Adrenal gland

Objectives: by the Doctor:

- the most important objective in this lecture is to know the Anatomy and physiology of Adrenal , **management** of each disease.
- you should know the function (physiology) and malfunction either overproduction or no production of each hormones.
- Conn's syndrome (Na and K)
- Addison disease
- Cushing syndrome
- Pheochromocytoma (management)
- Incidentaloma

Resources:

- Davidson surgery
- Surgical Recall
- Toronto Notes 2016

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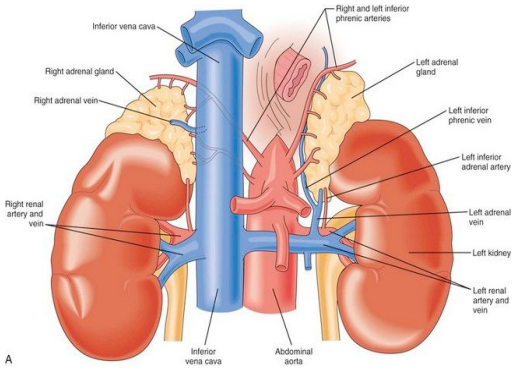
Basic review:

Anatomy:

The adrenal glands are located in the retroperitoneum superior to the kidney and lateral to the vena cava (right) and aorta (left). Three arteries supply each adrenal: superior adrenal artery (arise from the inferior phrenic artery), middle adrenal artery (branch of the aorta), and inferior adrenal artery (branch of the renal artery).
The right adrenal vein drains into the vena cava. The left adrenal vein drains into the left renal vein.



Physiology: (knowing the physiology is the key to know all the pathology ,you will be confused if you don't ,so understand physiology then it doesn't matter if the hormones increase or decrease)

1. **Adrenal cortex** (Remember there are **3** layers of cortex , from outer>inner GFR)

a. Zona Glomerulosa: responsible for **mineralocorticoids** production"Aldosterone" which increase the circulating blood volume by Increases Renal Tubular Reabsorption of Sodium (water retention) and Secretion of Potassium (MCQ). so when there is a dysfunction it gives hyperkalemia and hyponatremia

b. Zona Fasciculata: produce **glucocorticoids** it secret steroid and mainly "Cortisol" which induces the catabolic state in the body in response to stress , by increasing blood glucose concentration, stimulating lipolysis, enhancing adrenergic stimulation of the cardiovascular system, and reducing the inflammatory response of the immune system.

Cortisol is a **BIG FIB:** ↑ **B**lood pressure , ↑ **I**nsulin resistance, ↑ **G**luconeogenesis, lipolysis, and proteolysis, ↓ **F**ibroblast activity , ↓ **I**nflammatory and Immune responses , ↓ **B**one formation.

c. Zona Reticularis: produces the adrenal **sex hormone** androstenedione "androgen" if there is a malfunction ↑ of the hormone (in female) it will give the male characteristic.

What is the important for me as surgeon when the patient is taking steroid? 1-**Wounds** healing and leaks. 2- increasing blood sugar. 3- decrease the immunity by an indirect way.

How to test if the cortex working well or not? **By history taking and examination**:

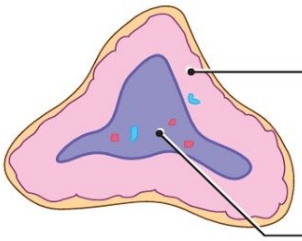
1. Hypertension ,hypokalemia, hypernatremia and either lower limb edema or generalized edema indicate **hyperaldosteronism.**
2. Moon face , central obesity, arthritis, diabetes and the other Cushing syndromes manifestation indicate **increase cortisol** , order 24h urine cortisol test.
3. When there are adrenal insufficiency (↓ of Aldosterone and cortisol) the patient will come with hypotension, hyponatremia, hypovolemia, hyperkalemia, weakness, hyperpigmentation , indicates Addison disease.

