Adrenal Gland

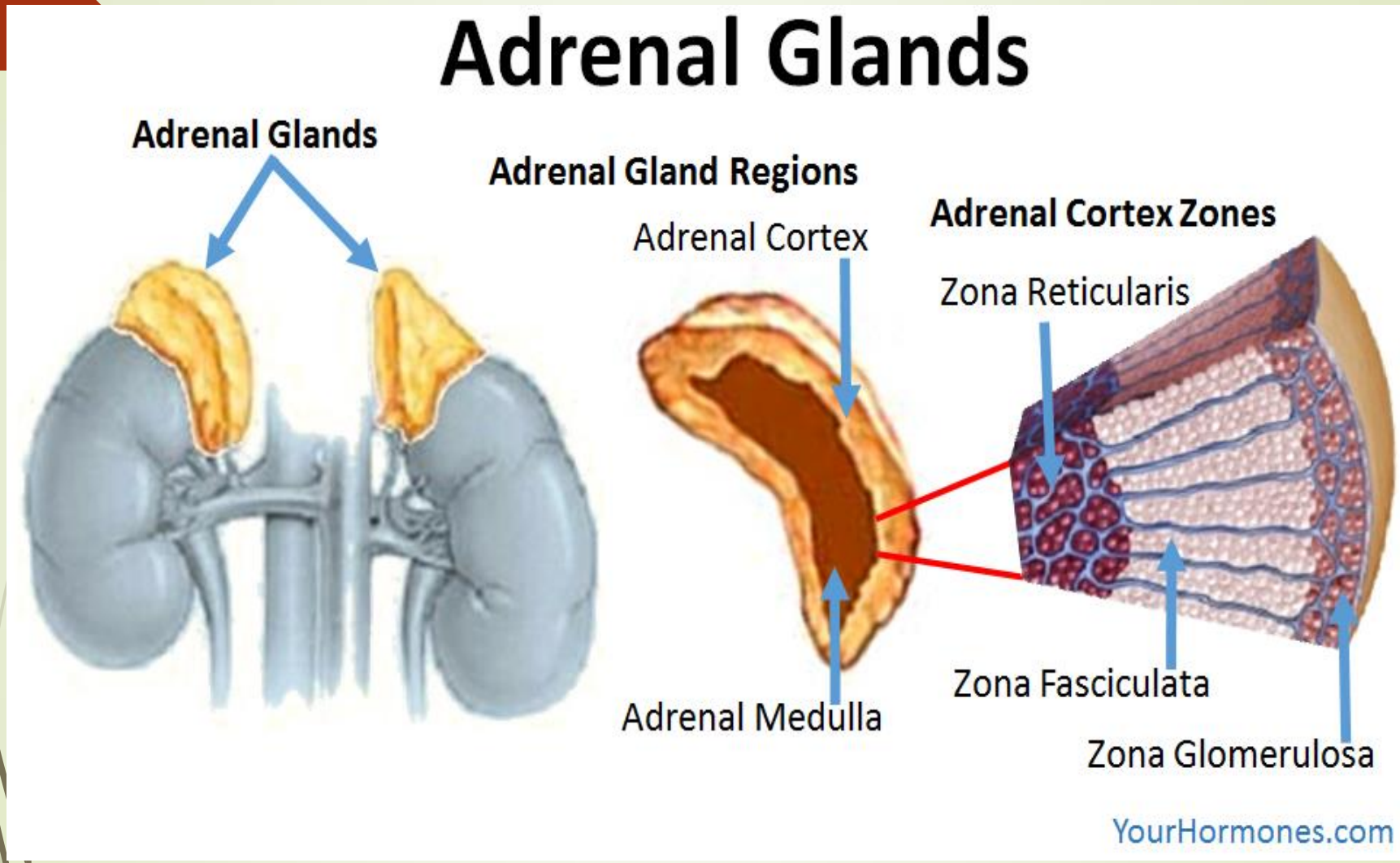
Objectives

- 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 and 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:

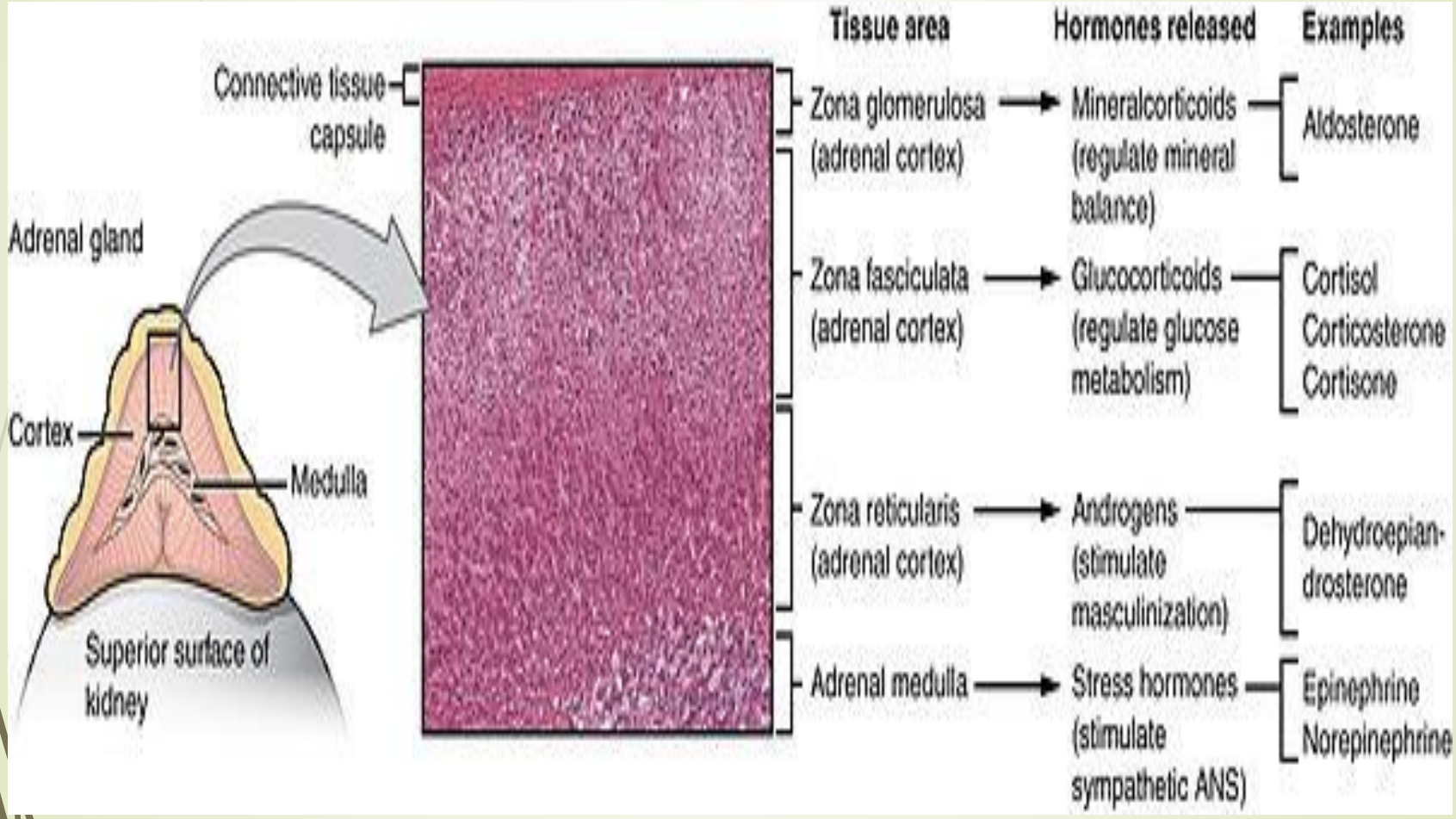
(1) Glucocorticoids (principally cortisol) zona fasciculata

