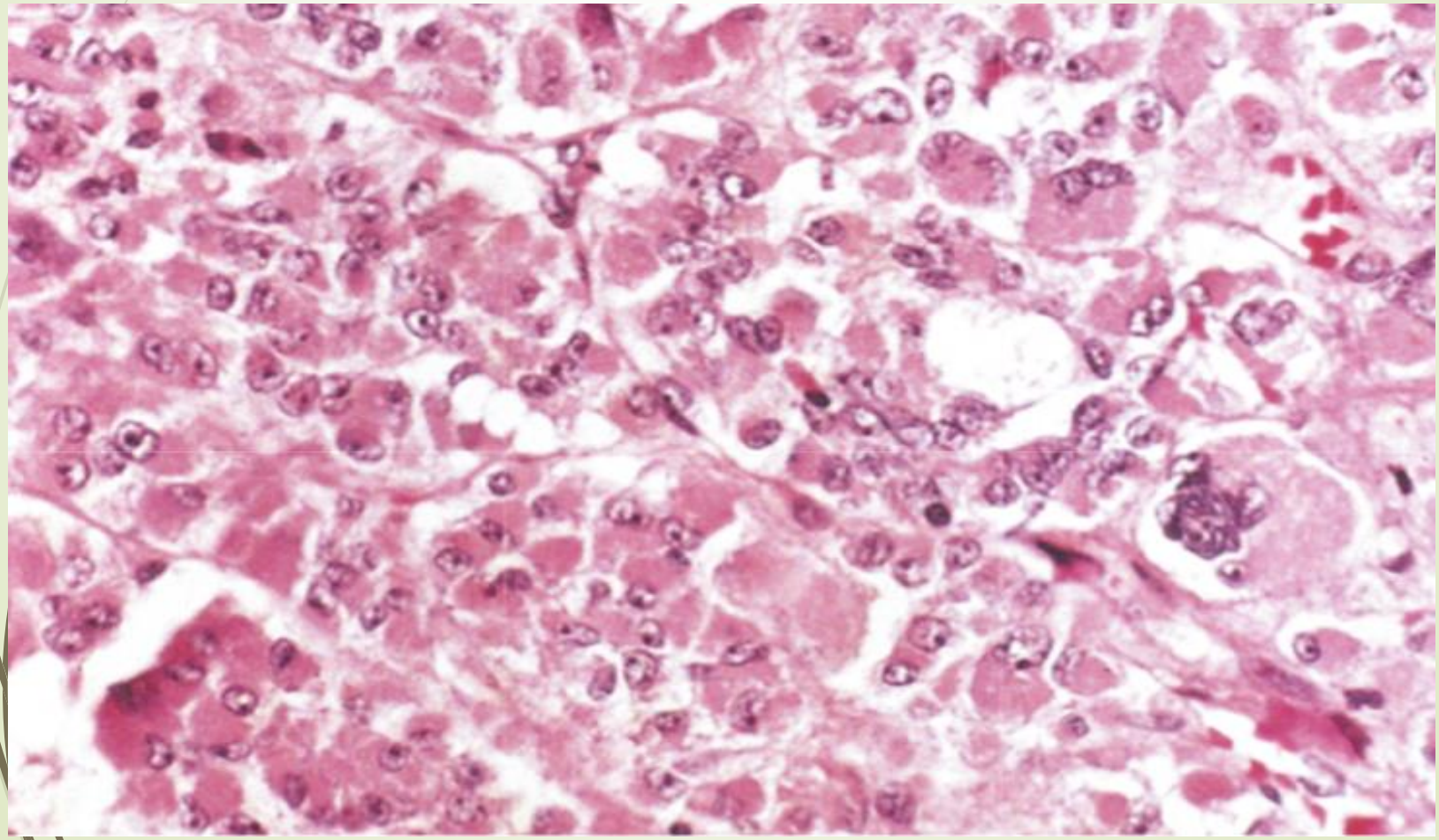
- Most cortical adenomas do not cause hyperfunction and usually are encountered as incidental findings at the time of autopsy or during abdominal imaging for an unrelated cause
- On cut surface, adenomas usually are yellow to yellow-brown, owing to the presence of lipid within the neoplastic cells .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



Anaplastic cells



Pheochromocytoma

- Pheochromocytomas(chromaffin cells) secret catecholamines
- Similar to aldosterone-secreting adenomas, give rise to surgically correctable forms of hypertension.