2. **Adrenal medulla** (one layer)

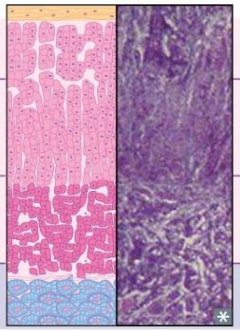
The adrenal medulla produces catecholamines "epinephrine and norepinephrine" that act on peripheral alpha and beta-receptors. one of the stimulation of medulla is stress (sympathetic manifestation)

Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).



	ANATOMY	PRIMARY REGULATORY CONTROL	SECRETORY PRODUCTS
CORTEX	Zona Glomerulosa	Renin-angiotensin	Aldosterone
CORTEX	Zona Fasciculata	ACTH, CRH	Cortisol, sex hormones
CORTEX	Zona Reticularis	ACTH, CRH	Sex hormones (e.g., androgens)
MEDULLA	Chromaffin cells	Preganglionic sympathetic fibers	Catecholamines (epinephrine, norepinephrine)



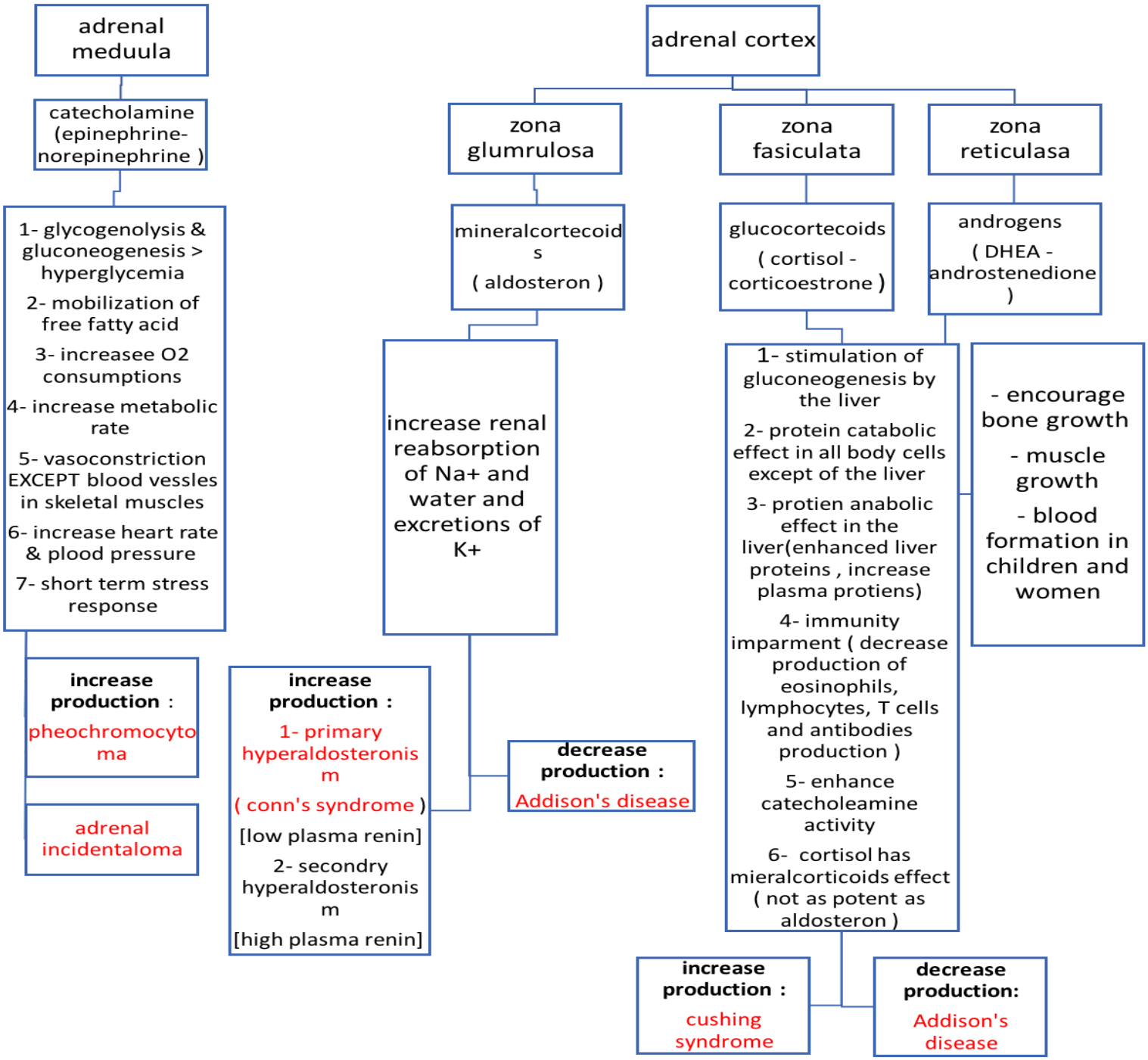
GFR corresponds with Salt (Na^+), Sugar (glucocorticoids), and Sex (androgens).
"The deeper you go, the sweeter it gets."

