



University of Jordan - Faculty of Medicine
(2013-19)



Endocrine System

☐ Anatomy/Embryology/Histology

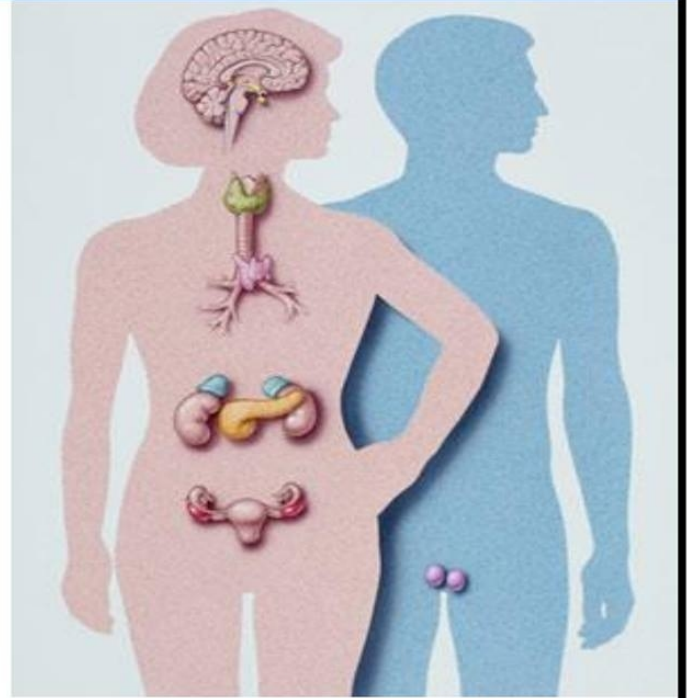
☐ Biochemistry

☐ Physiology

☐ Pharmacology

☒ Pathology

☐ PBL



Modified slides

☐ Slide

☐ Sheet

☐ Handout

☐ Other

Lecture #: **4**

Date:

Dr's Name: **Dr. Heyam**

Price:

Written by: **Aseil Khatib**

Designed by: Zakaria W. Shkoukani

Adrenal gland

Dr Heyam Awad

FRCPath

Slide notes

-A.K

As we all know the adrenal glands are made up of a cortex and a medulla

There are 3 zones in the cortex; Glomerulosa secreting aldosterone, Fasciculata secreting cortisol and reticularis secreting androgens

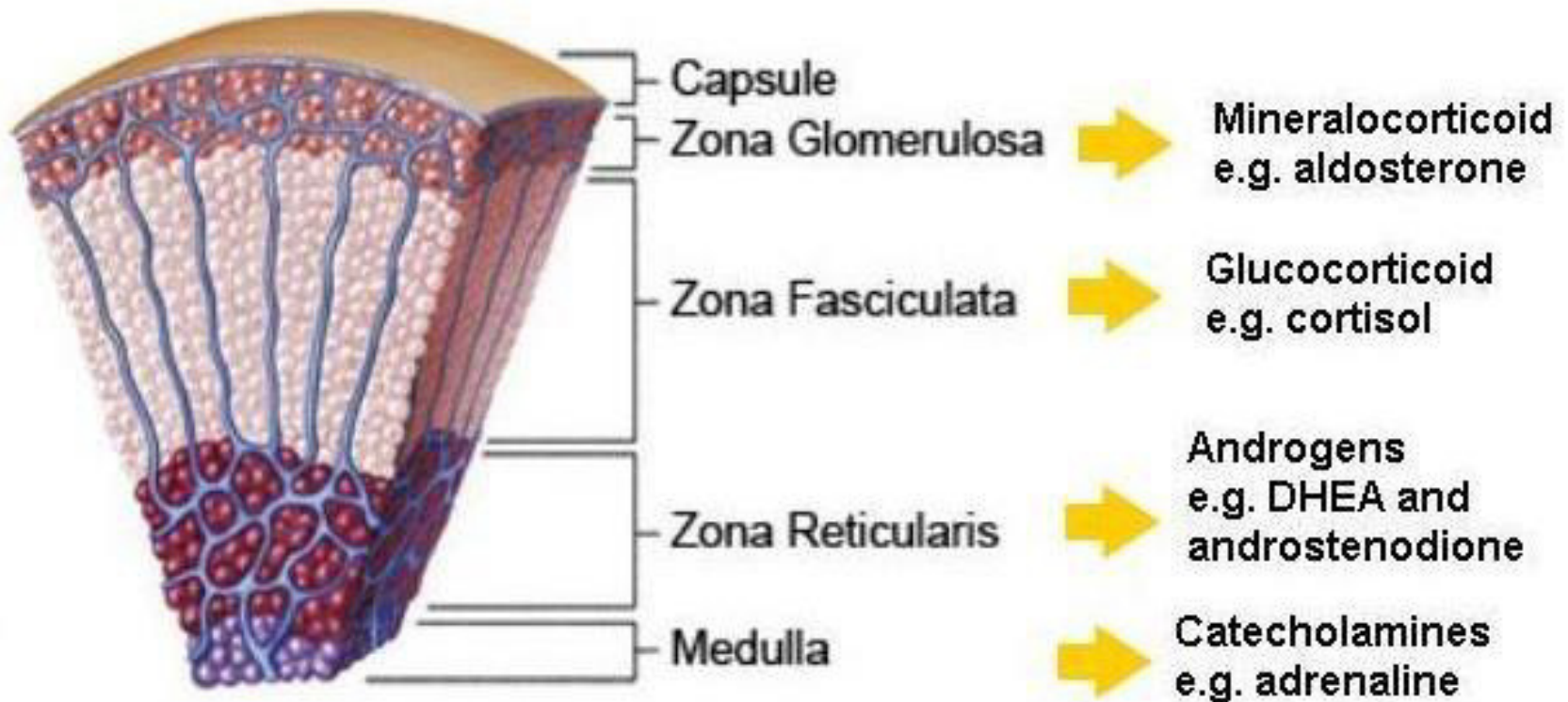
The medulla secretes catecholamines

To begin with, the diseases of the cortex could be related to:

- 1) Hypersecretion
- 2) Undersecretion
- 3) Mass effect

in the cortex the mass effect is not very prominent, usually it is from an incidental finding or from hormone-secreting pathologies

Adrenal gland



Adrenal cortex

- **Hyperadrenalism :**
 - *Hypercortisolism,
 - *hyperaldosteronism.
 - * adrenogenital syndromes (will not be discussed here)
- **Hypoadrenalism:**
 - *acute adrenal insufficiency
 - *chronic adrenal insufficiency (Addison disease)
 - *secondary adrenal insufficiency.
- **Masses = Neoplasms**
 - * adenoma
 - *carcinoma

Hypercortisolism (Cushing Syndrome)

- **Exogenous** glucocorticoids (iatrogenic) : **Most common cause.**

From administration of steroids as medication

- **Endogenous** causes

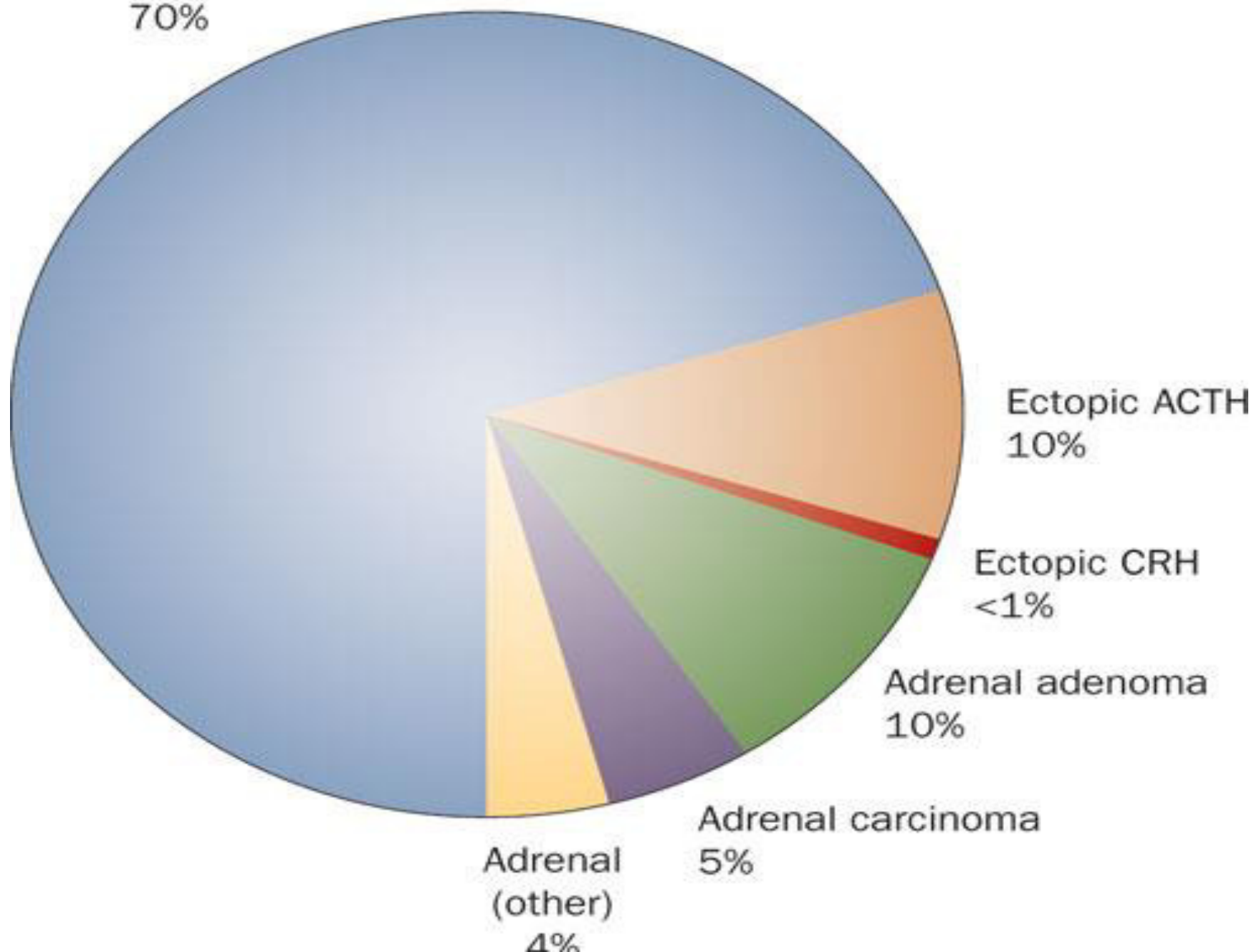
A. Primary hypothalamic-pituitary diseases ; hypersecretion of ACTH (Cushing disease)

When there is a disorder in the hypothalamus or pituitary making them secrete excess CRH or ACTH, this is referred to as Cushing DISEASE, while Cushing SYNDROME just means that there is excess cortisol in the body regardless of from where it came (exogenous or ectopic tissue etc...)

