Adrenal Gland

With all courtesy to our colleagues, Raslan and his team,
a lot of our work is based on their Manual to Surgery Booklet.

Important

Mentioned by doctors but not in slides

Additional notes from Surgical Recall 6th edition or Raslan's booklet

Not mentioned by the doctor

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The blood supply of adrenals: (Anatomy)

- The superior suprarenal artery is provided by the inferior phrenic artery
- The middle suprarenal artery is provided by the abdominal aorta
- The inferior suprarenal artery is provided by the renal artery

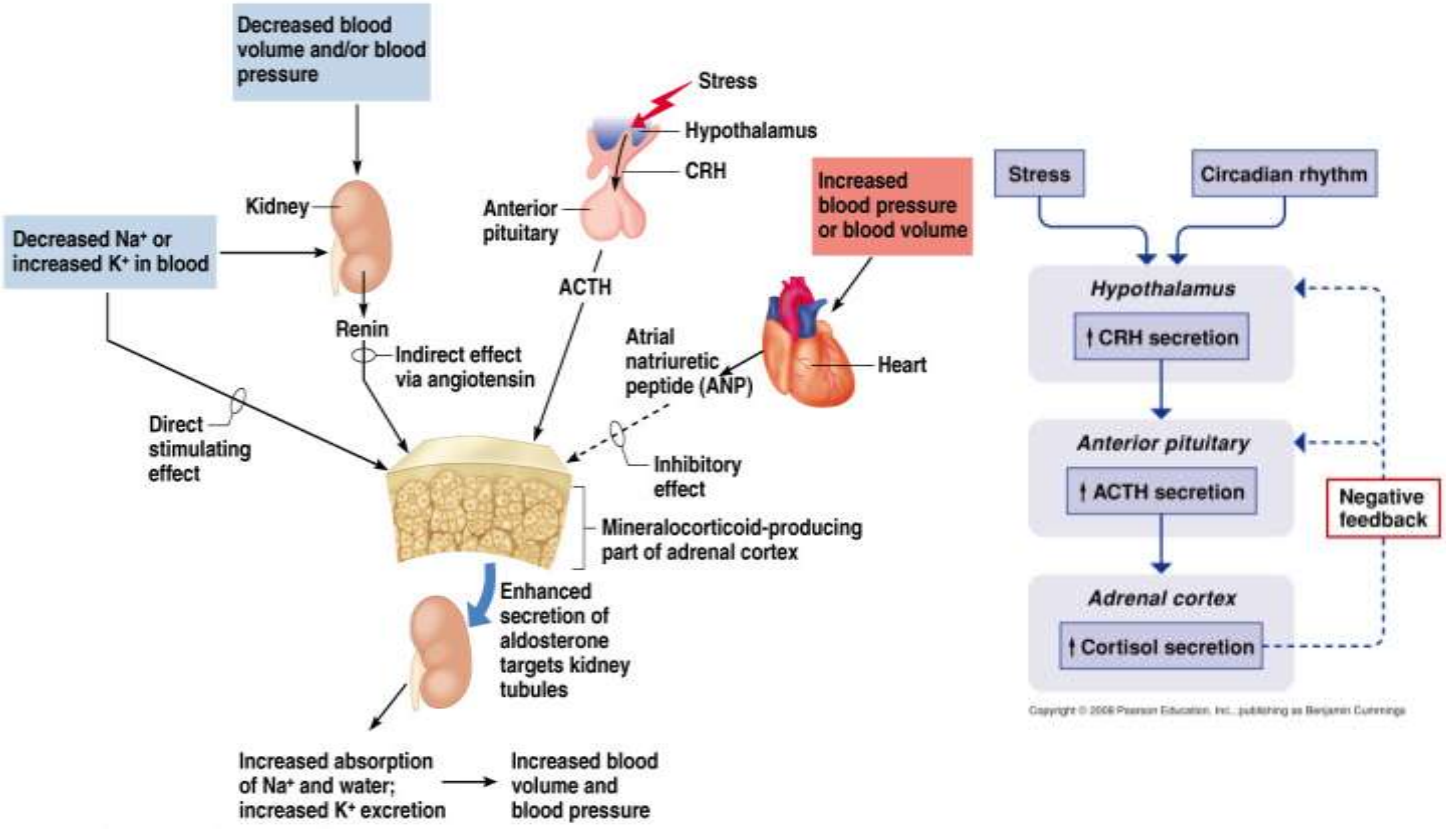
Adrenal gland is divided into two parts; each with separates functions:

A) Adrenal Cortex (3 parts)(Embryologic origin is coelomic epithelium)
Three specific zones and each produce a specific class of steroid hormone

1. Zonaglomerulosa – mineralocorticoids (**Aldosterone**)
2. Zonafasciculata – glucocorticoids (**Cortisole**)
3. Zonareticularis - androgens

B) Adrenal Medulla (1 part)(Embryologic origin is ectoderm; neural crest)
Epinephrine or Norepinephrine "catecholamine"

<u>Hormones of the adrenal cortex: (Physiology):</u>



You should know what is theSTIMULUSand what is theACTIONfrom the adrenals:
In zone 1:low sodium and high potassium in bloodis a direct stimulation to cortex to secrete aldosterone leading tohigh reabsorption of sodium and water as well as excretion of potassium.
Low blood pressure (hypotension)stimulates aldosterone secretion from cortex and indirectlyactivates the RAAS pathway leading to water retention.
So the blood pressure can be increased by two ways: one way by low sodium and high potassium, the other way when the blood pressure itself is low.
On the other hand, high blood pressure inhibits aldosterone secretion.

Q: if your serum sodium is low, what will happen to your aldosterone? Increase
Q: if your serum potassium is high, what will happen to your aldosterone? Increase

In zone2:

- Cortisol functions (It is like steroids):

- Decrease inflammatory and allergic responses
- Inhibit immune system; therefore patient is prone to infections
- Decrease wound healing.