Pheochromocytoma—most common tumor of the adrenal medulla in adults.
Episodic hypertension.

Neuroblastoma—most common tumor of the adrenal medulla in children.
Rarely causes hypertension.

Adrenal gland

Quick review



-Short term stress will stimulate adrenal medulla to release catecholamine.
-long term stress will stimulate adrenal cortex to release corticosteroid & mineralocorticoid

Cortex

1- Cushing's syndrome

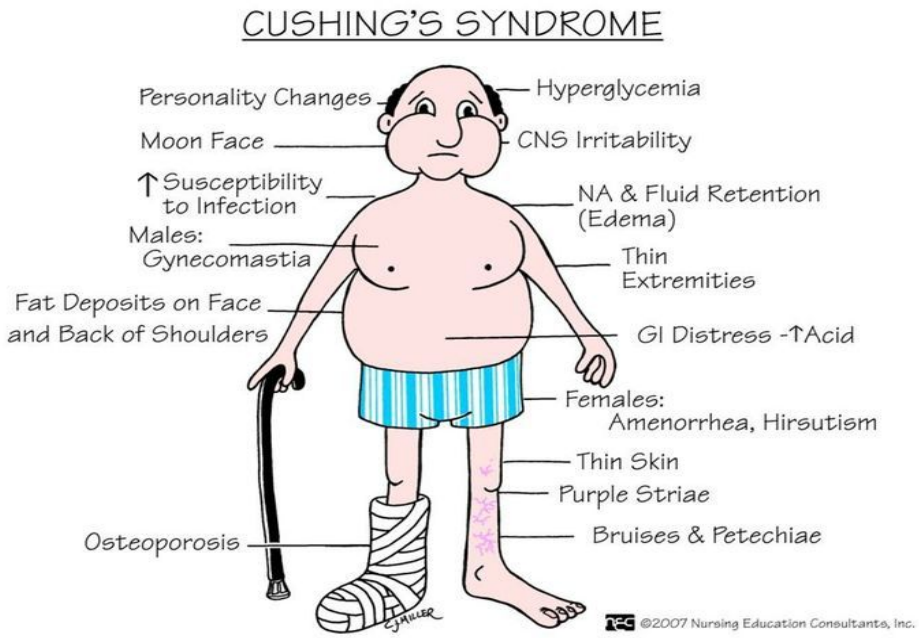
- Cushing's syndrome is produced by increased circulating corticosteroids (endogenous or exogenous)
- More frequent in females
- Usually occurs at 35-50 years of age

ETIOLOGY

- **ACTH-dependent** (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
  - ACTH-secreting pituitary adenoma (**Cushing's disease**; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, Carcinoid e.g. bronchial, pancreatic islet cell tumors, pheochromocytoma, or medullary thyroid tumours)
- **ACTH-independent** (15%):
  - long-term use of exogenous glucocorticoids.
  - primary adrenocortical tumours:
    - adenoma and carcinoma (uncommon) bilateral adrenal nodular hyperplasia

SIGNS & SYMPTOMS:

See the Picture >



Investigation

- 24-hour urine cortisol level.