B. Primary adrenal hyperplasia and neoplasms

C. Secretion of ectopic ACTH by nonpituitary tumors

Cushing disease
70%



1)HYPOTHALAMIC- PITUITARY CAUSES CUSHING DISEASE

- 70% of cases of spontaneous, endogenous Cushing syndrome are due to Cushing disease.
- Occurs most frequently during young adulthood (the 20s and 30s)
- mainly affecting women.

CUSHING DISEASE

Causes?

majority: *pituitary gland contains an ACTH-producing
adenoma*

- In the remaining patients, the anterior pituitary contains areas of corticotroph cell hyperplasia which may be:
 - a. Primary
 - b. or, less commonly, secondary to CRH producing tumor

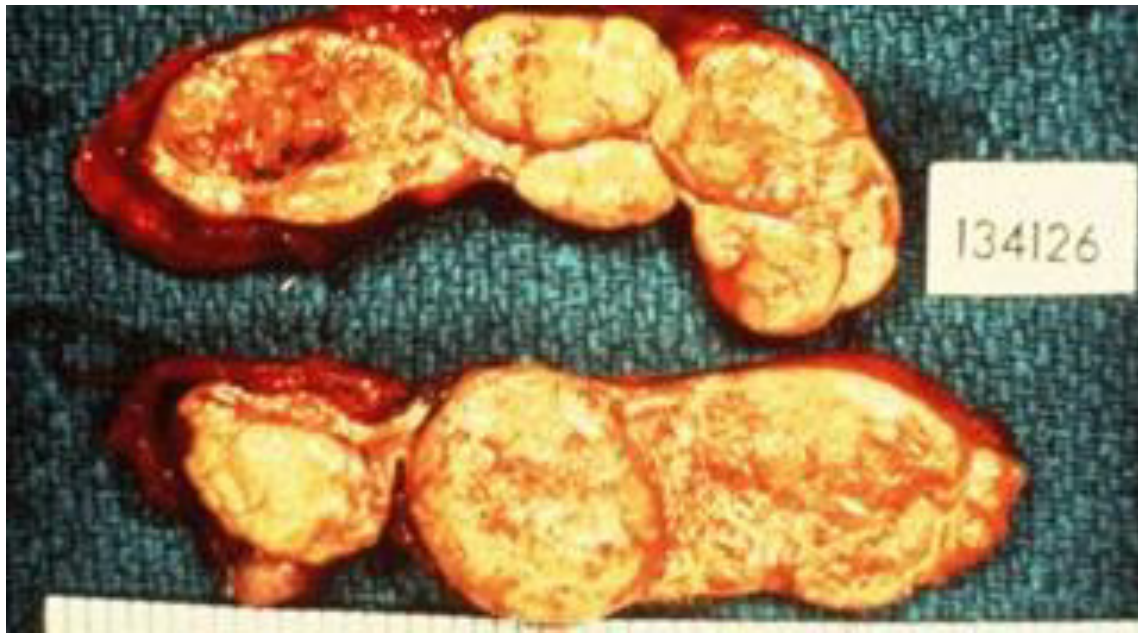
IMPORTANT NOTE: ACTH regulates cortisol and androgens, it does NOT affect aldosterone secretion in any way nor is it affected by it.

****extra note: the pituitary negative feedback for ACTH is from cortisol, androgens do not effect the release of ACTH but are affected by it**

MORPHOLOGY

The adrenal glands in Cushing disease show **bilateral nodular cortical hyperplasia** secondary to the elevated levels of ACTH ("ACTH-dependent" Cushing syndrome).

Nodular cortical hyperplasia



2)PRIMARY ADRENAL HYPERPLASIA AND NEOPLASMS

- 10% to 20% of cases of endogenous Cushing syndrome
- ACTH-independent Cushing syndrome, or adrenal Cushing syndrome ; low serum levels of ACTH
- Caused by adrenal adenoma or carcinoma.
- primary hyperplasia can cause it but is very rare.

ECTOPIC ACTH BY NONPITUITARY TUMORS

- mostly caused by *small cell carcinoma of the lung*,
- The adrenal glands undergo bilateral hyperplasia due to elevated ACTH.

****pay attention to each cause and whether the ACTH level is elevated or decreased**

Changes in adrenal in cases of Cushing syndrome:

- 1) **Cortical atrophy** : If the syndrome results from **exogenous** glucocorticoids, suppression of endogenous ACTH results in **bilateral cortical atrophy**.

what happens here exactly is that since you are administering cortisol the pituitary is being inhibited and being stopped from secreting ACTH (via negative feedback of cortisol), >> adrenal cortex not being stimulated >> atrophy

- The zona glomerulosa is of normal thickness because it functions independently of ACTH *remember aldosterone isn't regulated by ACTH*

- 2) **Diffuse and nodular hyperplasia**: Is found in 60% to 70% of Cases of **endogenous** Cushing syndrome.