(2) Mineralocorticoids (aldosterone) zona glomerulosa

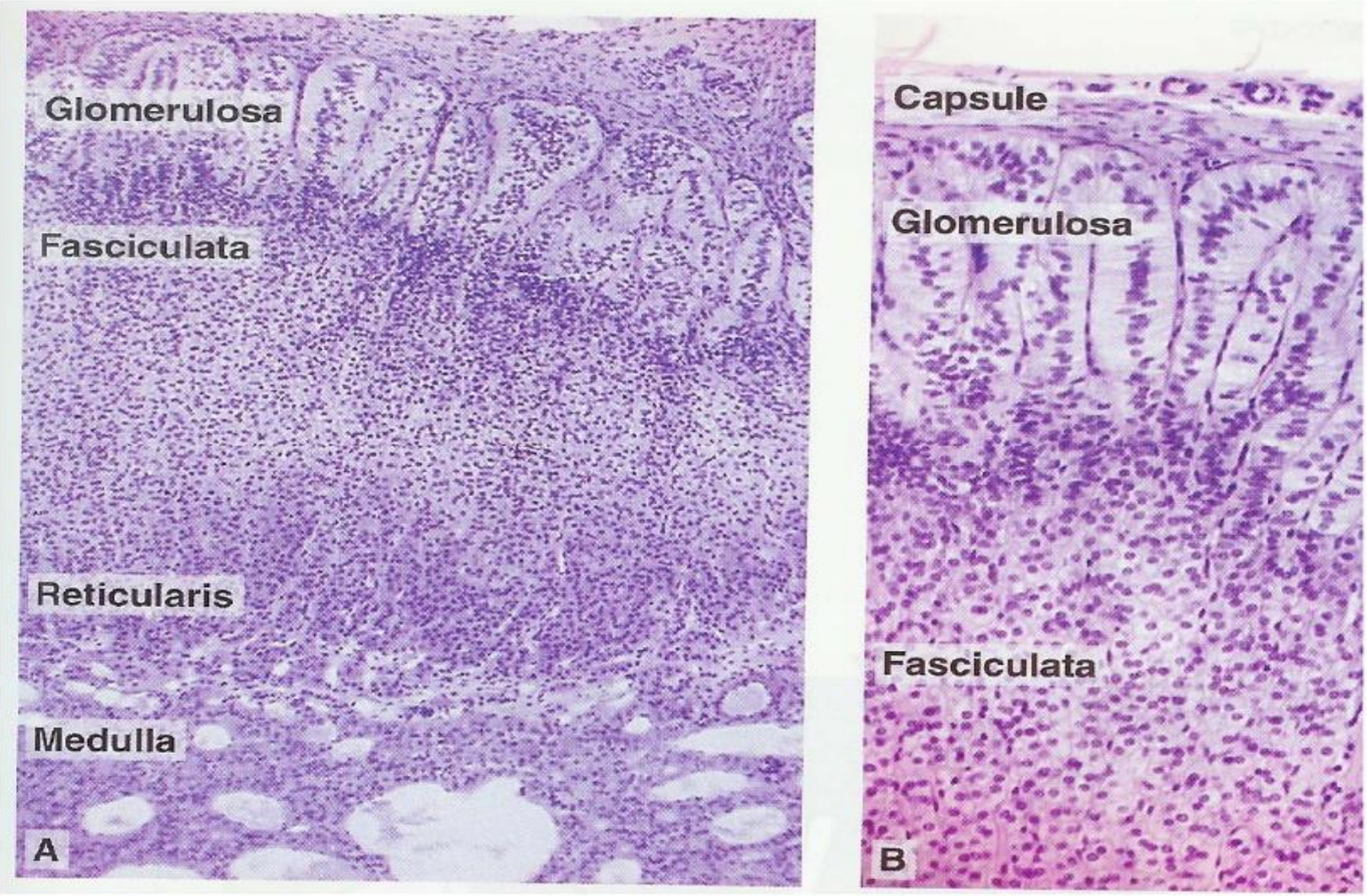
(3) Sex steroids (estrogens and androgens) zona reticularis.

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

Adrenal Gland



Adrenal Gland



ADRENOCORTICAL HYPERFUNCTION

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

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

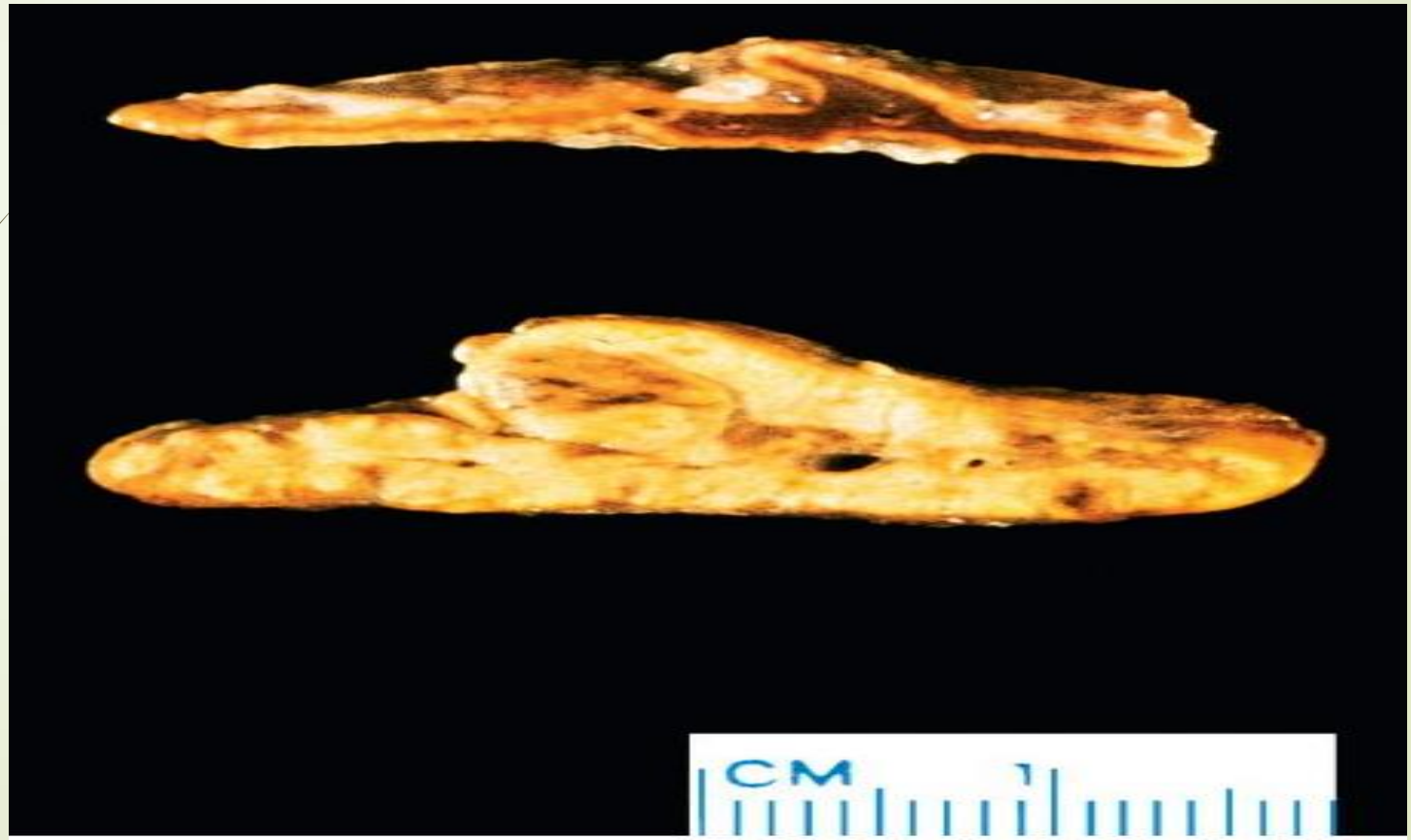
(1) Cortical atrophy: results from exogenous glucocorticoids

