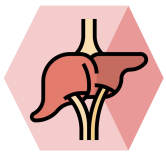
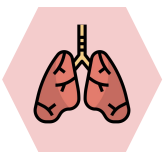
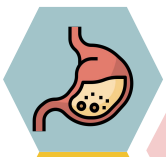
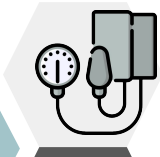
Medicine TEAM 437

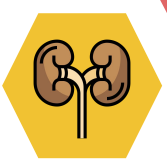
MED437 KING SAUD UNIVERSITY

Adrenal disorders






Objectives :

1. Understand anatomy, physiology and biochemistry of adrenal glands
2. Understand clinical approach and management of adrenal disorders:
   a. Function: hyper and hypo-secretion
   b. Structure

Done by :

Team leader: Salem Al-Ammari

Team members: - Naif Almutairi - Rahaf Althnayan

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Revised by :

Yazeed Al-Dossare

Resources :

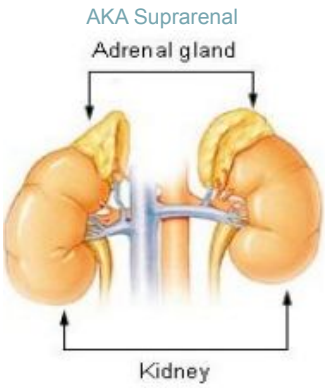
Doctor's slides

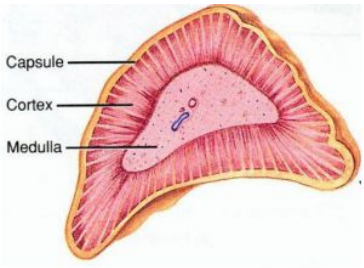
Lecturer: Dr. Muhammad Mujammami & Dr. Mona Fouda

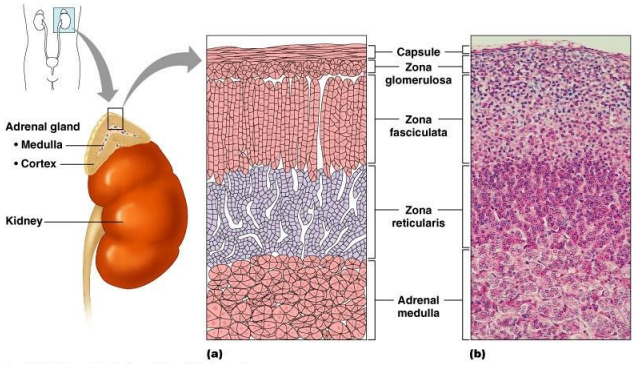
Same as 436 slides: Yes

Anatomy & Physiology

AKA Suprarenal







Adrenal gland			
Tissue area	Hormones	Effects	Regulation
Zona **G**lomerulosa	**S**alt Mineralocorticoids (aldosterone)	Kidney: Maintain intravascular volume by increase reabsorption of Na+ and water Maintains BP	angiotensin II, K+ ؛Na+ Mainly regulated by RAAS and ACTH
Zona **F**asciculata	**S**weet Glucocorticoids (cortisol)	Lipolysis Increase blood sugar Maintains BP	ACTH From Pituitary gland
Zona **R**eticularis	**S**ex Androgens	It is the main source of androgen in human But it is important in the disorders (Androgens coming from the adrenals are not significant. Most important sources are the testes and ovaries)	
Medulla	Catecholamines (Epinephrine,Norepinephrine, Dopamine) Originally from neurons (ectoderm)	Most of the time activate sympathetic fibers and increase (BP, HR, blood sugar) But could present with activations of parasympathetic as pathologic disorders	

It's important to know the regulation of these hormones because if the adrenals were removed for any reason, we would need to know which hormones to replace eg:

- Adrenals removed - replace both aldosterone and cortisol (no need to replace androgens/testosterone)
- Pituitary removed - need to replace cortisol but no need for aldosterone replacement as the RAAS can compensate for a lack of ACTH

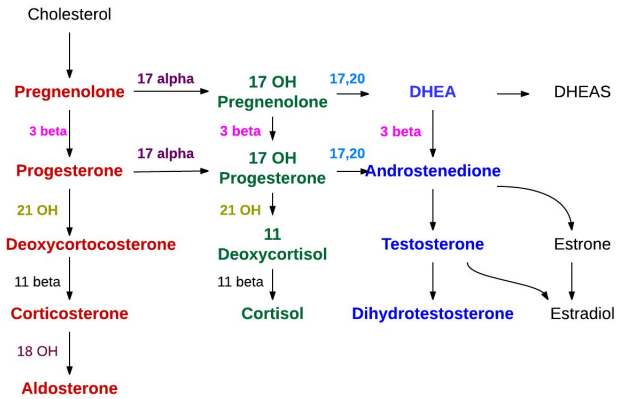
Biochemistry

• The zona **glomerulosa** produces **aldosterone** and lacks 17 hydroxylase activity and cannot synthesize cortisol and androgens.
The synthesis of aldosterone is primarily **regulated by the renin angiotensin** system and by **potassium**.

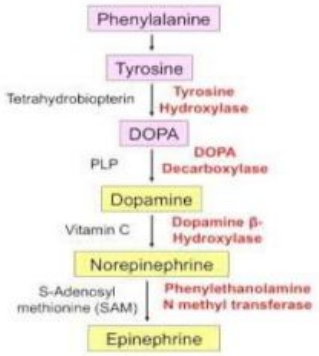
• The zona **fasciculata** and reticularis produce **cortisol, androgens** and small amounts of estrogens and they do not contain the enzymatic system necessary for production of aldosterone.

• All adrenal cortex hormones are originating from Cholesterol (Cortisol, aldosterone, androgens)
• All adrenal medulla hormones are originating from amino acid Tyrosine

Adrenal Cortex



Adrenal Medulla



A deficiency in the 21-Hydroxylase enzyme will lead to shunting of the pathway and the accumulation of excess testosterone, while the levels of aldosterone and cortisol would be low. In males this excess of testosterone is not usually noticeable. However, in females, testosterone excess may lead to several signs and symptoms.

Congenital adrenal hyperplasia (CAH) is a result of deficient 21-OH enzyme which leads to a reduction in aldosterone and cortisol levels. With accumulation of testosterone. This will lead to female newborns having ambiguous or male-like genitalia

Adrenal Disorders

Function:
• Hypersecretion
• Hyposecretion

Primary and **Secondary**

Structural: Adenoma or cancer
• Adenoma
• Hyperplasia
• Bilateral vs unilateral
• Adrenal vs extra-adrenal

Evaluation of Adrenal disorders

CBA Approach

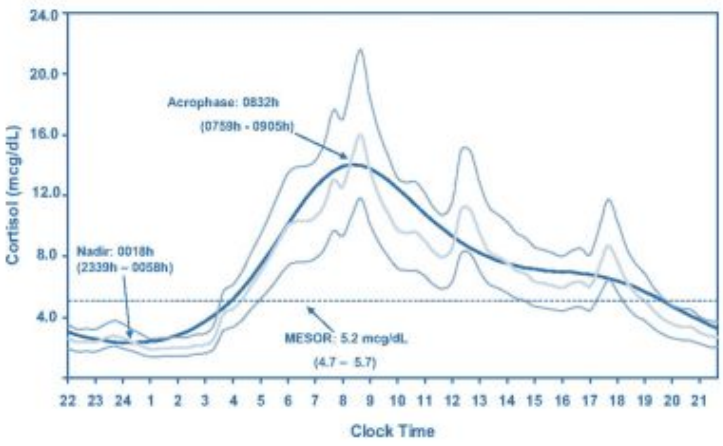
- **C: Clinical** (History and Examination)
  - function (hypersecretion or hyposecretion)
  - Structural (headache, visual symptoms)