- ACTH stimulates secretion of cortisol.
- ACTH is released from anterior pituitary orit could be ectopic EX: from small cell lung cancer
- Decrease levels of cortisol causes stimulation of ACTH secretion and vise versa

Circadian rhythm and cortisol:

Cortisol is an essential steroid hormone secreted by the adrenal gland and like many other physiological processes in the body has a circadian rhythm. This rhythm is distinct and is regulated by the main circadian oscillator (pacemaker) in the suprachiasmatic nucleus (SCN), which is located in the hypothalamus. Normal individuals, without disease of the hypothalamo—pituitary— adrenal (HPA) axis, at midnight, have very low or undetectable cortisol levels that build up overnight to peak first thing in the morning. Cortisol levels then decline slowly throughout the day

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475279/

In zone3: Androgen hormones, which increase male characteristics

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Most IMP thing to know in this lecture, if a certain hormone increases or decreases what happens in the body

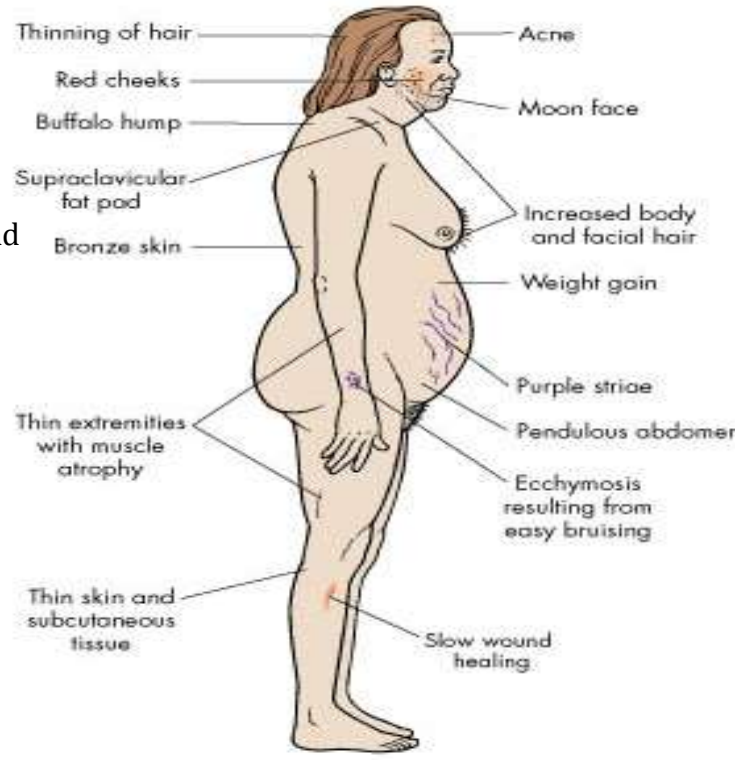
A) HYPER AND HYPOFUNCTION ADRENAL CORTEX HORMONES:

1) CUSHING'S (TOO MUCH CORTISOL!)

-High secretion of cortisol from adrenal cortex
- 4X more frequent in females
- Usually occurs at 35-50 years of age
-Death usually occurs from infection

- Etiology:

- Primary-tumor on the adrenal cortex
- Secondary-tumor on the anterior pituitary gland
- Ectopic ACTH secreting tumor (lung, pancreas)
- Iatrogenic-Steroid administration



- Signs and symptoms:

*Increase protein catabolism → muscle wasting, decrease strength,
loss of collagen support "thin, fragile skin, bruises easily", & poor wound healing.
*Increase CHO metabolism → hyperglycemia and insulin resistance →diabetes"polyuria"
*Increase in fat metabolism→truncal obesity, buffalo hump, moon face, weight gain
*Decrease immune response → more prone to infection, and decrease resistance to stress.
*Increase androgen secretion → excessive hair growth, acne, change in voice, and receding hairline
*Increase in mineralocorticoid activity → sodium and water retention "increase in blood pressure"

ACTH and hyperpigmentation: (Wikipedia)

Excess ACTH result in hyperpigmentation. This is due to Melanocyte-Stimulating Hormone production as a byproduct of ACTH synthesis from Pro-opiomelanocortin (POMC). A variant of Cushing's disease can be casused by ectopic, i.e. extra-pituitary, ACTH production from for example a small cell lung cancer. When Cushing's syndrome is caused by an increase of cortisol at the level of the adrenal glands (via an adenoma or hyperplasia), negative feedback ultimately reduces ACTH production in the pituitary. In these cases, ACTH levels remain low and no hyperpigmentation develops.

What is the difference between Cushing's syndrome and Cushing's disease? (Wikipedia)

Cushing's syndrome describes the signs and symptoms associated with prolonged exposure to inappropriately high levels of the hormone cortisol.

Cushing's disease is a cause of Cushing's syndrome characterized by increased secretion of ACTH from the anterior pituitary (secondary hypercortisolism). This is most often as a result of a pituitary adenoma. Or due to excess production of CRH from hypothalamus (tertiary hypercortisolism)