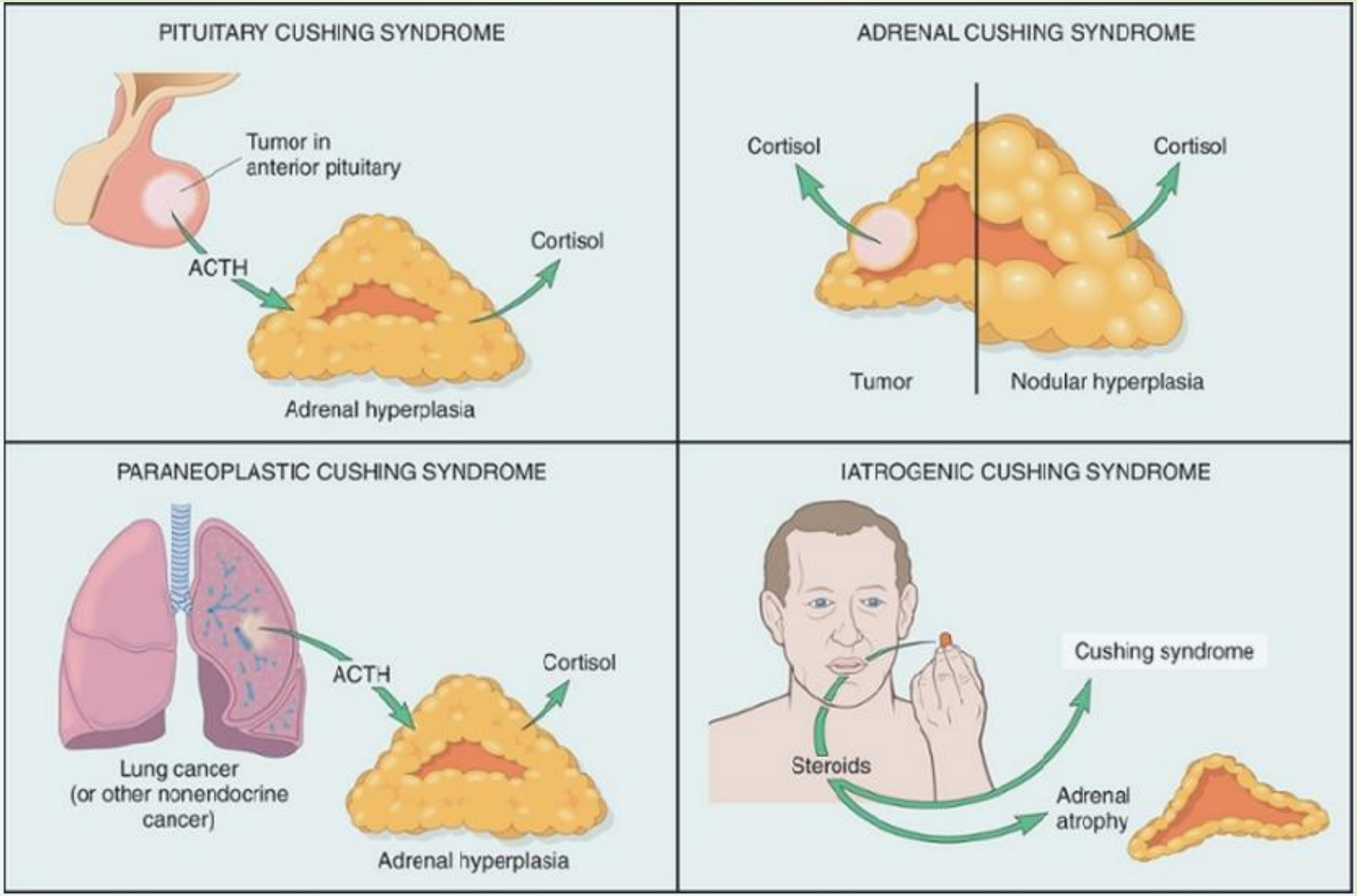
(2) Diffuse hyperplasia: individuals with ACTH-dependent Cushing syndrome