- **B: Biochemical**
  - Screening Test
  - Confirmatory Test

- **A: Anatomical**
  - CT or MRI adrenal (adenoma, hyperplasia, uni or bilateral, adrenal , extra-adrenal, benign or malignant)

- Then treatment

Physiological cortisol circadian rhythm



Cortisol reaches peak levels in the early morning. Therefore always measure cortisol levels in the morning after the patient is well rested.

If you suspect adrenal insufficiency, measure cortisol levels in the morning:
- If very high you can rule out adrenal insufficiency
- If levels very low - suspect adrenal insufficiency and confirm via other more accurate tests

❖ Adrenocortical hypofunction

1. Adrenal insufficiency
A- Primary
B- Secondary/ Tertiary

2. Congenital Adrenal Hyperplasia same as adrenal insufficiency but with ambiguous genitalia.

1- Disorders of Adrenocortical insufficiency:

You don't need to know this in detail just get a general idea of the causes

A- Primary adrenocortical insufficiency (Addison's disease)

Causes	
Major	Minor
•Autoimmune 80%: The most common cause NOT all causes are autoimmune Often positive adrenal antibodies Could be an isolated problem or associated with other autoimmune diseases: - Type I (APECED) : affects children: Adrenal insufficiency, hypoparathyroidism, pernicious anaemia, chronic candidiasis, chronic active hepatitis, and hair loss) - Type II (Schmidt's syndrome) usually affects young adults : hypothyroidism, adrenal insufficiency and diabetes mellitus, vitiligo **•Tuberculosis 20%**	• **Infection** (fungal: Histoplasmosis, CMV, HIV, Syphilis, ..etc) • **Infiltration** (lymphoma, Hemochromatosis, Amyloidosis, Sarcoidosis, malignancy) • **Iatrogenic** (Surgical removal, Anticoagulation and hemorrhage) • **Medications** (ketoconazole, rifampin, phenytoin, Phenobarbital, Mitotane, Metyrapone, Aminoglutethimide) • **Hereditary** (Congenital adrenal hyperplasia,adrenal unresponsiveness to ACTH, adrenoleukodystrophy, adrenomyeloneuropathy, Refsum disease, Wolman disease) • **Miscellaneous:** -Triple A syndrome= Allgrove syndrome -Adrenal hemorrhage Trauma

C: Clinical

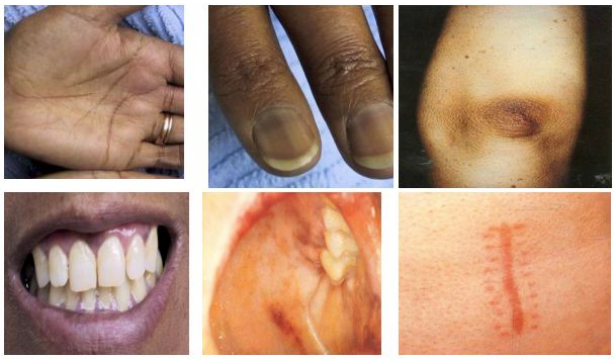
There's destruction of adrenal cortex (3 layers)

- Weakness, Tiredness, Fatigue.
- Nausea, Vomiting, Constipation, Abdominal pain, Diarrhea, weight loss.
- Hyperpigmentation (specific)
  - only in Primary adrenal insufficiency due to melanocyte stimulating hormone (MSH) from pro-opiomelanocortin (POMC) Not ACTH

    POMC is the precursor of ACTH and MSH. If cortisol is low due to primary AI, there will be an increase in the production of POMC. Leading to increased levels of ACTH and MSH (causing darkening of the skin) However, in cases of central AI or pituitary trauma there will be AI without darkening of the skin as little POMC is being produced. *This is a way to differentiate between primary and central AI.