- **Secondary hyperplasia** is found in patients with ACTH-dependent Cushing syndrome (due to Cushing disease or ectopic production of ACTH)

- **IMPORTANT NOTE:** when you are giving a patient cortisol as medication and you want to stop you need to taper the dose i.e stop it gradually, if you do it **SUDDENLY** the adrenals would become hypertrophic and that could be very dangerous to the patient and result in adrenal insufficiency (explained in next slides)

Primary adrenocortical neoplasms

- Are more common in women in their 30s to 50s.
- a. Adrenocortical adenomas: Are yellow **soft** tumors surrounded by thin capsules, and most weigh less than 30 g
- b. Carcinomas tend to be nonencapsulated masses , exceeding 200 to 300 g in weight

Recall that atypia is seen in both benign and malignant endocrine tumors

CLINICAL MANIFESTATIONS OF CUSHING SYNDROME

- a. Hypertension and weight gain
- b. truncal obesity, "moon facies," accumulation of fat in the posterior in **abdomen** , neck and back ("buffalo hump") .
- c. Glucocorticoids induce gluconeogenesis with resultant *hyperglycemia, glucosuria, and polydipsia >> diabetes*
- d. The catabolic effects on proteins cause loss of collagen and resorption of bone and bone resorption results in *osteoporosis and* susceptibility to fractures.
- e. The skin is thin, fragile, and easily bruised; cutaneous striae are particularly common in the abdominal area (**from loss of collagen**)
- f. Patients are at increased risk for a variety of infections.
- g. Hirsutism and menstrual abnormalities
- h. Mental disturbances ,mood swings, depression, psychosis

Clinical features

Cushing's Syndrome mnemonic: **CUSHING**

C – **C**entral obesity, **C**ollagen fiber weakness, **C**omedones (*acne*)

U – **U**rinary free cortisol and glucose increase

S – **S**triae, **S**uppressed immunity

H – **H**ypercortisolism, **H**ypertension, **H**yperglycemia, **H**ypercholesterolemia

I – **I**atrogenic (Increased administration of corticosteroids)

N – **N**oniatrogenic (**N**eoplasms)

G – **G**lucose intolerance, **G**rowth retardation



Moon face



Buffalo hump



buffalo



stria



HYPERALDOSTERONISM

Primary hyperaldosteronism:

- autonomous overproduction of aldosterone with secondary suppression of renin-angiotensin system and decreased plasma renin activity

problem in adrenals

Secondary hyperaldosteronism:

- Secondary to activation of renin-angiotensin system characterized by increased levels of plasma renin

Plasma level of renin determines whether the cause is primary or secondary

CAUSES OF SECONDARY HYPERALDOSTERONISM

- a. Decreased renal perfusion
- b. Arterial hypovolemia and edema e.g heart failure
- c. Pregnancy (caused by estrogen-induced increases in plasma renin substrate)