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

(4) Adenoma or carcinoma

Diffuse Cortical Hyperplasia

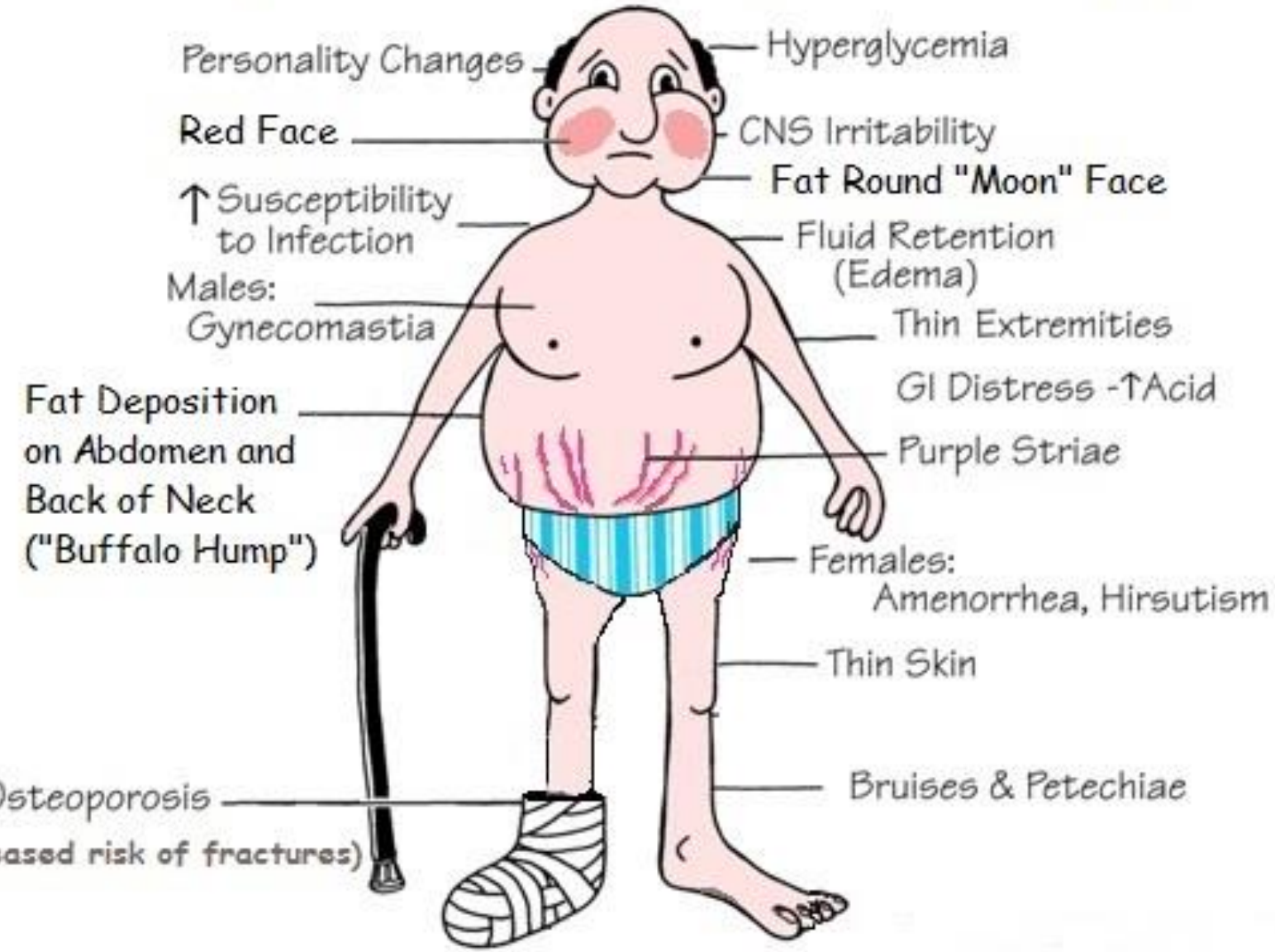



PITUITARY CUSHING SYNDROME
Tumor in anterior pituitary
ACTH
Cortisol
Adrenal hyperplasia
ADRENAL CUSHING SYNDROME
Cortisol
Cortisol
Tumor
Nodular hyperplasia
PARANEOPLASTIC CUSHING SYNDROME
ACTH
Cortisol
Lung cancer (or other nonendocrine cancer)
Adrenal hyperplasia
IATROGENIC CUSHING SYNDROME
Cushing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