- Fasting hypoglycemia. Loss of cortisol.
- **Hypotension**, Shock and death Loss of aldosterone.
  - BP and HR
  - Standing and supine
  - Think about AI (adrenal insufficiency), if not respond to IVF and initial management

  Postural hypotension: measure BP in supine position then again after standing up for 3 minutes. If systolic BP drops by >20 or diastolic BP drops by >10 mmHg, this is positive for postural hypotension.
- Decreased axillary and pubic hair due to decrease in Androgens (? NOT Clinical significant)



Q. A 21 year old presents to the ER with hypotension. What could be the cause?

Adrenal insufficiency is an important and treatable disease. However, it is NOT common and should not be the first thing you think of in cases of hypotension. You should first consider more common causes of such symptoms (eg. gastroenteritis, appendicitis, sepsis, trauma, diarrhea).

Consider Adrenal insufficiency in 2 cases:

- Hypotension NOT responding to regular medication
- Typical (text book) presentation (eg.patient with autoimmune thyroid diseases, nausea, vomiting, abdominal pain, weight loss, hypotension and **darkening of the skin** - typical adrenal crisis)

B: Biochemical

- Measure a.m. cortisol
  - If high : R/O (rule-out)
  - If very low : diagnosis
  - If borderline result : proceed for confirmatory test (ACTH stimulation test)
- Measure ACTH: to differentiate primary or secondary

	Primary	Secondary
ACTH	high	low
cortisol	low	low
Androgen (adrenal)	Low High in CAH	low
Aldosterone	low	Normal N.B: RAS
K	high	Normal/high
Na	low	Low/ normal
Glucose	low	low
Hb	Normal or low	low

If a patient presents to the ER with hypotension how do we prove its AI?

- If it's in the morning measure cortisol, if low proves AI (Not very accurate)
- Dynamic test (AKA short selection test, best test!!!). Give exogenous ACTH. if cortisol level increases exclude AI. if cortisol level normal or low, diagnose AI

A: Anatomical

Usually not needed

- Adrenal insufficiency is clinical and biochemical diagnosis
- No indications to do imaging unless clinically indicated such as:
  - Patient on anticoagulation
  - Malignancy with metastasis
  - Or other infiltrative disease

Treatment

Replace missing hormones

- IVF: dextrose and salt for:
  - Rehydration and to restore intravascular volume
- Electrolytes replacement
- Steroid replacement
- If primary: replace both
  1-Glucocorticoids (by hydrocortisone)
  2-Mineralocorticoids (by Fludrocortisone)
- if secondary: replace
  - Glucocorticoids (by hydrocortisone only)

- NB: Hydrocortisone has some Mineralocorticoids activity, so if you use hydrocortisone in high IV dose, stop **Fludrocortisone**

In ER give D5NS and I.V. Hydrocortisone

B- Secondary/ Tertiary adrenal insufficiency

- Panhypopituitarism (congenital / acquired):
  - Tumors, surgery, radiation therapy
  - Hypothalamic / pituitary disorders

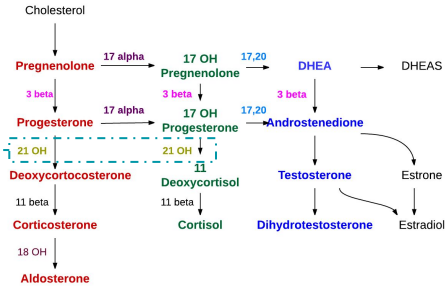
- Isolated ACTH deficiency
- Withdrawal from glucocorticoid therapy
- Inadequate glucocorticoid replacement
- Infant born to steroid-treated mother
- Surgical removal of ACTH-producing adenoma of the pituitary gland (Cushing's disease)