MANAGEMENT

- **Adrenal Adenoma :** are rarely bilateral; unilateral adrenalectomy is most commonly indicated.
- **Adrenal carcinoma :** Adrenal carcinomas should be completely removed whenever possible; debulking may be helpful if chemotherapy is to be used.
- **Pituitary disease :** The symptoms of bilateral adrenal hyperplasia due to pituitary hyperfunction can be relieved by bilateral adrenalectomy, but at the price of lifelong steroid therapy. Or treated by pituitary surgery (the best)

2- Conn's syndrome

HYPERALDOSTERONISM

primary hyperaldosteronism (PH) = Conn's syndrome	Secondary hyperaldosteronism (SH)
excess aldosterone production (intra-adrenal cause)	Aldosterone production in response to excess RAAS (extra adrenal cause)
Ratio of the plasma aldosterone level to plasma renin is elevated (High aldosterone & Low renin).	Ratio of the plasma aldosterone level to plasma renin is normal (High aldosterone & High renin).

- Conn's syndrome Usually is caused by adrenal tumor most common in young or middle-aged women.
- The high circulating levels of aldosterone suppress renin secretion – a helpful biochemical diagnostic observation.
- Usually the patient comes with: symptoms of **hypokalemia** (arrhythmias) and hypernatremia. How'd you manage this patient? history and examination then do ECG to make sure there are no cardiac manifestation due to electrolytes changes then come up with differential diagnosis for hypokalemia (diarrhea, diuretic) and hypernatremia (severe dehydration hypovolemia), then refer the patient to endocrinologist to roll-out conn's.

*What is the normal serum K+ level? 3.5-5 (mEq/L)

SIGNS & SYMPTOMS:

1. Na and water retention (hypernatremia): headache secondary to HTN and visual disturbance
2. K+ (hypokalemia): Worsening hypokalemia, episodes of muscle weakness and nocturnal polyuria.
   - Usually no edema

DIAGNOSIS

- Urinary K (Low in blood but high in urine. not specific nor sensitive because some medications can ↑ the potassium in the urine)
- Plasma: ↑Na and ↓K
- Confirm hypokalaemia: By repeated blood sampling and 24-hour urine collections usually → ↑ K excretion.
- Giving the aldosterone antagonist, **Spironolactone**, should ↓ blood pressure and reverse hypokalaemia.
- CT scan (To rule-out masses)
- EKG changes **(Flattening of T waves, U waves appear with severe hypokalemia)**
- Localize the adenoma: To localize the adenoma we have to use CT or MRI, failure to 'see' an adenoma mean there is no discrete tumour and that the patient has bilateral cortical hyperplasia.

MANAGEMENT:

- Surgery (ADRENALECTOMY) but after correcting the hypokalaemia with oral potassium and spironolactone.
- Pre operative for hypertension: Spironolactone
- Post operative Monitor because patient may go into crisis: severe hypotension.

3- Addison's disease

Adrenocortical Insufficiency : Hypofunction of adrenal cortex

PRIMARY (ADDISON'S DISEASE)	SECONDARY ADRENOCORTICAL INSUFFICIENCY
All hormones will be decreased: from **all 3 cortical layers**.	Only glucocorticoids will be decreased.
autoimmune , idiopathic, infection (TB) , iatrogenic	inadequate pituitary ACTH secretion.
ACTH normal or high	ACTH is low
- **Hyperpigmentation** - High K and low Na - Metabolic Acidosis	- No pigmentation - Normal K and normal Na or low - No metabolic Acidosis

SIGNS & SYMPTOMS:

- fatigue, weight loss, anorexia; due to low cortisol.
- Muscular weakness.
- Fluid & electrolyte imbalances (opposite of conn's by having hyponatremia and hyperkalemia due to decrease aldosterone)
- Hypotension.
- Hypoglycemia: because of low cortisol
- Androgens are low causing: pubic hair loss and decreased sexual drive for women. (men are not affected
- Mental disturbances: anxiety, irritability, etc.
- Salt craving: because of low aldosterone

MCQ : Dysfunction of aldosterone; in **Serum**: ↓Na and ↑K , but in **Urine**: ↑Na and ↓K.