Clinical Features of Cushing Syndrome

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%

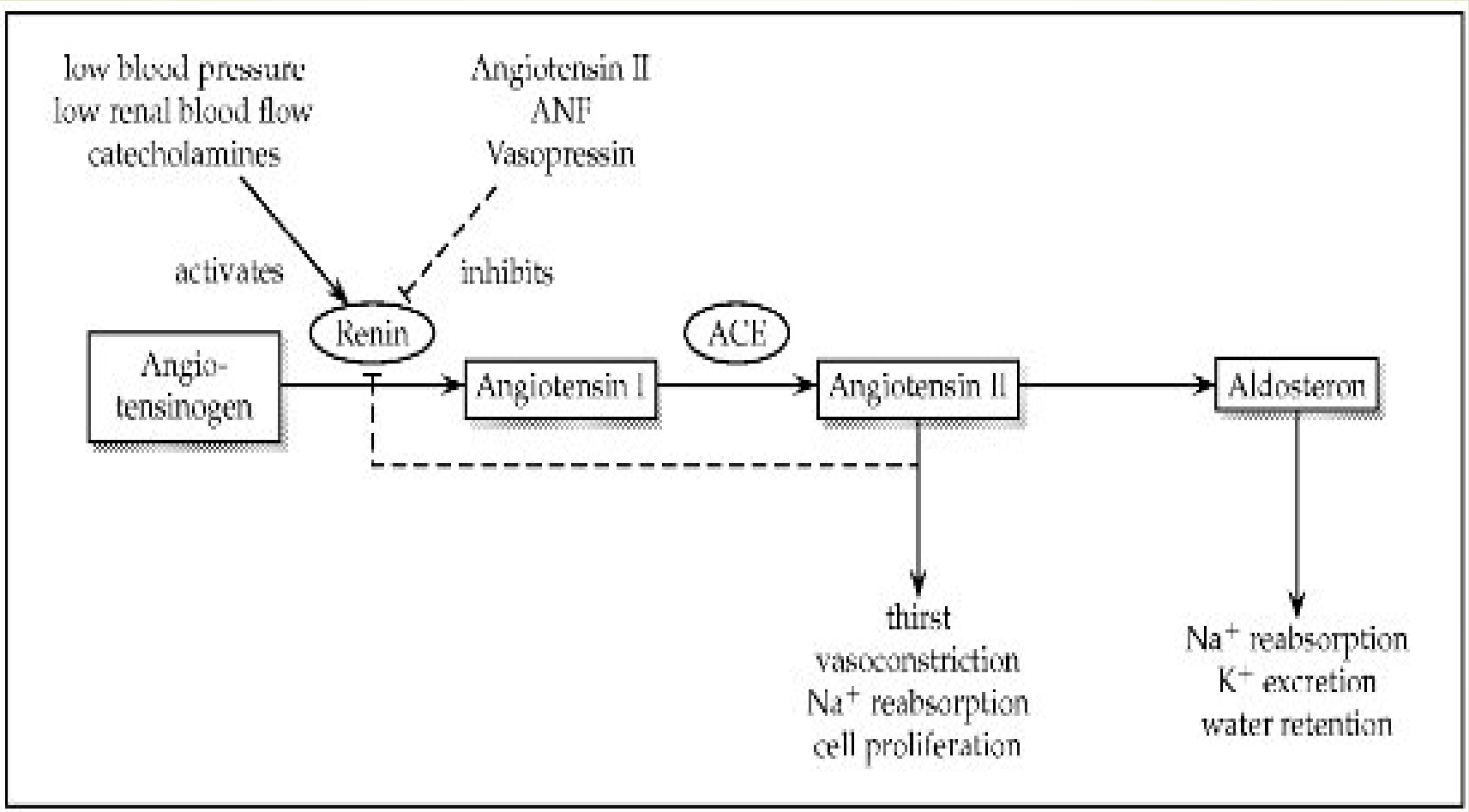
Cushing's Disease or Syndrome Symptoms



Hyperaldosteronism

Excess aldosterone secretion

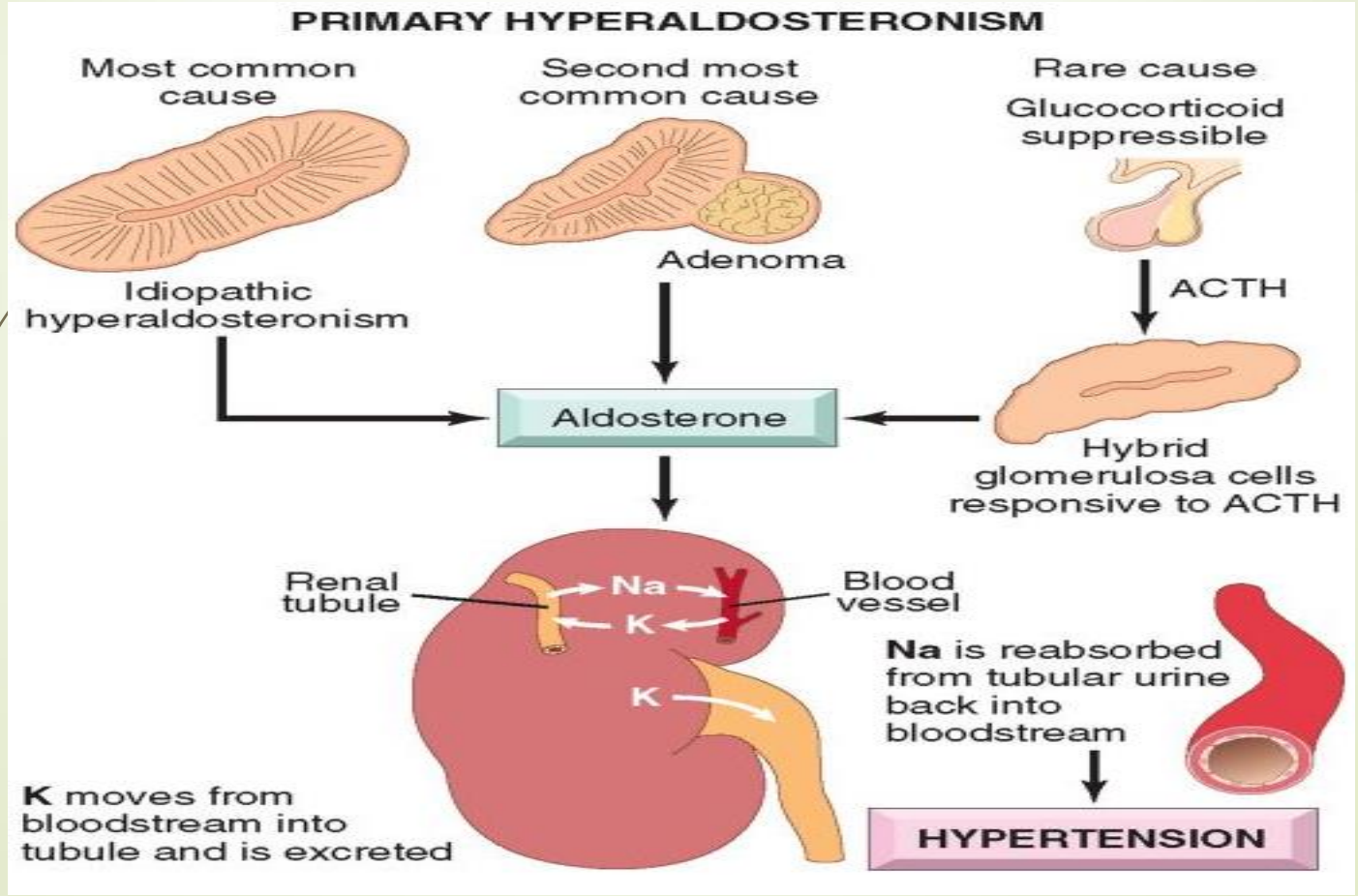
- ***Primary aldosteronism (autonomous overproduction of aldosterone) with resultant suppression of the renin-angiotensin system and decreased plasma renin activity***
- ***Secondary hyperaldosteronism, in contrast, aldosterone release occurs in response to activation of the renin-angiotensin system***


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

Hyperaldosteronism, Clinical

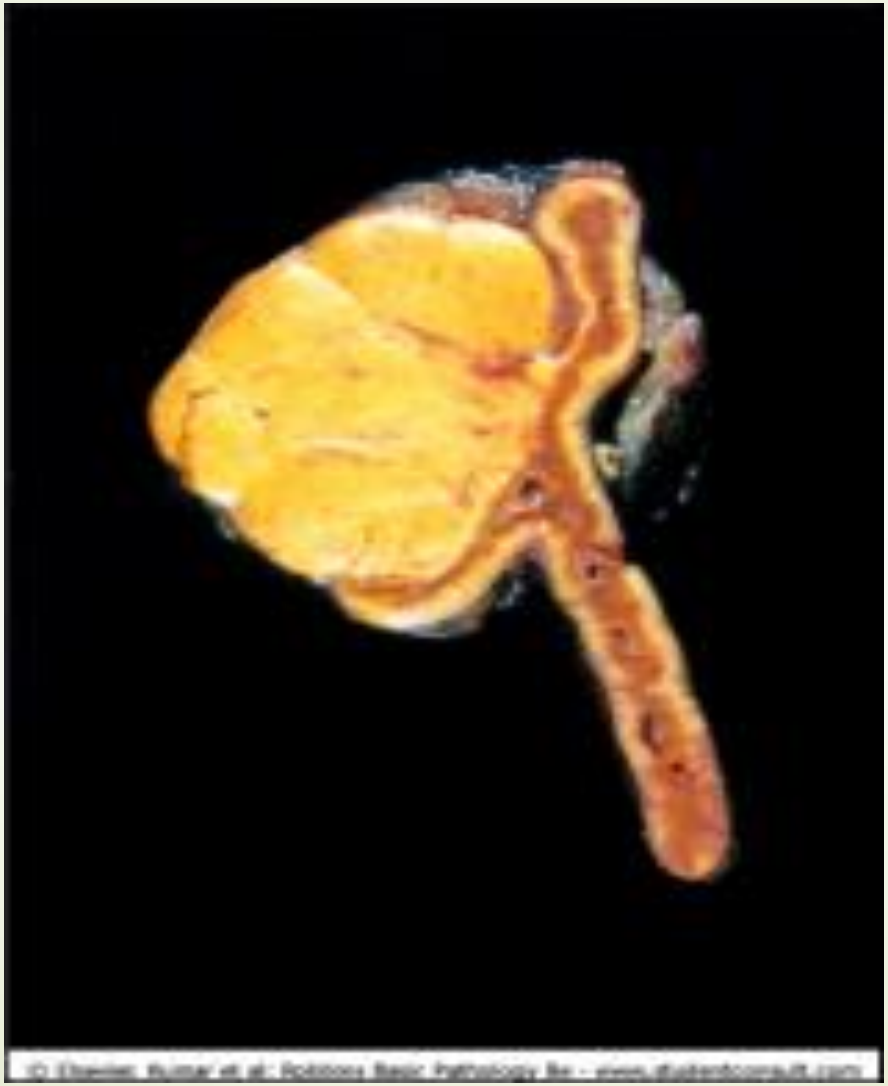
- ***Presents with hypertension*.**
- **Primary hyperaldosteronism may be the most common cause of secondary hypertension (i.e., hypertension secondary to an identifiable cause).**
- **Aldosterone promotes sodium reabsorption.**
- ***Hypokalemia* results from renal potassium wasting and, when present,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