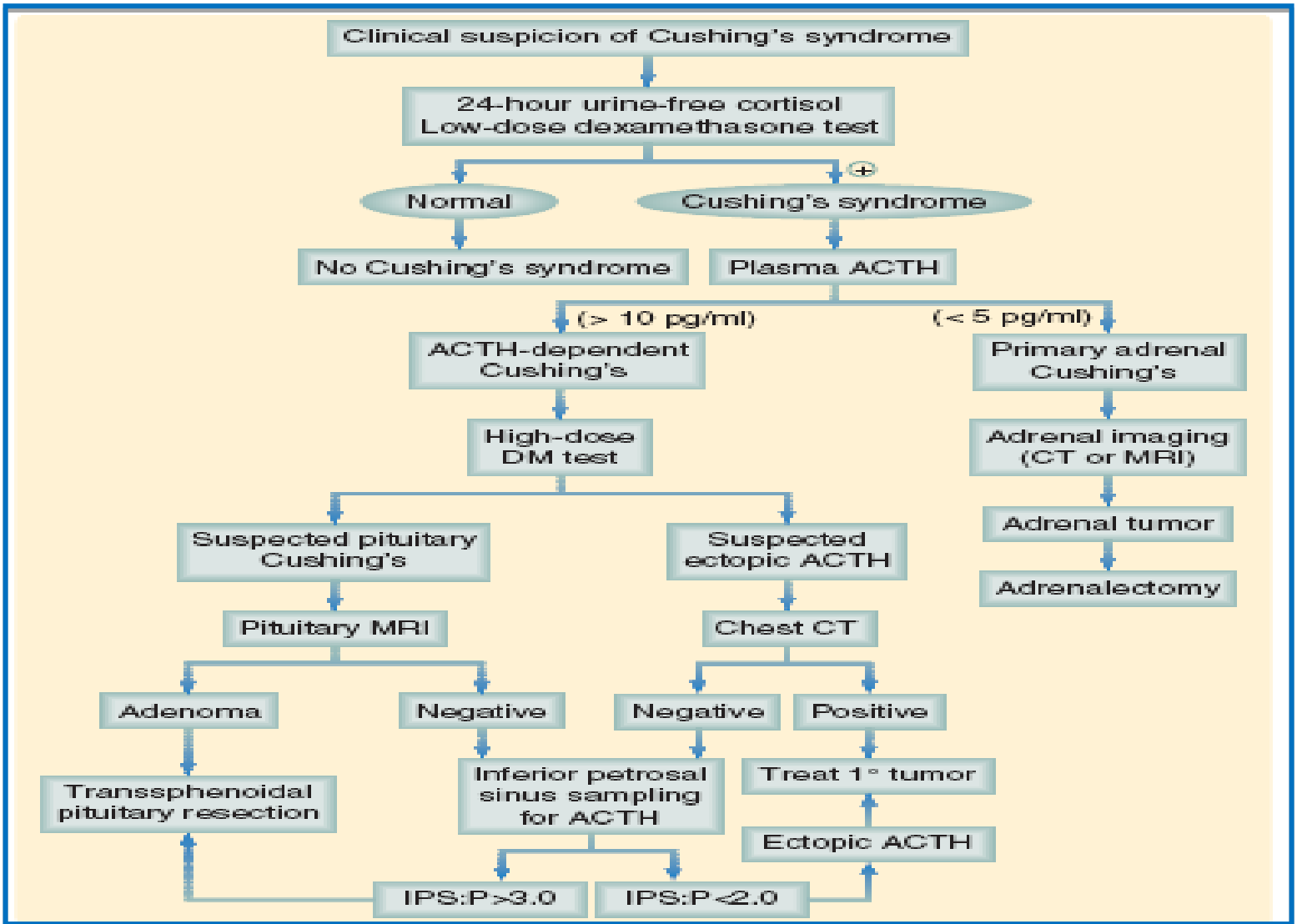
Dx Cushing's:

1ry:

STEP 1: High cortisol and Low ACTH , STEP 2: IMAGING

2ry:

STEP 1: H igh cortisol and High ACTH, STEP 2: IMAGING



- If we suspect Cushing first we do simple **low dose** (screening test) → suppression = normal patient
- If "+ve" (there is no suppression) = Cushing's
- Next step: ACTH dependent or not?
- In **high dose** test: if not suppressed it's either ectopic e.g. pulmonary carcinoma OR adrenal tumor (difference is in ACTH level: undetectable in adrenal & very high in ectopic), if pituitary it will be suppressed by high but not low dose dexamethasone

"All will be suppressed by high dose but there is a difference in the reading -so we do CT chest (for ectopic) & MRI for brain (Cushing' s disease) to confirm the diagnosis"

2) Conns syndrome (TOO MUCH ALDOSTERONE!)

- Main thing it will lead to uncontrolled high blood pressure
- Usually caused by adrenal tumor
- Signs and symptoms

*Sodium and water retention"Hypertension"
*Hypokalemia
*Usually no edema
* Metabolic alkalosis

- Investigations:

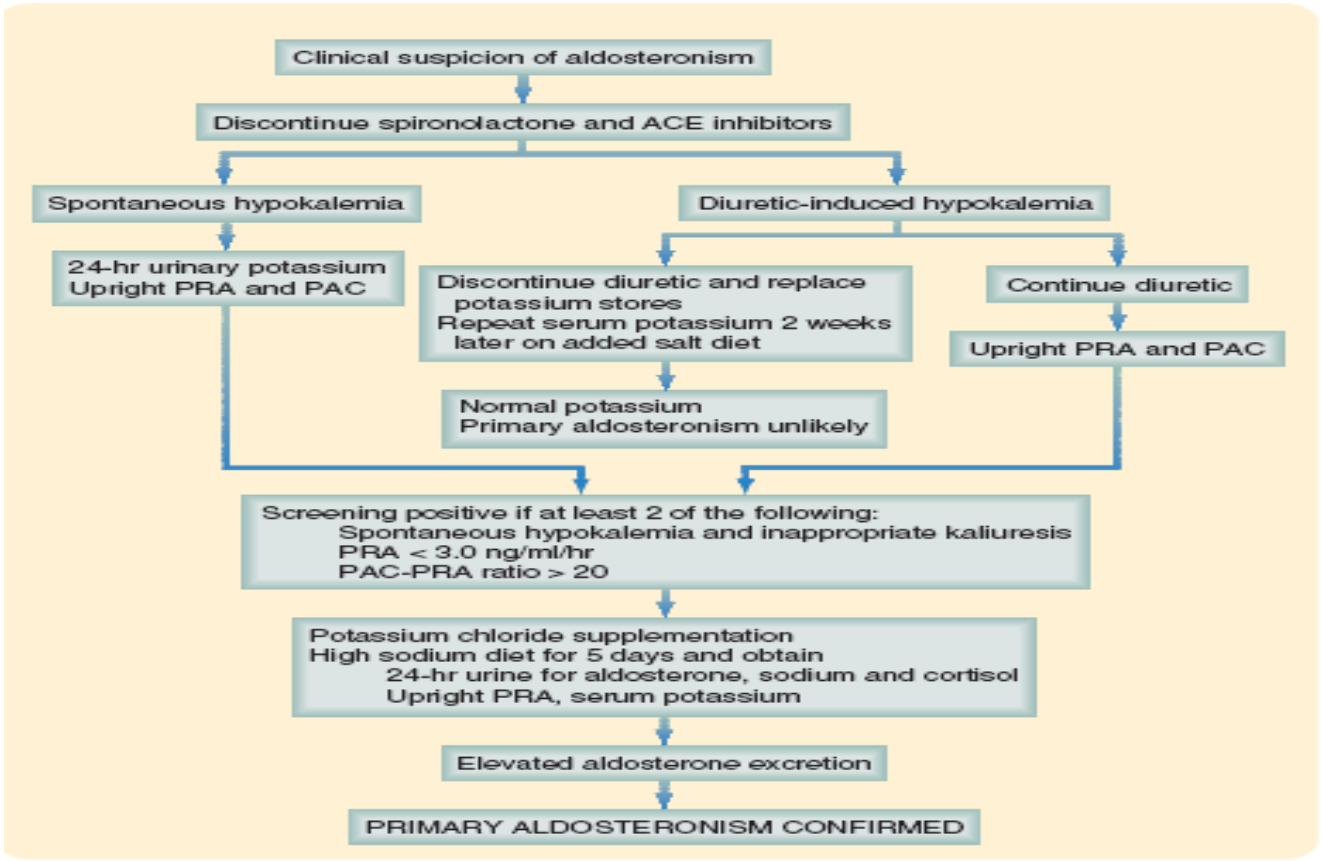
*High urinary potassium
*High plasma aldosterone levels with low plasma renin levels
*CT scan → to see if there is adrenal tumor
*EKG changes → because of the potassium changes

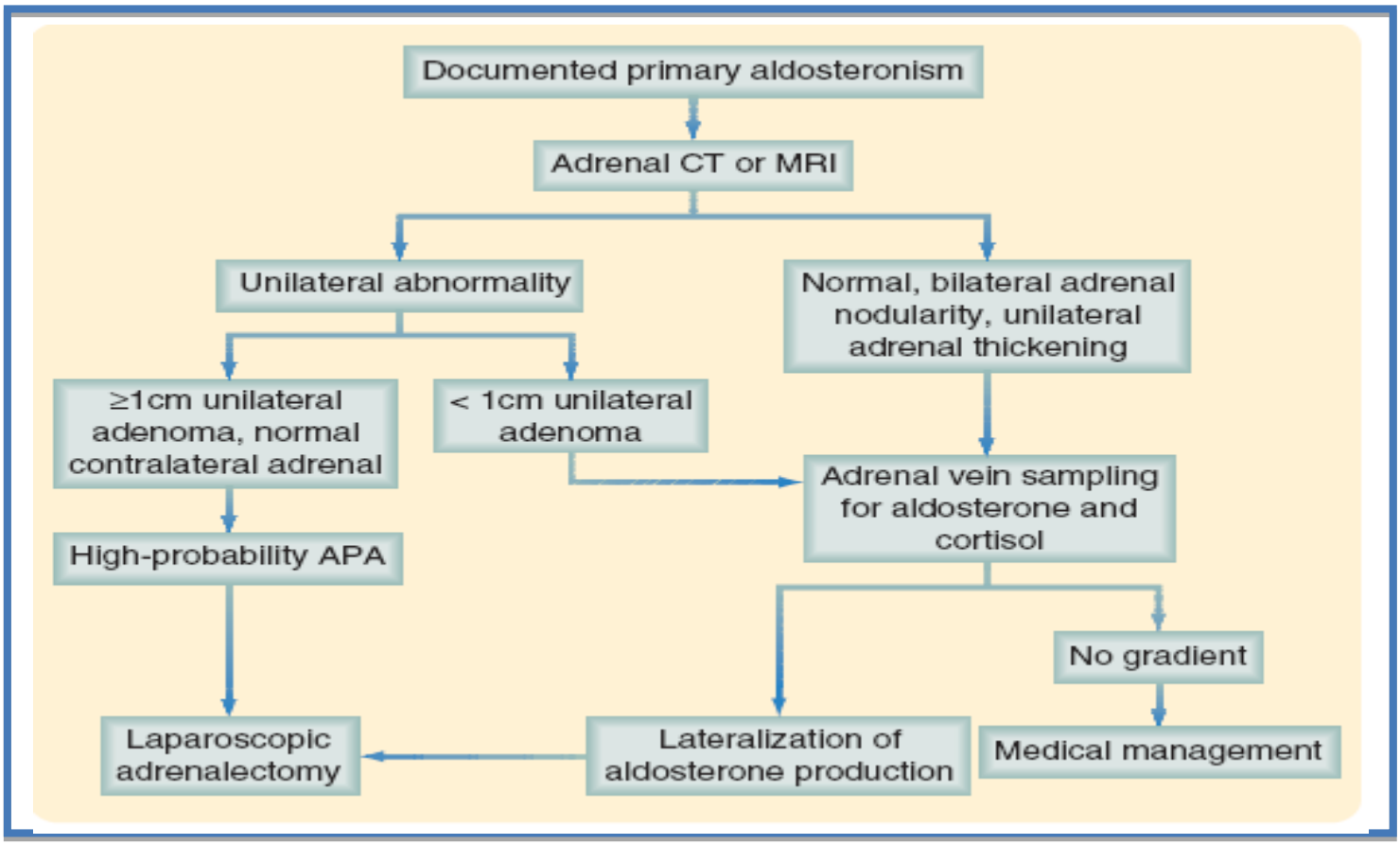
- Management: (Adrenalectomy)

Pre-operative → Stabilize hormonally, correct fluid and electrolytes(by sprinolactone), and give cortisol night before surgery, morning of surgery, and during OR.
Post-operative → give IV cortisol for 24 hours, then IM cortisol in 2nd day, then PO cortisol in 3rd day. Remember to examine the wound because of poor wound healing caused by cortisol.