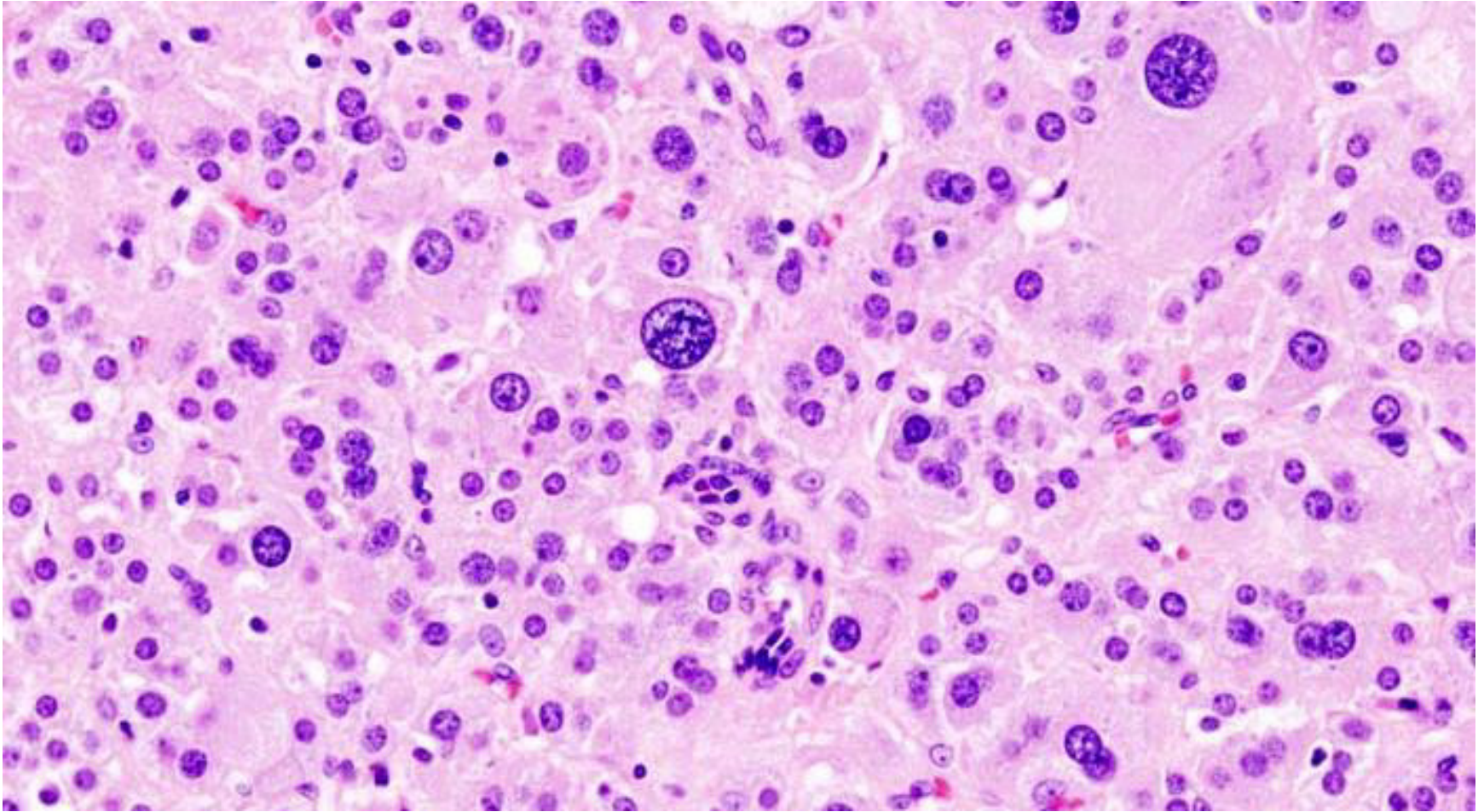
PRIMARY HYPERALDOSTERONISM

- a. Bilateral idiopathic hyperaldosteronism,
 - bilateral nodular hyperplasia of adrenals
 - **the most common** underlying cause (60% of cases)
- b. Adrenocortical neoplasm, adenoma (the most common cause) or, rarely, an adrenocortical carcinoma.
 - In approximately 35% of cases, the cause is a solitary aldosterone-secreting Aldosterone-producing adrenocortical adenoma referred to as Conn syndrome. **NORMAL ACTH LEVEL**
- c. Rarely, familial hyperaldosteronism may result from a genetic defect that leads to overactivity of the aldosterone synthase gene, CYP11B2 *which upregulates the enzymes of the aldosterone pathway*

Adrenocortical adenoma



Adrenocortical adenoma



Atypia of cells

CLINICAL FEATURES OF HYPERALDOSTERONISM

The clinical hallmark is hypertension

- Hyperaldosteronism may be the most common cause of secondary hypertension

Note: if a young person comes to you with hypertension then the cause is most probably secondary and can be from hypertaldosteronism but it is rare

- *Hypokalemia* results from renal potassium wasting and, can cause neuromuscular manifestations, including weakness, paresthesias,, and occasionally frank tetany.
- Parasthesia = abnormal sensation, typically tingling or pricking (“pins and needles”), caused chiefly by pressure on or damage to peripheral nerves.
- Tetany = intermittent muscular spasms.

ADRENAL INSUFFICIENCY

not enough hormones being produced by the
adrenals

Causes could be primary (acute or chronic) or secondary

Acute Adrenocortical Insufficiency :

causes

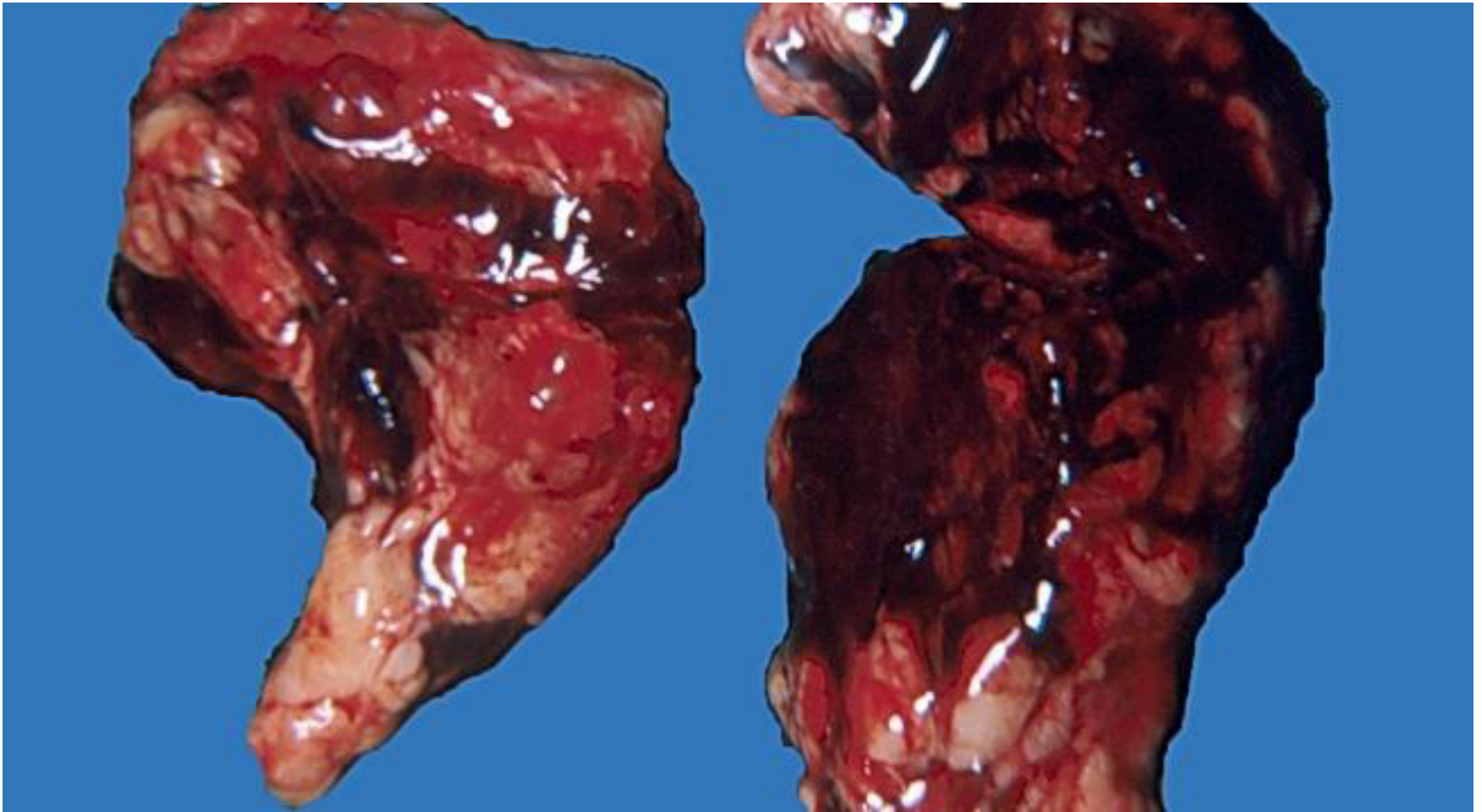
- a. Crisis in patients with chronic adrenocortical insufficiency precipitated by stress
- b. In patients maintained on exogenous corticosteroids .. Sudden withdrawal, or stress
- c. Massive adrenal hemorrhage. **Must lose at least 90% of gland's function**