DIAGNOSIS:

- Serum cortisol is low (if low then will be diagnostic for addison's)
- Urinary 17-OHCS2 and 17 KS3 is low
- K is high, Na is low and Serum glucose is low

INTERVENTION:

- Lifelong hormone replacement.
- Kit of 100 mg hydrocortisone IM (IMPORTANT for all patients to have this kit).
- Keep parenteral glucocorticoids at home for injection during illness.
- Avoid infections/stress.

COMPLICATION:

- Adrenal crisis
- Electrolyte imbalance
- Hypoglycemia

Medulla

History taking and Examination for any Adrenal mass

If you see any patients with adrenal mass, you should ask yourself Three questions:

1. **Is it functional (producing hormones) or not?**
    a. by history e.g. causing headache, truncal obesity, HTN (controlled or not? how long?)
    b. by investigation: blood and urine test : metanephrine and normetanephrine , cortisol level …
2. **Is it benign or malignant , primary or secondary?**
    a. Previous history of cancer? ask about any history of breast, skin (melanoma) or renal cancer (RCC) because it could be metastasis from any one of them (roll-out secondary)
    b. Radiological imaging: usually when the tumor is cancer it will be aggressive and penetrate other organs near to it. So when we do CT it will tell me if the mass is:
        i. Aggressive
        ii. Irregular edge
        iii. Penetrating to other structure surrounding to it.
    c. If the image highly suspect the cancer then we will go with biopsy **after you roll-out Pheochromocytoma. (as biopsy is contraindicated in case of pheochromocytoma)**
3. **From where the patient comes to you?** (Is it incidentaloma or not) ? Is the patient coming to you with the compliment or just send by the other doctor who found the mass by chance?

1- Incidentaloma

- **Scenario 1 (Incidentaloma)**: You are a family doctor and you saw a patient referred to you from Gyne, she had US that showed a mass in adrenal of 1 cm in size without any symptoms.
    a. **what do you wanna do ?** Refer her to a surgeon.
    b. **What will he do (the surgeon) ?** He will ask the 3 question of the classical **history**
    c. **What is the management?** Mass in adrenal Medulla, found by chance, patient is asymptomatic, so you must take a proper history and examine the patient, then move to the investigation. Then if it's all normal we will go with management of incidentaloma **(Manage it by size)**:
        i. if the mass size more than 4 cm surgery is indicated. So you will take it out, because you can't roll-out the risk of the cancer
        ii. but if it is less than 4 cm for example 1cm: follow up every 6 months: do CT then after 6 months then MRI after one year, we investigate with CT or MRI (interchangeably). if the mass increases 1 cm in one year we should **take it out** but if there is no increase in size or there is increase less than 1 cm then observation is recommended!
- It is adrenal mass discovered by investigation of unrelated symptoms.
- Serendipitously discovered by radiologic examinations. Such as US or CT

Typical scenario :

- A 50-year-old male has an abdominal CT scan. Appendicitis is confirmed, and the patient undergoes a successful appendectomy and uneventful recovery.
- The CT scan also revealed a 2-cm adrenal mass. What's your next step? Think: Test for functionality , If the mass is functional, it should be resected regardless of its small size