How to differentiate between primary and secondary Hyperaldosteronism
In normal patient: Low sodium → stimulates renin secretion →, which stimulate aldosterone
Inprimary hyperaldosteronism: adrenals produce high levels of aldosterone →renin is suppressed
Insecondary hyperaldosteronism(Ex: renal artery stenosis):High levels of reninare produced → leading tohigh secretion of aldosterone

Therefore, the aldosterone-to-renin ratio (ARR) is the most sensitive means of differentiating primary from secondary causes of hyperaldosteronism.





3) Addisons Disease (ADRENAL INSUFFICIENCY!)

Think☺

ADDison's Disease:
Adrenal **D**own

-Etiology:

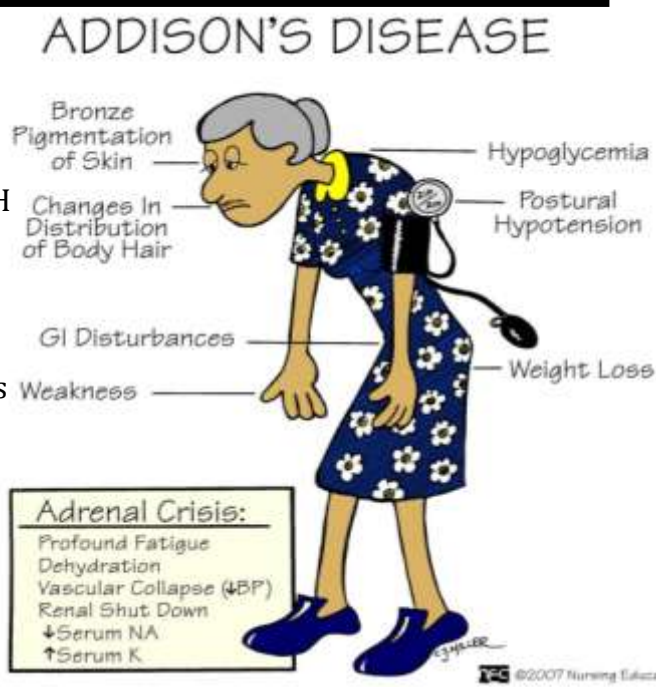
*idiopathic atrophy →An autoimmune condition where antibodies attack adrenal cortex
*TB/fungal/ infections
*Iatrogenic →adrenalectomy, chemo, anticoagulants

Waterhouse–Friderichsen syndrome = hemorrhagic adrenalitis = Fulminant meningococcemia: (Wikipedia)

is defined as adrenal gland failure due to bleeding into the adrenal glands, caused by severe bacterial infection (most commonly the meningococcus Neisseria meningitidis). The bacterial infection leads to massive hemorrhage into one or (usually) both adrenal glands It is characterized by overwhelming bacterial infection meningococcemia leading to massive blood invasion, organ failure, coma, low blood pressure and shock, disseminated intravascular coagulation (DIC) with widespread purpura, rapidly developing adrenocortical insufficiency and death.

-Signs and symptoms:

*Fatigue, weight loss, anorexia
*Changes in skin pigment (Black freckles)→ due to high ACTH
*Muscular weakness
*Fluid and electrolyte imbalance → Low blood pressure, hyponatremia, and hyperkalemia.
*Hypoglycemia
*Decreased androgens →hairloss, and loss of sexual functions
*Menstrual disturbances
*Anxietu and irritability
*Salt craving → due to the urinary losses of sodium.



- Investigations:
Low serum cortisol, hyperkalemia, hyponatremia, hypoglycemia,
Low urinary 17-OHCS and 17 KS

17-OHCS and 17 KS
The 17-OHCS is an inactive product in the liver (17-hydroxycorticosteroid). It is produced when the liver breaks down cortisol.
17-KS (ketosteroids) are substances that form when the body breaks down androgens and other hormones released by the adrenal glands in males and females and in the testes in males

- Manaement: Life long Hormone replacement(No need to know the names)+ also patient must always keep parenteral glucocorticoids with him for injection during illness and stress.
Scenario: a patient is a known case of Addison's disease presented with hernia. The surgeon took him to the OR for hernia repair and the patient had adrenal crisis. Why? Patient should've been prepared and got steroids.

-Complications: Adrenal crisis, electrolyte imbalance, and hypoglycemia.

Do not confuse acute adrenal crisis with Addison disease !!
Addison is a syndrome of long-term adrenal insufficiency that develops over months to years, with weakness, fatigue, anorexia, weight loss, and hyperpigmentation as the primary symptoms. In contrast, an acute adrenal crisis can manifest with vomiting, abdominal pain, and hypovolemic shock

B) ADRENAL MEDULLA HORMONES:

4) Pheochromocytoma (TOO MUCH CATECHOLAMINES!):

- Rare, benign tumor of the adrenal medulla

- Signs and symptoms:
*Hallmark is Hypertension 200/150 or greater "Severe HTN" →Not responding to treatment(+/- Paroxysms)
*Headache
*Pounding heart, palpitations
*Deep breathing,
* Moist cool hands and feet "sweating"
*Visual disturbances → multifactorial, you can't say this is due to adrenals