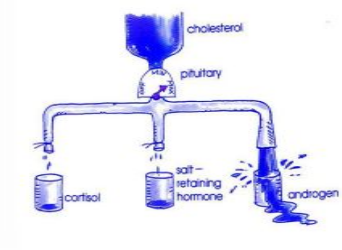
In cases if panhypopituitarism cortisol levels will be low while aldosterone levels may not be affected (as they are also regulated by the RAAS)

2- Congenital Adrenal Hyperplasia

Same as AI but with ambiguous genitalia in females.
Treat the same as AI (give cortisol and aldosterone) with correction of the genitalia

- 90–95% of CAH cases are caused by 21- OHD
- Ambiguous genitalia (Female)
- Failure to thrive
- Dehydration & Shock (usually male)
- Salt-loss presentations with electrolytes imbalance:
  - Hyponatremia
  - Hyperkalemia
  - Hypoglycemia
- Hyperpigmentation

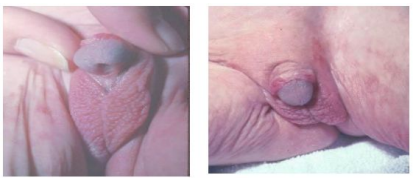




Diagnosis

- **C: Clinical**:
  - History and examination (B.P)
- **B: Biochemical:**
  - Serum electrolytes & glucose:
    - Low Na & high K
    - Fasting hypoglycemia
    - Elevated serum urea due to associated dehydration
  - Elevated plasma Renin & ACTH levels
  - Low Cortisol
  - **High 17 – OHP** (Sufficient for diagnosis)
  - **High androgens** especially testosterone level
  - Low Aldosterone (in salt losing types only)

Is it a boy or a girl ?!



On the left is the ambiguous genitalia of female newborns with CAH, notice how the labia majora appears like a scrotum. While the picture on the right is of a male newborn with normal genitalia

Management

- Hydrocortisone: 10-20 mg/m2/day divided into three doses. Adult usually 10-5-5 mg
- Fludrocortisone 0.05 - 0.2 mg/day
- During adrenal crisis intravenous hydrocortisone 50-100 mg Q 6-8hrs
- IVF D5 0.9% saline
- During fever or sickness 2-3 fold increment in hydrocortisone dose
- In vomiting or diarrhea, parental therapy is indicated
- Medical Alert: bracelet (in case of emergencies)

In case a patient with AI is sick or experiences any sort of stress (eg URTI or pneumonia or surgery) their dose of corticosteroids should be increased, to mimic the physiological response of cortisol secretion due to stress

❖ Adrenocortical Hyperfunction

1- Hypercortisolism: Cushing syndrome

• First described by Cushing in 1932

• A constellation of clinical abnormalities due to chronic exposure to excesses of cortisol

- **• ACTH dependent (pituitary or ectopic)**
- **• ACTH independent (Iatrogenic *most common*, adrenal adenoma or carcinoma)**

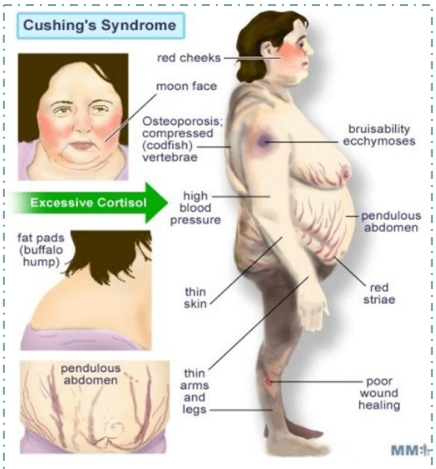
2- Hyperaldosteronism

If cortisol is high: do ACTH

- If ACTH is also high, **Cushing Disease** (pituitary)
- If ACTH is low, its cushing syndrome

1- Hypercortisolism (Cushing Syndrome)

• Rounded "moon" facies with a plethoric appearance
• Truncal obesity with prominent supraclavicular and dorsal cervical fat pads "buffalo hump"
• Distal extremities and fingers are slender
• Muscle wasting and weakness
• The skin is thin and atrophic, with poor wound healing and easy bruising
• Purple striae may appear on the abdomen
• Hypertension
• Renal calculi
• Osteoporosis



Many patients are obese, diabetic and hypertensive! But when should you consider cushing?
When there are typical symptoms and features, including: Central obesity (thin limbs), Striae...