Primary Hyperaldosteronism, Causes

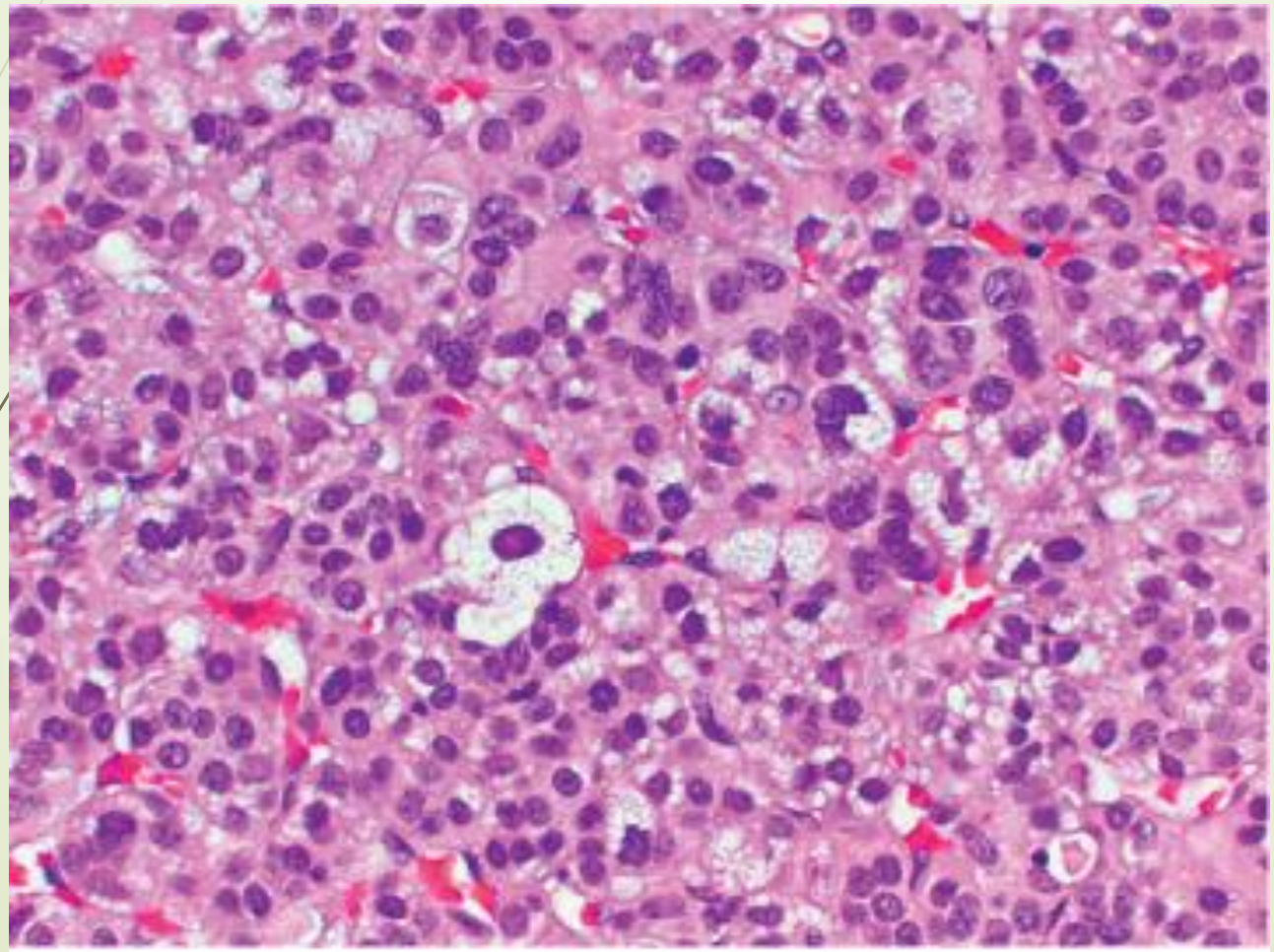


Aldosterone-producing adenomas , Morphology

- **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



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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

- **Caused by either primary adrenal disease or decreased stimulation of the adrenals due to 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

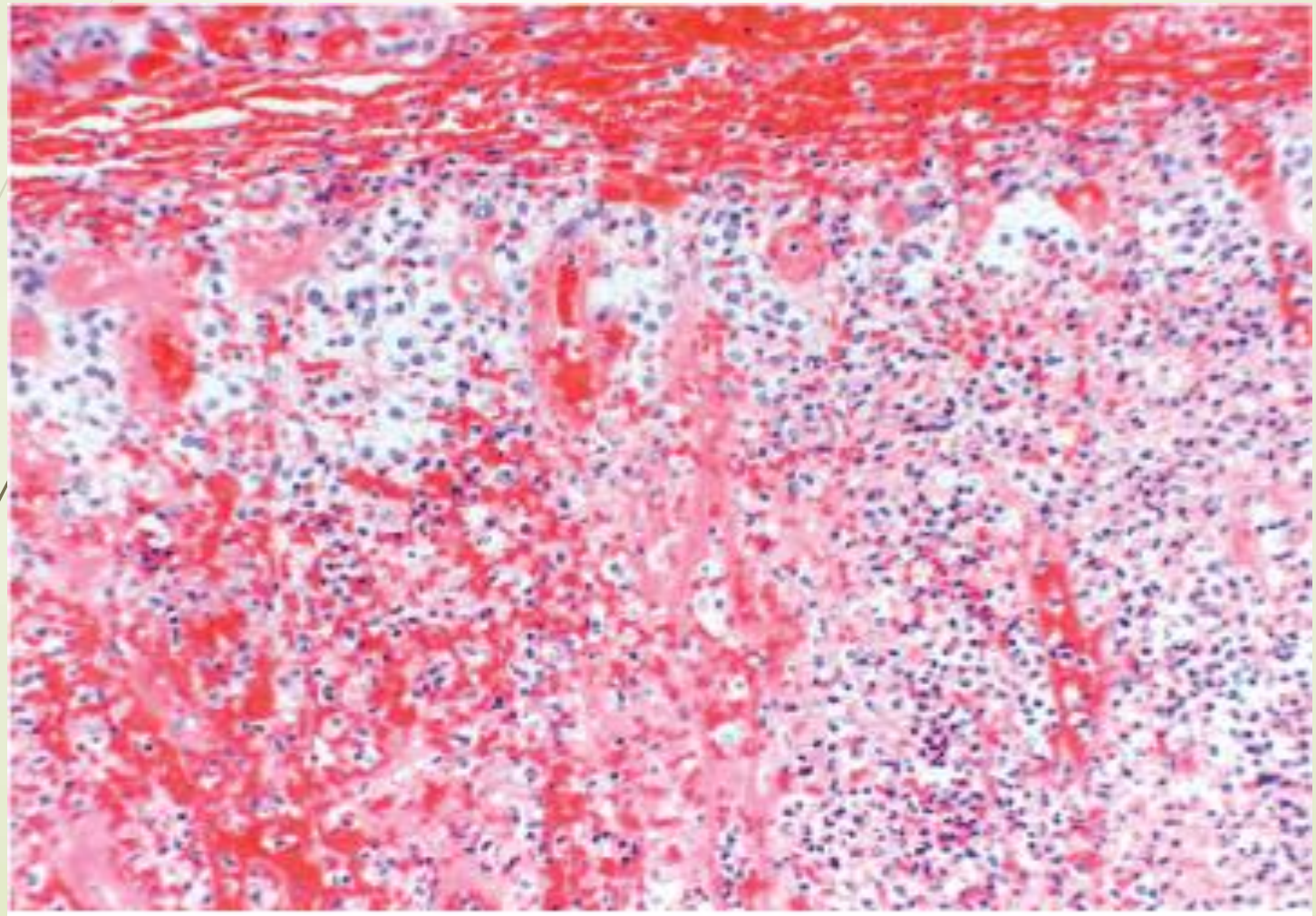
- **Three patterns of adrenocortical insufficiency**

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

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

(3) Secondary adrenocortical insufficiency

Adrenocortical Insufficiency



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Acute Adrenocortical Insufficiency

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

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: autoimmune adrenalitis, tuberculosis,the acquired immune deficiency syndrome (AIDS), or metastatic cancer