2-Pheochromocytoma

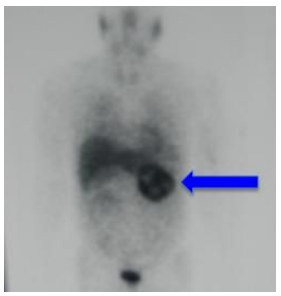
- rare catecholamine secreting tumour derived from chromaffin cells of the sympathetic system
- **Scenario 2 (Pheochromocytoma) :** classical history, patient comes to you with high blood pressure that is not responding to treatment (recently diagnosed with hypertension and it's not controlled)
    - **What you will do as intern ?** Informe your senior.
    - **What do you think your senior will do** ? He will Order metanephrine blood and urine , cortisol 24h and refer the patient to endocrinologist.
    - Not controlled with medication and Surgery is the only option
    - **What you will worry about it in OR** ? Adrenal crisis
    - **What will happen after we take the lesion out?** Severe hypotension, so all the time keep IV hydralazine with you in the OR for hypertension then after resection give IV adrenaline and noradrenaline for severe hypotension.
- Rare, benign tumor of the adrenal medulla and 10% could be malignant (Remember the rule of 10%)
- May be associated with neurofibromatosis, medullary carcinoma of the thyroid (MEN II), Von Hipple–Lindau disease, duodenal ulcer and renal artery stenosis
- pheochromocytoma may cause sudden and unexplained death after trauma or during surgery, owing to severe hypertension causing a cerebrovascular accident or by precipitating a fatal arrhythmia.
- When a patient presents with hypertension and you suspect pheochromocytoma then you take a biopsy, the patient may die due to Adrenal crisis. So **NEVER** take a biopsy if pheochromocytoma was expected; start with the work up to see if it the tumor is functional or not.

SIGNS & SYMPTOMS

- Hallmark is hypertension: 200/150 or greater (complaining of headache all the time that can't be controlled even with antihypertensive medications)
- classic triad (not found in most patients): episodic "pounding" headache, palpitations/ tachycardia, diaphoresis
- Paroxysmal attacks
- adrenaline excess has metabolic effects (e.g.diabetes and thyrotoxicosis).
- Visual disturbances and Glycosuria is common

DIAGNOSIS

- By history and examination then tests.
- Plasma and 24h urine studies (metanephrines, catecholamines, VMA levels) plasma is more sensitive, usually used for Screening. 24h urine is more specific, used for Confirmation to know if he has functional pheochromocytoma or not **MCQ**.
    - the main 2 problems are:
        - It will take 24h and it is expensive so not available in all the hospitals.
- CT to locate tumor.
- **Imaging**: metaiodobenzylguanidine (MIBG) scanning. **(Confirmatory)**



INTERVENTION

Surgical resection of the tumor is the treatment of choice for pheochromocytoma and usually results in cure of the hypertension. Careful preoperative management is required to regulate heart rate, correct fluid volume, and prevent intraoperative hypertensive crises. Preferred method is to use α-blocker agent (Phenoxybenzamine) 1 to 2 weeks before surgery. Followed by B-blocker to oppose α-blocker induced tachycardia.

PRE-OP	- **Adrenergic blocking agents:** Minipress[1] to lower BP - **Beta blocking agents:** Inderal to lower HR, BP & force of contraction - **Diet:** high in vitamin, mineral,calorie, no caffeine - **Sedatives** - **Monitor BP** (and control it) - **Eliminate attacks** - **If attack** → complete bed rest and head of bed 45 degrees
DURING SURGERY	GIVE REGITINE AND NIPRIDE TO PREVENT HYPERTENSIVE CRISIS(in high BP we give antihypertensive, in hypotension we give fluid)
POST-OP	BP. may be high initially, BUT CAN BOTTOM OUT - Volume expanders - Vasopressors - Hourly I and O - Observe for hemorrhage

SUMMARY BOX **20.9**

Management of adrenal pathologies

- Hyperfunctioning benign adrenal masses should be removed surgically (phaeochromocytoma, cortisol secreting adenomas and Conn's syndrome). The laparoscopic approach is the preferred one
- Careful preoperative assessment to exclude multiple hormone secretions from a single or bilateral adrenal masses must be undertaken (e.g. a phaeochromocytoma that is also secreting cortisol)
- In primary hyperaldosteronism (Conn's syndrome) preoperative selective venous sampling from both adrenals should be considered to confirm the site of maximal secretion. It can be misleading to assume this will be the side with the mass lesion in it
- Incidentally found adrenal masses must be investigated for possible hypersecretion of all adrenal hormones prior to their removal or a decision to leave them in situ and follow up.
- Have a low threshold to remove non-functioning incidentalomas > 3.5 cm in size, as the incidence of adrenocortical carcinomas increases significantly above this size
- Only biopsy an adrenal mass if you think it is due to a metastasis from a previous known malignancy. Always exclude a phaeochromocytoma before biopsy of any adrenal mass.