-Investigations:
-Serum Metanephrine→which is catecholamine that result when adrenaline breaks down.
-24 hour urine-VMA (metabolite of epinephrine)
(IMPORTANT SITE OF MCQ *Raslan*)
-Plasma catecholamine
-CT to locate tumor. →Is the mass in cortex or medulla - Size of the tumor – homogenous or heterogeneous – lymph node involvement?→if these are not clear, perform MRI

Diagnostic Clues

Six "H's"
Hypertension
Headache - throbbing (90%)
Hyperhidrosis or excessive sweating (69%)
Heart consciousness or Palpitations (73%)
Hypermetabolism
Hyperglycemia

Rule of 10
Familial (10%)
Malignant (10%)
Multiple or Bilateral (10%)
Extra-adrenal (10%most common in abdomen)
Childhood onset (10%)
Recurrence after Surgery (10%)

Most IMP thing in investigations is SERUM METANEPHRINE. It has 97% sensitivity. If it is negative, then there is no pheochromocytoma. Doctor said: Most of the time we give scenarios of adrenals and we ask what is the next step to do?
A) Urine metanephrine
B) Serum metanephrine→ Correct answer
C) 24 HRS cortisol

Management:

1) Consult endocrinologists
2) 3 weeks before surgery start a-blockers
3) Admit patient 3 days before surgery → rehydrate the patient and start B-blockers to control heart rate
4) ALL pheochromocytomas**should be removed surgically** unless: meatastatic disease or inadequate medical preparations with a-blockers prior to surgery.
5) "When there is a patient with pheochromocytoma in the ward everyone is ready; the physician, surgeon, anesthetist and ICU physician- to arrange an ICU bed, administer α- & β-blockers, and prepare the OR. Why? B/c they might lose him if BP shoots up >bleeding > death."

If the patient is**SYMPTOMATIC(Functioning)**regardless whether the tumor is benign or malignant, **WE REMOVE THE TUMOR(unless it is bilateral or the patient is unfit)**

The surgeon decide to perform laparoscopy or open surgery based on
A) The size of the tumor & B) the suspicion of cancer

Perform open surgery if you think it is cancer or size is more than 4 CM

You must follow up patients: because if the mass is increasing in size, this is more likely to be cancer
Guidelines: If the mass increases by 1 CM within 6 months,surgery is indicated

EX: patient came to you with an adrenal mass of 2CM, and you follow her up after 6 months and you see that the mass is 3.5CM now →remove the tumor

*Intraoperative: monitor BP:
if patient develops hypertensive crisis→ control with Na nitrogloside
if patient develops hypotension → control with fluids and Phenylephrine

To avoid hypertensive crisis, it is IMP to ligate the vein first then the artery so the catecholamines will not be released into circulation

Adrenal Incidentaloma:
Adrenal masses are often discovered incidentally and are then termed adrenal incidentalomas (AIs). They are often discovered after an imaging procedure is performed that is unrelated to the adrenal gland. Usually, the patient has no signs of hormonal excess or obvious underlying malignancy.

Ex: a patient came to you referred from Gyne because of an incidental finding of an adrenal mass during US for the uterus.
You should take detailed history and do physical examination to make sure this is not a functional tumor. Also ask about previous history of tumors and cancer to see whether it is a metastasis from other site or not…etc
When facing **ANY incidentaloma** you have to **RULE OUT Pheochromocytoma first**!
The most IMP questions to answer for any adrenal mass are:

1- Is it malignant or benign
2- Is it primary or secondary "metastasis"
3- Is it functional or not

The doctor said: WHAT YOU SHOULD KNOW FROM THIS LECTURE IS:
1) Hormones comes from which part of the adrenals
2) If there is a disturbance of that hormone, this will cause what, which disease or which syndrome?
3) most IMP is the pheochromocytoma:
A-you should know the diagnosis, if someone is known to have pheochromocytoma what you should do, how do you prepare the patient for surgery, which investigation I should ask for, and which treatment I should give the patient.
B- If the patient has adrenal mass sent from other doctors, how I should act?
C- management is based on what?

The following was NOT given by the doctor but it was discussed last year so we are quoting from Raslan's Notes:

ADRENAL IMAGING

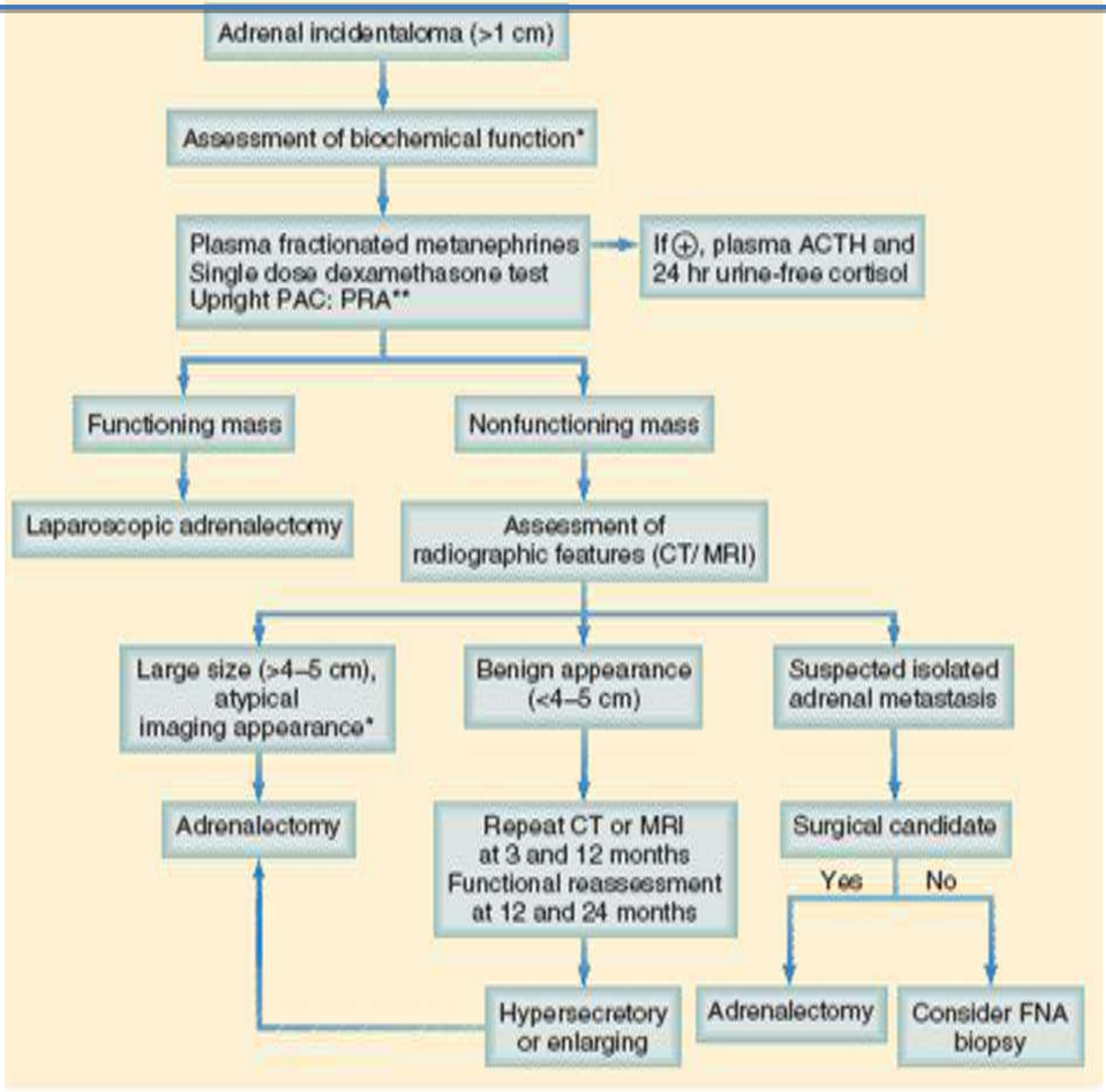
- **CT scan: (Gold standard)**(but biopsy gives the definitive Dx)

to differentiate between benign and malignant

- Benign
  - Intensity, texture similar to liver
  - Low attenuation
  - Homogeneous (one color, there is no hypo & hyper density at the same time)
  - Smooth border
  - Smooth contour
  - < 4 cm in greatest dimension (**the first criteria to be checked** and then the others, size should be less than 4)
- Malignant lesions:
  - High attenuation (>30 HU) [hyper-vascular – more white]
  - Heterogeneous
  - Irregular borders
  - Local/ vascular invasion
  - Lymphadenopathy
  - Metastases.
  - Large size (>6cm)) (black size 6cm-12cm →malignant .. remove it black size 2cm - 4cm → cyst)

- **MRI.** (CT still gold standard but if MRI is available, it'll give a better picture)
- **Nuclear scan.** (If you suspect pheochromocytoma - to look at the function of the mass > see uptake of gland)
- **PET scan.** (If you are looking for cancer > hot spots)

Approach to Adrenal Incidentaloma:

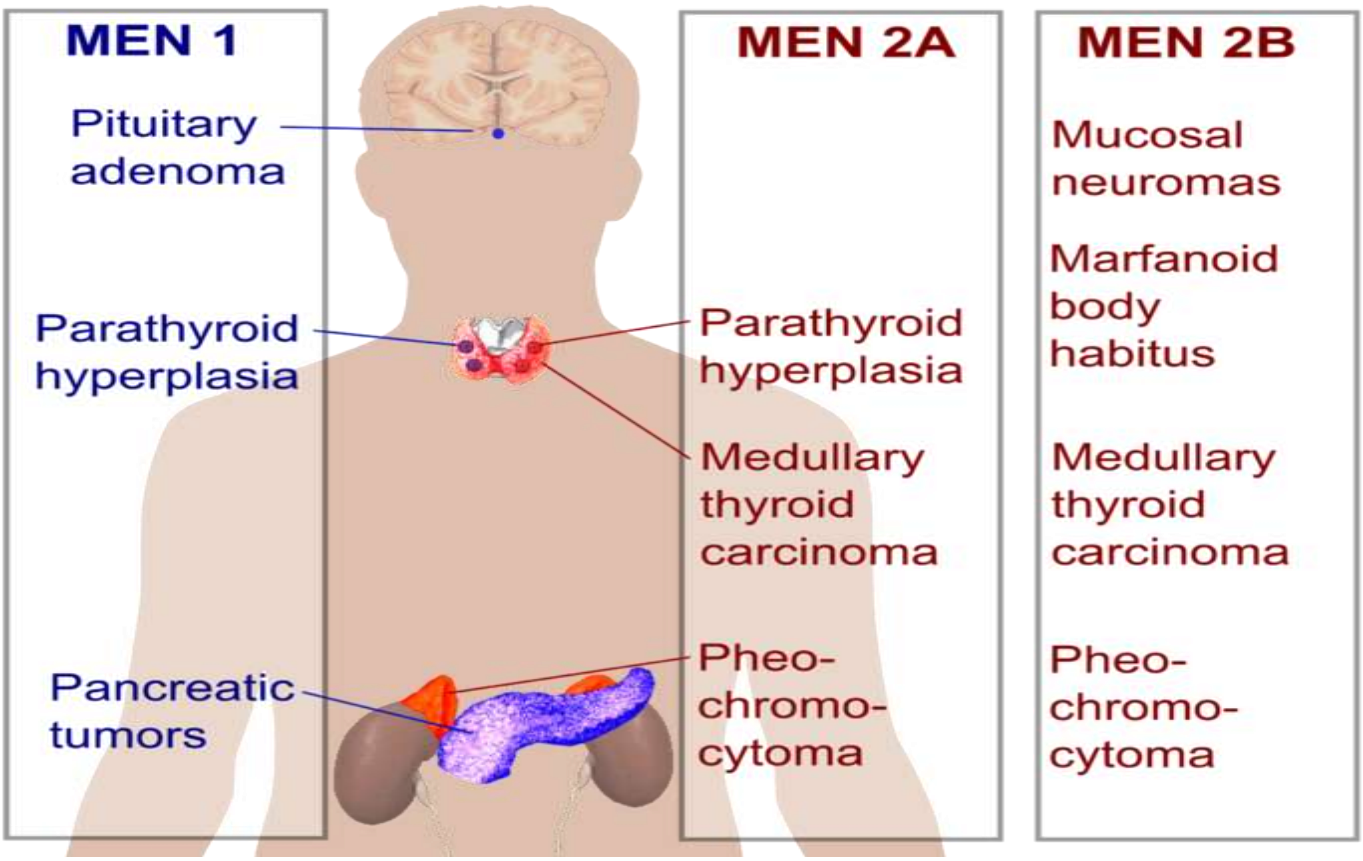


PAC: Plasma aldosterone concentration
PRA: Plasma renin activity
PAC: PRA for Conn's. Metanephrine: look for pheochromocytoma. Single dose dexamethasone: for Cushing's.

- **If functioning mass → Surgery.**
- **If non-functioning mass → CT scan**
- **CT may show:**
- **Benign appearance (< 4 cm) you repeat the scan after 3-12 months.**
- **If it secretes or has a malignant appearance we perform surgery.**
- **Handled based on the Size and function.**

Associated with familial syndromes, such as:

- Multiple endocrine neoplasia type2 (MEN2A) 40%
- MEN 2B
- Recklinghausen disease
- VonHippel-Lindau disease



Summary

	What ?	Signs and symptoms	Diagnosis	Treatment
CUSHING'S Syndrome	**TOO MUCH CORTISOL**	TOO MUCH CORTISOL, so ?	- Dexamethasone Tests(low and high doses) - 24h urine free cortisol - CRH stimulation test - Imaging Tests	**Depends on the cause :** -iatrogenic: stop the medication - pituitary adenoma : surgery -adrenal tumors : Adrenalectomy
Conn's Syndrome	Hyperaldosteronism	Increase in Aldosterone means ?	- Increase K+ in urine - Measure Aldosterone/rennin ration - ECG - Imaging Test	Surgery , (but don't forget the management before ,in and after the surgery)
Addison's disease	Hypofunction of the Adrenal gland	All the hormones are decreased , so ?	- Decreased in Adrenal hormones - Hyperkaemia - Hyponatremia - Hypoglycemia - ACTH level to differentiate between primary and secondary causes.	Lifelong hormonal replacement therapy .
Pheochromocytoma	Increase in the Catecholamines due to tumor in Adrenal Medulla	Six "H's"	- Serum metanephrines - Urine VMA - Serum/urine Catecholamines - Imaging Test	Surgery

TEST YOUR KNOWLEDGE!

1- Which one of the following is a direct stimulus of the Aldosterone secretion :

A. High potassium and low sodium
B. high sodium and Low potassium
C. low blood pressure
D. All of the above

2- to differentiate between primary and secondary Conn's disease you will perform which of the following :

A. Aldosterone /Rennin ratio
B. Serum Aldosterone level
C. Renin serum level
D. All of the above

3- In patient with Pheochromocytoma , you want to prevent the " Hypertensive crises " What are you going to do first ? :

A. Ligate the vein
B. Ligate the artery
C. Remove the tumor without ligation
D. All of the above

4- Pre-operative preparation for an adrenalectomy procedure in Conn's syndrome patients involves:

A. Thiazide diuretics
B. Spironolactone
C. Amiloride (potassium-sparing diuretic)
D. B & c

5- All of the following is true about pheochromocytoma, except:

A. 5% of tumors discovered incidentally on CT scan
B. Most occur sporadically
C. Associated with multiple endocrine neoplasia type 1
D. Associated with Recklinghausen disease

6- A child presents with episodic headache, excessive sweating, weight loss & change in bowel habits. The most likely diagnosis is:

A. Addison's disease
B. Conn's syndrome
C. Pheochromocytoma
D. Hyperthyroidism

7- An essential feature of pheochromocytoma is:

A. Hypertension
B. Elevated urinary catecholamines or their metabolites
C. Hyperglycemia
D. All of the above

8- According to the "Rule of 10's", which of the following is true?

A. 10% of pheochromocytomas are benign
B. 10% of pheochromocytomas are extra-adrenal
C. 10% of pheochromocytomas are unilateral
D. 10% of pheochromocytomas are sporadic

9- Most of extra-adrenal pheochromocytomas are located in:

A. The abdomen
B. The head
C. The pelvis
D. The chest

10- The imaging technique that useful in case of extra-adrenal, multiple, or malignant pheochromocytomas is:

A. MRI
B. CT
C. MIBG
D. U/S

11- Lab. Findings corresponding to a diagnosis of pheochromcytoma:

A. Elevated urinary vanillylmandelic acid (VMA)
B. Hyperglycemia
C. Elevated 24-hour urine metanephrines
D. All of the above

12- Surgery is indicated in pheochromocytoma in which of these situations?

A. No response to α-blockers
B. Metastatic disease
C. All pheochromocytomas
D. None of the above.

13- A female patient presents with a recent increase in weight – specifically in the trunk and face areas, changes in hairline, acne & excessive facial hair growth, back pain, abdominal pain and a palpable left abdominal mass. What would you expect to find?

A. Low serum adrenocorticotropic hormone (ACTH)
B. A mass that is hyper-dense relative to liver on T2-weighted MRI
C. Radiographic evidence of metastases
D. All of the above

❖ **Answers Keys:**

1- A
2- A
3- A
4- D
5- C
6- C
7- D
8- B
9- A
10-C
11-D
12-C
13-D