Clinical features

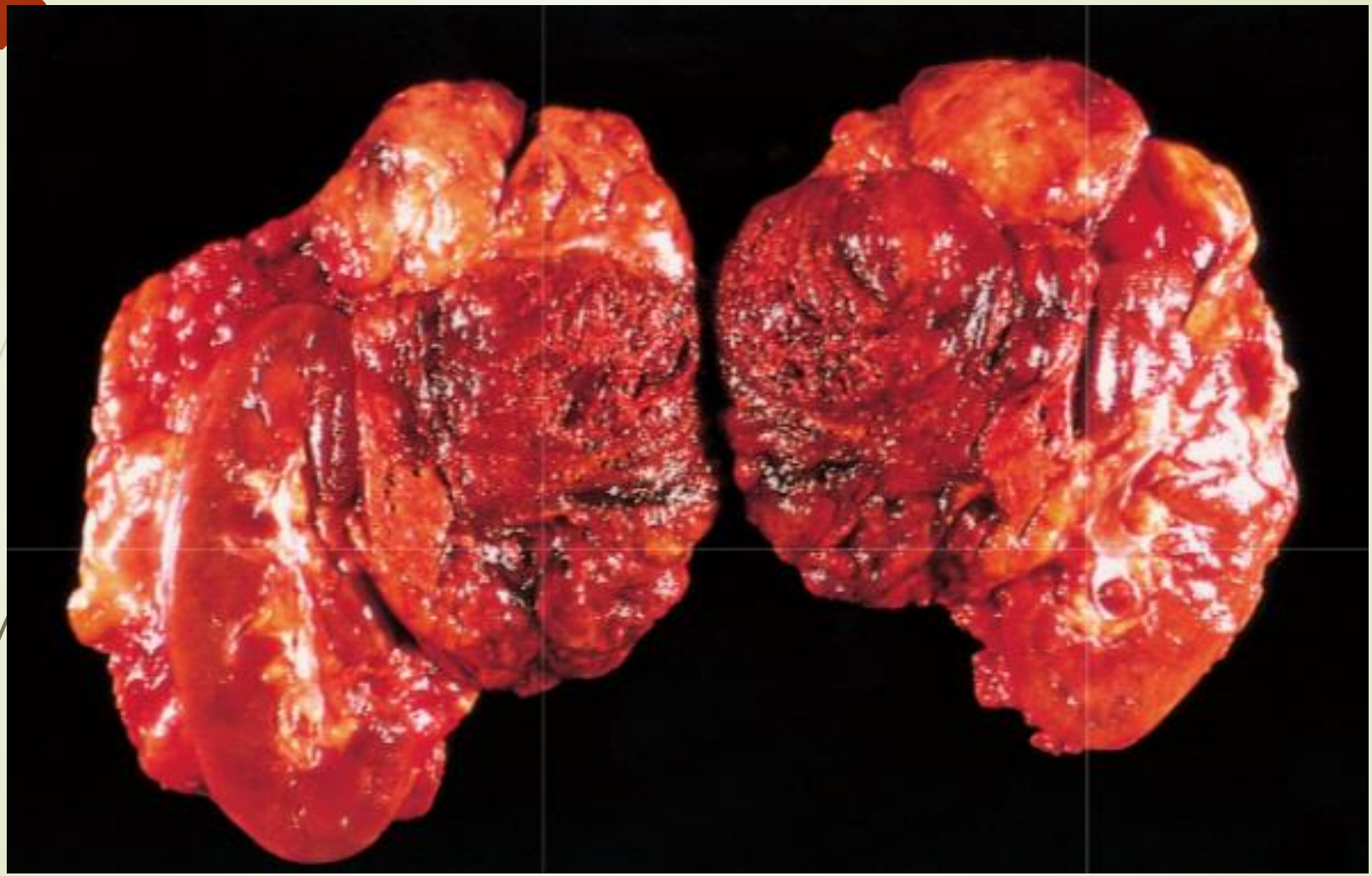
- ***Gastrointestinal disturbances*** **are common and include anorexia, nausea, vomiting, weight loss, and diarrhea.**
- **In patients with primary adrenal disease, increased levels of ACTH precursor hormone stimulate melanocytes, with resultant *hyperpigmentation* of the skin and mucosal surfaces.**
- **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.**

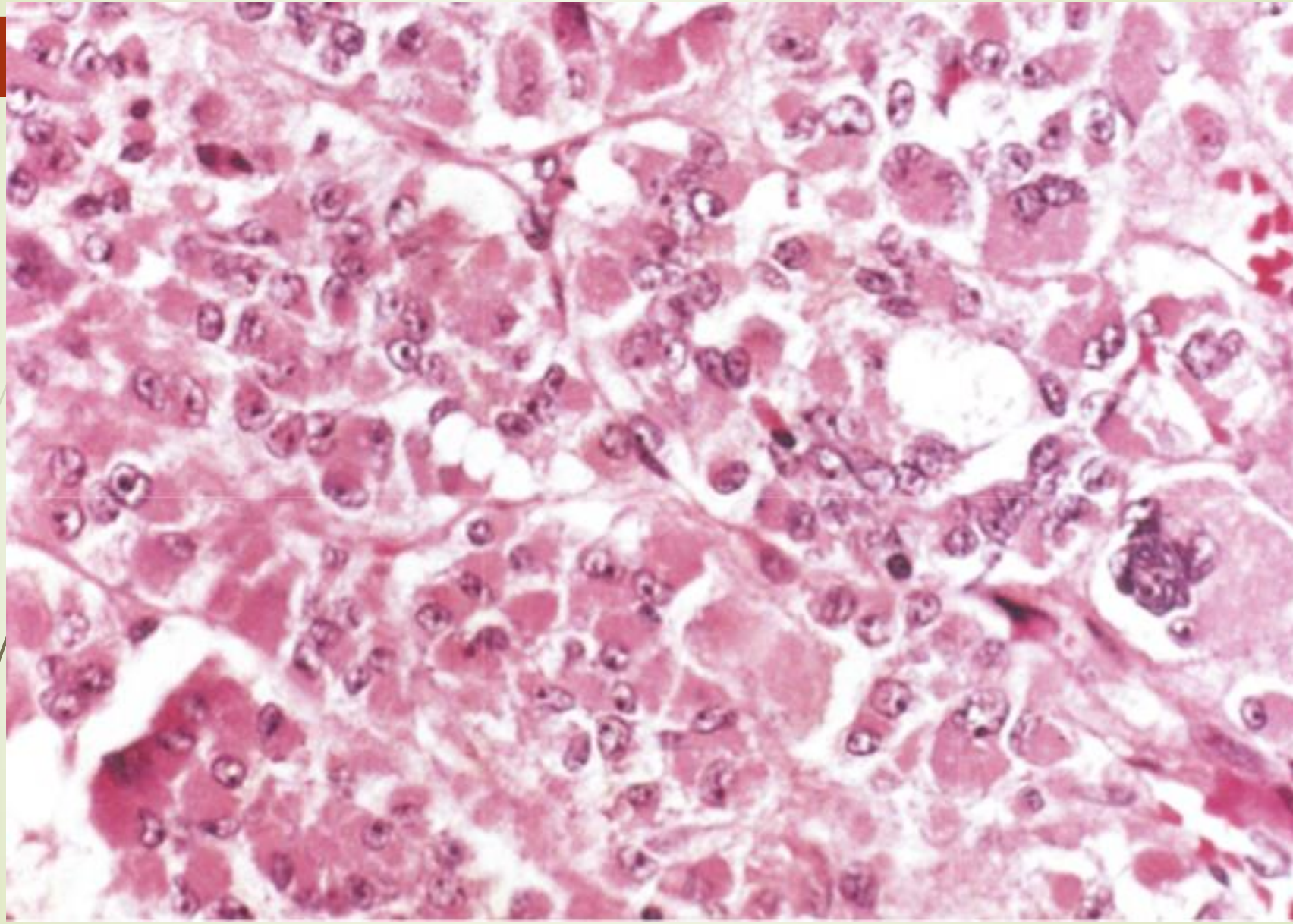
ADRENOCORTICAL NEOPLASMS

- 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** 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