Massive adrenal hemorrhage

may destroy enough of the adrenal cortex to cause acute adrenocortical insufficiency.

- This condition may occur :
 1. In patients maintained on anticoagulant therapy
 2. Patients suffering from sepsis : a condition known as the Waterhouse-Friderichsen syndrome
- Sepsis due to: *Neisseria meningitidis* (*most common cause*)
, *Pseudomonas* spp., , and *Haemophilus influenzae*
- *Underlying cause???* unclear but probably involves endotoxin-induced vascular injury .

Massive adrenal hemorrhage



primary chronic adrenocortical insufficiency (Addison disease):

-uncommon disorder resulting from **progressive destruction** of the adrenal cortex.

ALL adrenal hormones are affected (even aldosterone)

Causes:

- Autoimmune adrenalitis. **(Most common right now)**
- Infections **(before it was the most common, due to TB)**
- Metastatic tumors
- **Basically anything that destroys the gland**

ADDISON DISEASE

1. Autoimmune adrenalitis

- 60% to 70% of Addison disease cases and is the most common cause of primary adrenal insufficiency in developed countries.
- There is autoimmune destruction of steroid-producing cells, and **autoantibodies to several key steroidogenic enzymes** have been detected in affected patients

Addison disease

2. Infections,: Tuberculosis and Fungal infections

- Tuberculous adrenalitis, which once accounted for as many as 90% of cases of Addison disease, has become less common with the advent of anti-tuberculosis therapy
- Disseminated infections caused by *Histoplasma capsulatum* and *Coccidioides immitis* also may result in chronic adrenocortical insufficiency.
- Patients with AIDS are at risk for the development of adrenal insufficiency from several infectious (cytomegalovirus and TB) and noninfectious (Kaposi sarcoma) .

ADDISON DISEASE

3- *Metastatic neoplasms* involving the adrenals:

Carcinomas of the lung and breast are the most common primary sources.

Secondary adrenocortical insufficiency

Hypothalamic- pituitary diseases (aldosterone not affected *reminder*) including:

- Metastasis
- Infection.
- Infarction
- Irradiation
- Can be part of panhypopituitarism.
- Again basically anything that can destroy the hypothalamus or pituitary

Clinical features of adrenal insufficiency

- Clinical manifestations of adrenocortical insufficiency do not appear until at least **90%** of the adrenal cortex has been compromised.
- a. progressive weakness and easy fatigability, **the less hormones secreted the more weakness there is**
- b. *Gastrointestinal disturbances* are common and include anorexia, nausea, vomiting, weight loss, and diarrhea
- c. In patients with **primary adrenal disease**, increased levels of ACTH precursor hormone stimulate melanocytes, with resultant ***hyperpigmentation*** of the skin and mucosal surfaces: The face, axillae, nipples, areolae, and perineum are mainly affected

Note: hyperpigmentation is not seen in patients with secondary adrenocortical insufficiency.

So if the adrenals are damaged like in primary hypoadrenalism, no cortisol is negatively inhibiting the secretion of CRH and ACTH, therefore more ACTH is being produced, if you recall we have one long polypeptide chain precursor containing ACTH, MSH, and two unimportant thingies, if we keep producing ACTH, we will also be producing MSH which is responsible for the dark colour of the skin, that is why patients with Addison's disease are dark coloured and hyperpigmented in certain areas. For secondary hypoadrenalism the ACTH level is low so the synthesis of MSH is low too that's why we do not see hyperpigmentation there.