British Association of Endocrine and Thyroid Surgeons' Guidelines at www.BAETS.ORG.UK

[1] medications.

Recall :

What is the second most common cause of Cushing's Syndrome?
Cushing's disease (most common non iatrogenic cause)
What is Cushing's disease?
Cushing's syndrome caused by excess production of ACTH by anterior pituitary
How can cortisol levels be indirectly measured over a short duration?
By measuring urine cortisol or the breakdown product of cortisol, 17 hydroxycorticosteroid (17-OHCS), in the urine
What is a direct test of serum cortisol?
Serum cortisol level (highest in the morning and lowest at night in healthy patients)
How are the following tumors treated:
Adrenal adenoma? Adrenalectomy (almost always unilateral)
Adrenal carcinoma? Surgical excision (only 33% of cases are operable)
Ectopic ACTH-producing tumor? Surgical excision, if feasible
Cushing's disease? transphenoidal adenectomy

What is the normal physiology for aldosterone secretion?
BP in the renal afferent arteriole is low
Low sodium and hyperkalemia cause renin secretion from juxtaglomerular cells Renin then converts angiotensinogen to angiotensin I
Angiotensin converting enzyme in the lung then converts angiotensin I to angiotensin II
Angiotensin II then causes the adrenal glomerulosa cells to secrete aldosterone
Classically, what kind of hypertension in Conn's Syndrome?
Diastolic hypertension
What is the saline infusion test?
Saline infusion will decrease aldosterone levels in normal patients but not in Conn's syndrome
What are the causes of Conn's syndrome?
Adrenal adenoma (66%),Bilateral idiopathic adrenal hyperplasia (30%), Adrenal cancer (< 1%)
What is the treatment of the following conditions:
Adenoma Unilateral adrenalectomy (laparoscopic)
Unilateral hyperplasia Unilateral adrenalectomy (laparoscopic)
Bilateral hyperplasia Spironolactone (usually no surgery)
What are the renin levels in patients with PRIMARY hyperaldosteronism?
Normal or low (key point!), the plasma aldosterone to plasma renin will be > 30

How can the pheochromocytoma SYMPTOMS triad be remembered?
Think of the first three letters in the word Pheochromocytoma: Palpitations, Headache and Episodic diaphoresis
What are the other common lab findings?
Hyperglycemia (epinephrine increases glucose, norepinephrine decreases insulin) Polycythemia (resulting from intravascular volume depletion).
Can histology be used to determine malignancy?
No; only distant metastasis or invasion can determine malignancy
What is the classic pheochromocytoma "rule of 10's"?
10% malignant, 10% bilateral, 10% in children, 10% multiple tumors, 10% extra-adrenal and 10% familial What is differential **diagnosis of pheochromocytoma ?**
Renovascular hypertension , hyperthyroidism and carcinoid syndrome
How can you remember phenoxybenzamine as a medical treatment of pheochromocytoma?
Pheochromocytoma = Phenoxybenzamine (alpha- blockers) → increase in intravascular volume
What is the surgical treatment?
Tumor resection with early ligation of venous drainage (lower possibility of catecholamine release/crisis by tying off drainage) and minimal manipulation
In the patient with pheochromocytoma, what must be ruled out?
MEN type II (almost all cases are bilateral)

What is the most common cause of incidentaloma?
Nonfunctioning adenoma (>75% of cases)
What is the differential diagnosis ?
Non-functioning adenoma, aldosteronoma and metastatic disease.