Pheochromocytoma

"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

Von Hippel-Lindau disease

Von Recklinghausen's Neurofibromatosis Type I

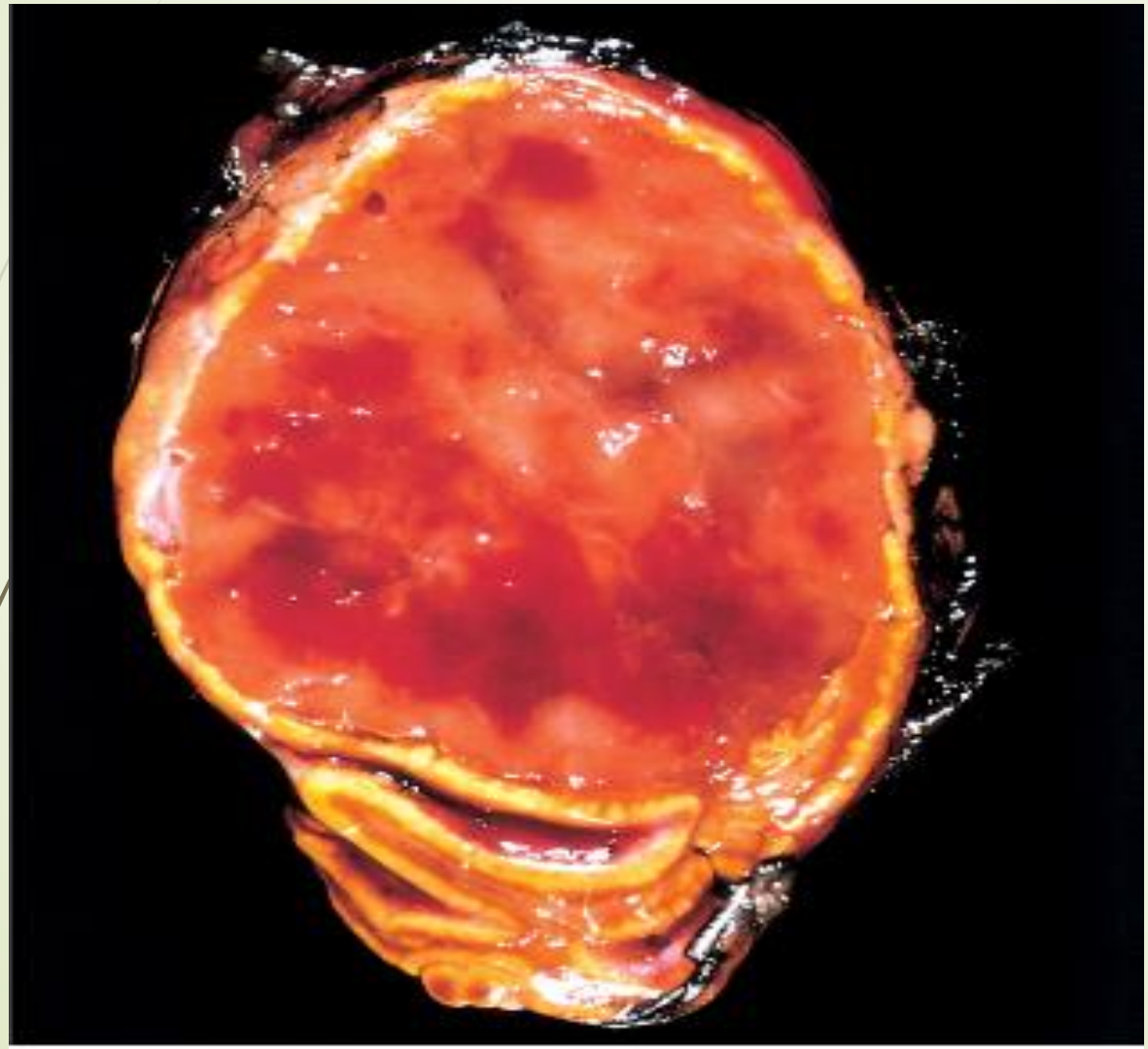
Pheochromocytoma Gross

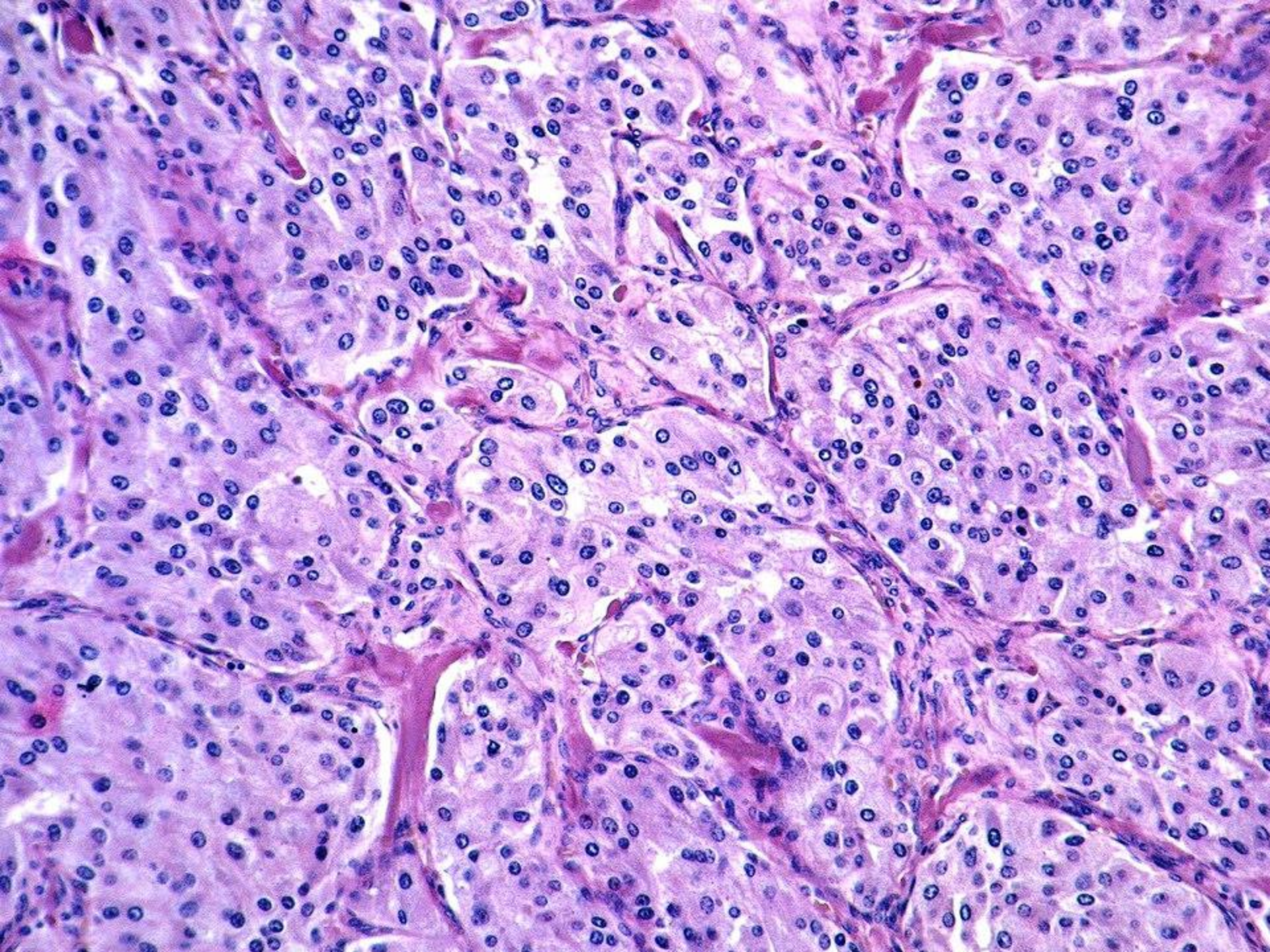
- range in size from small, circumscribed lesions confined to the adrenal to large, hemorrhagic masses weighing several kilograms.
- On cut surface, smaller pheochromocytomas are yellow-tan.

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.

Pheochromocytoma





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