- d. Decreased aldosterone in **primary** hypoadrenalism results in potassium retention and sodium loss , with consequent - *hyperkalemia, hyponatremia, volume depletion, and hypotension,*
- In **secondary** hypoadrenalism is characterized by deficient cortisol and androgen output but normal or near-normal aldosterone synthesis. Why?
- I'm not gonna write why, you should be able to answer that by now :P

Adrenal medulla

- Chromaffin cells... derived from the neural crest.
- Secrete catecholamines.
- Most important disease: neoplasms.
- **ONLY PCC is going to be discussed here, it is a tumor that could be benign or malignant, the majority are benign 90%**

TUMORS OF THE ADRENAL MEDULLA

Pheochromocytoma

- give rise to a surgically correctable form of hypertension.
(since they secrete epinephrine and norepinephrine)
- Pheochromocytomas usually subscribe to "rule of 10s":
 - a. 10% of pheochromocytomas are extraadrenal, called paragangliomas, *i.e they occur in other tissues*
 - b. 10% of adrenal pheochromocytomas are bilateral; this proportion may rise to 50% in cases that are associated with familial syndromes.

To explain more about the previous point, if you find a tumor that is bilateral, i.e both glands are affected, and you want to determine the genetic cause, there is a 50% chance that this is a familial case. (for the 10% that is bilateral)

*If you notice there is a trend that familial cases are usually bi-lateral because what is the probability of both adrenals for example being hit with a mutation sporadically, but if you have a genetic mutation then wouldn't all your cells be at a higher risk of developing a tumor? **not the doctors words***

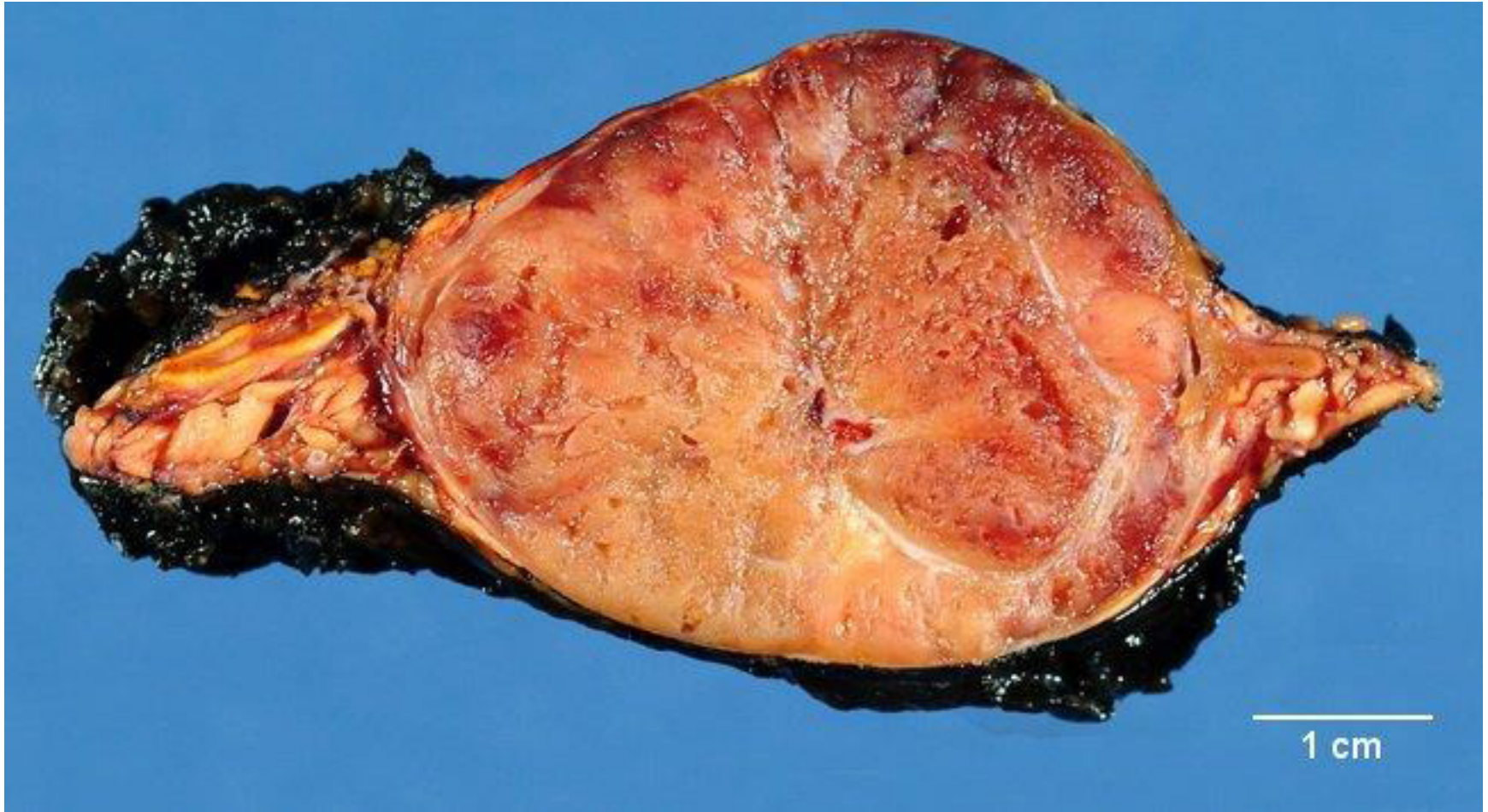
- c. 10% of adrenal pheochromocytomas are malignant,
 - Frank malignancy is somewhat more common in tumors arising in extraadrenal sites.
 - So if you have an extra-adrenal PCC it is more likely to be malignant