MCQ

1) Addison's Disease is associated with all except?

A. Hyponatremia
B. Hypoglycemia
C. Sexual Dysfunction
D. Mild Alkalosis

2) The diagnosis of pheochromocytoma include all except?

A. Biopsy
B. 24 hour urine-VMA
C. Plasma Catecholamines
D. CT-Scan

3) What is most common site of extra-adrenal pheochromocytoma ?

A. bladder
B. Scrotum
C. Organ of Zuckerkandl
D. Spinal cord

4) 30-year-old female patient came to the clinic with truncal obesity, purple striae, hypertension, diabetes and amenorrhea. What is the most common cause of her presentation?

A. Adrenal cortical adenoma
B. Anterior pituitary adenoma
C. Ectopic ACTH producing tumor
D. Steroid or cortisone therapy

5) A patient came to the ER with a history of "Adrenal crisis". What do you expect to find him complaining of?

A. Hyperkalemia, hyponatremia and hypercalcemia
B. Mimicking acute abdomen.
C. Hypokalemia and kidney stones
D. Hyperglycemia

6) A 37-year-old female was diagnosed with hypertension. While doing the hypertension workup, she was found to have left adrenal mass which was suspected to have caused the hyperaldosteronism symptoms. What do you expect to see in her electrolytes?

A. Normal Na, high K
B. High Na, low K
C. High Na, high K
D. Low Na, high K\

7) A 44-year-old otherwise healthy man has a 3-cm left adrenal mass found during CT evaluation for acute appendicitis. Following his appendectomy, a serum metanephrine level during his hospitalization revealed mild elevation in value. Which of the following is the most appropriate next step?

A. A 24-hour urine collection for VMA, metanephrine, and normetanephrine
B. MIBG scan
C. CT-guided needle biopsy of the adrenal gland
D. Alpha blockage for 1 week followed by laparoscopic adrenalectomy
E. Monitor the lesion with CT scans annually

8) A 3.5-cm right adrenal mass was discovered incidentally on an abdominal CT scan obtained for a 62-year-old man who was a victim of motor vehicular trauma. His medical history was notable for a right upper lobe lung resection 3 years previously for a stage I carcinoma. He is asymptomatic. Which of the following is the next most appropriate step in the evaluation?

A. FNA biopsy of the adrenal mass.
B. Repeated CT scanning in 3 months.
C. A functional assessment of the adrenal mass.
D. MRI of the adrenal gland.
E. Perform a PET scan to look for other sites of possible metastatic disease.

9) For which of the following patients is observation alone appropriate?

A. A 53-year-old healthy man with a 8-cm nonfunctioning left adrenal mass
B. A 46-year-old man with a history of hypertension and unexplained hypokalemia
C. A 32-year-old woman with elevated serum metanephrines and urinary VMA, metanephrines, and an asymptomatic 2-cm right adrenal mass.
D. A 66-year-old man with a history of malignant melanoma on the leg at age 50, who presents with a newly diagnosed 4-cm right adrenal mass.
E. A 44-year-old woman with a 8-cm left adrenal mass that appears to be a myolipoma based on CT.

10) Which of the following is the most appropriate management for an 85-year-old nursing home resident, with severe dementia and congestive heart failure (CHF), and a 6-cm left adrenal mass?

A. Evaluate for the tumor for functionality and treat with laparoscopic adrenalectomy.
B. Evaluate the tumor for functionality and perform CT-guided biopsy.
C. Expectant management.
D. Medically optimize the patient and perform laparoscopic adrenalectomy.
E. Monitor the lesion with repeat CT scan every 6 months.

11) Which of the following statements regarding adrenalectomy for a pheochromocytoma is most correct?

A. It results in blood pressure improvement, but blood pressure rarely normalizes.
B. It corrects hypertension only in patients with benign disease.
C. It may lead to profound intraoperative hypotension.
D. It should be reserved for patients with hypertension refractory to drug therapy.
E. Preoperative management is not needed if laparoscopic surgery is planned.

Answers:

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