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

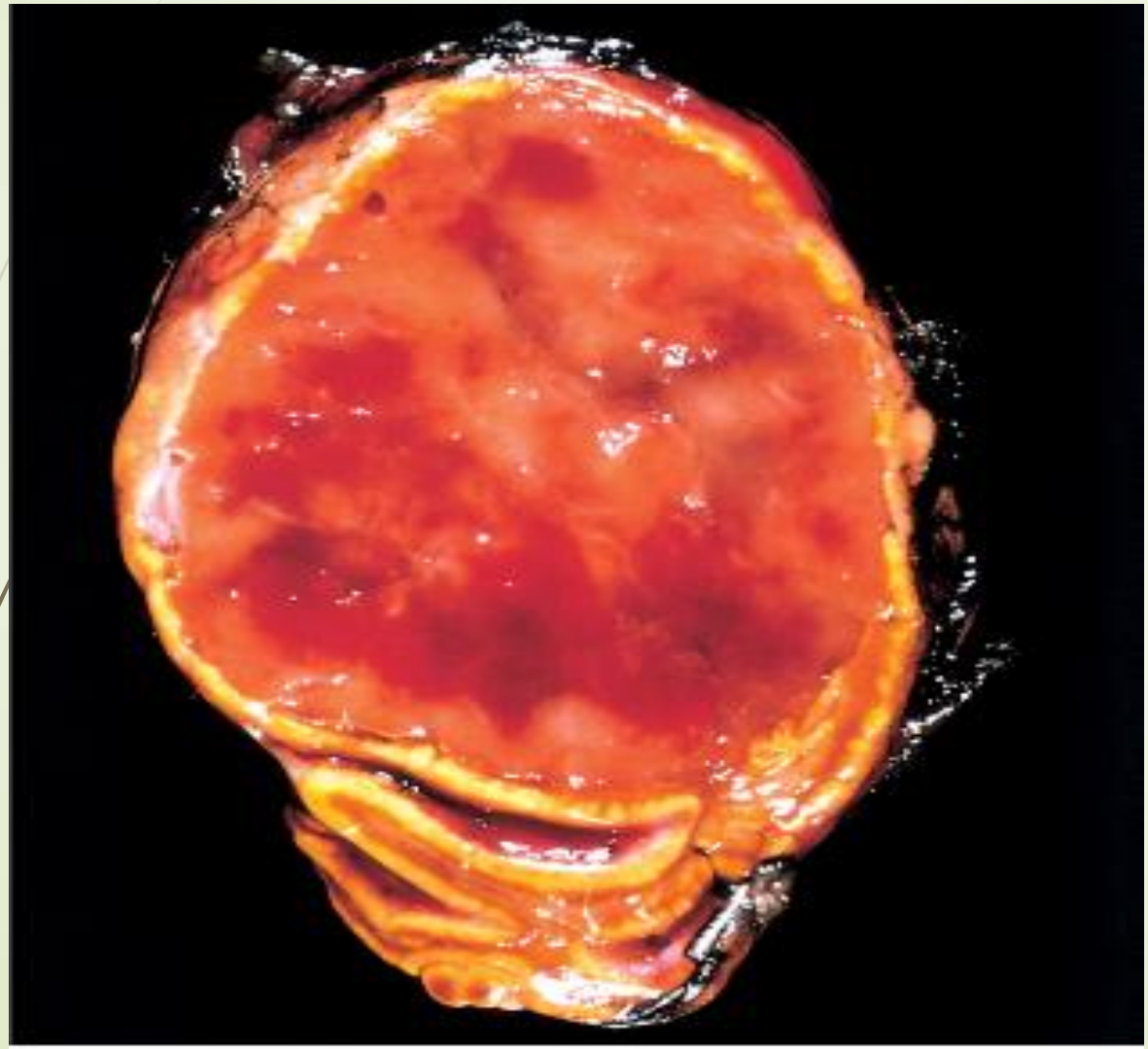
Pheochromocytoma Gross

- 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



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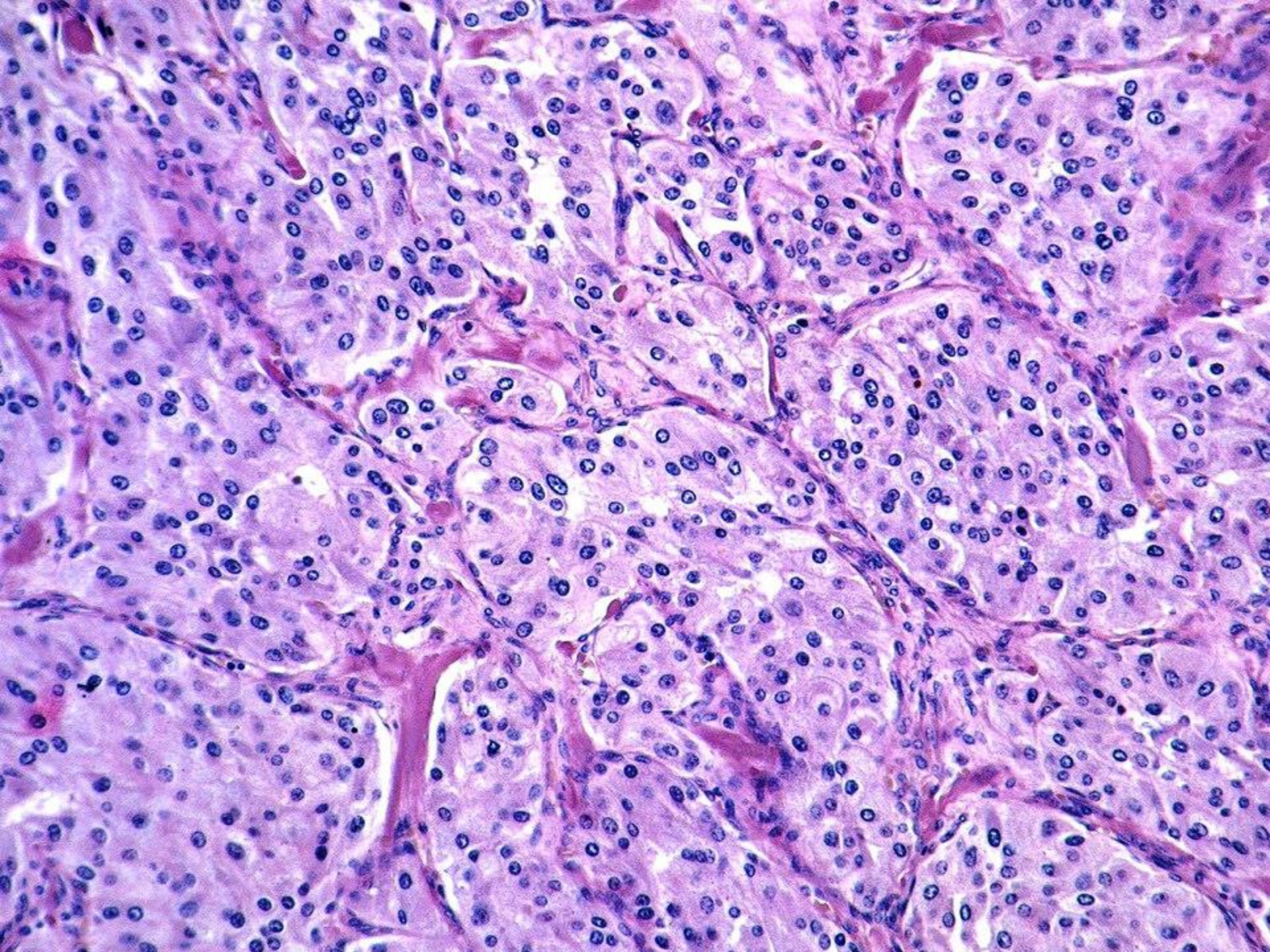

Clinical features

- 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