pheochromocytoma

Areas of hemorrhage

Tan-coloured

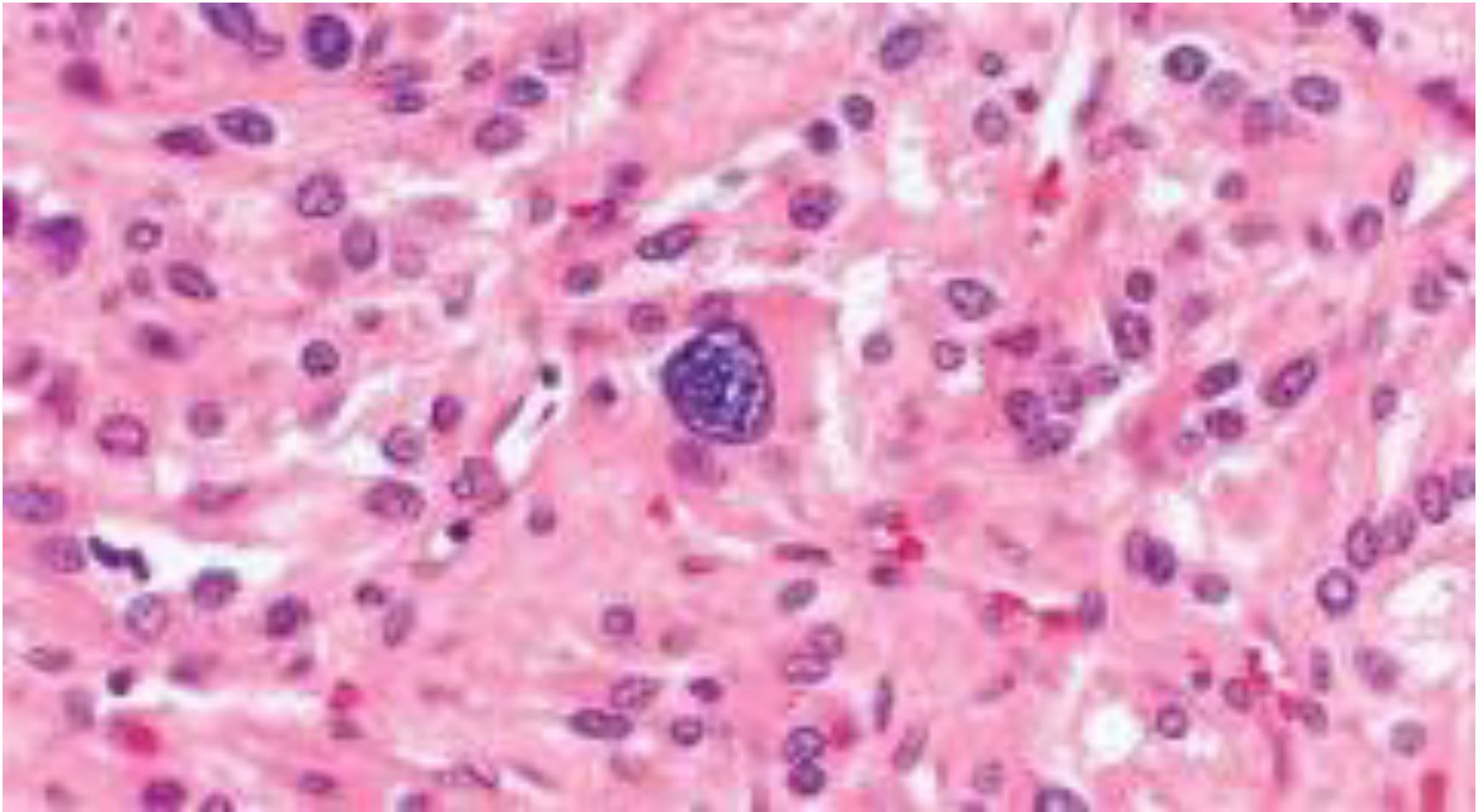
Bigger than cortical adenomas (usually)



On microscopic examination

- Are composed of polygonal to spindle-shaped chromaffin cells and their supporting cells, compartmentalized into small nests, or **Zellballen**, by a rich vascular network
- The cytoplasm has a finely granular appearance, because of the presence of granules containing catecholamines.
- The nuclei of the neoplastic cells are often pleomorphic
- **Anaplasia of cells (not necessarily a feature of malignancy)**
- ****PCC could secrete ectopic hormones**

pheochromocytoma



Pheochromocytoma..

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

Metastasis = malignant

- These may involve regional lymph nodes as well as more distant sites, including liver, lung, and bone. **(like most metastasizing tumors)**

Clinical Features

- The predominant clinical manifestation is *hypertension*
- Sudden cardiac death may occur, probably secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias.
- In some cases, pheochromocytomas secrete hormones such as ACTH and somatostatin.
- 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.