C: Clinical	Function : Hirsutism, acne, easy bruising, DM, HTN, irregular period, proximal weakness, recurrent infections, depression O/E: hirsutism, acne, moon face, central obesity, stria, proximal weakness, supraclavicular fat pad,
B: Biochemical	High cortisol , high ACTH (ACTH dependent) and low if (non-ACTH dependent). There are 3 ways of measuring cortisol: • 24hrs for UFC (urine free cortisol) • 1MG DST we give 1 mg of Dexamethasone and later measure cortisol levels. If cortisol levels are high and not suppressed you can diagnose cushing syndrome. (normally cortisol levels would be suppressed) • Midnight salivary cortisol Cortisol levels should be lowest at night. If there are high levels of cortisol at midnight it can confirm your diagnosis
A: Anatomical	If ACTH: - high: MRI pituitary - low: history then CT adrenals
Treatment	Surgical or Medical

2- Conn's Syndrome

Suspect Conn's syndrome in cases of hypertension NOT responding to medication

- **Primary hyperaldosteronism**
- Adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex
- rarely, adrenal carcinoma
- Hyperplasia
- The clinical picture may mimic CAH from of 11 α-hydroxylase deficiency
- Secondary HTN
- High Na, high Cl, high Aldosterone
- Alkalosis
- low K (episodic weakness, Paresthesias, transient paralysis, tetany, nephropathy with polyuria and polydipsia)

Important Case: What is the most common cause of hypertension in a 60 year old?
ESSENTIAL HYPERTENSION!! (90% of the time)

When should you consider secondary causes of hypertension (eg.Pheochromocytoma, Conn's or Cushing):

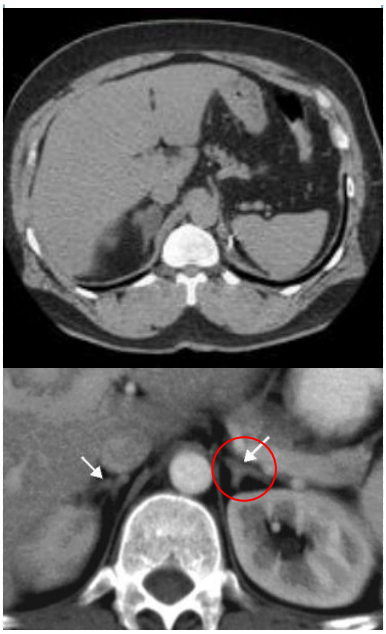
- HTN in a young patient <40
- Very high blood pressure >180
- Resistant to treatment

B: Biochemical

- Screening test:
  - aldosterone/renin ratio
    - If high: do confirmatory test
    - If low: look for secondary causes
- Confirmatory test:
  - Saline infusion test
  - Oral salt loading test
  - Captopril test
  - Fludrocortisone suppression test

A: Anatomical

CT adrenal



Mercedes sign or inverted Y-shape

Treatment

- Adenoma (if unilateral) → Surgical resection

- Adrenal hyperplasia (if bilateral) → Spironolactone.

Pheochromocytoma

- Adrenal **medulla**: sympathetic nervous system
- **50%** are silent. (NO symptoms)
- **Pheochromocytoma:** • Isolated • or part of MEN type II A or MEN type II B
- **Secondary HTN**
- **Episodic (spells): sweating, palpitation, headache**

When you should think about Pheochromocytoma ?

- **Typical symptoms**
- **Secondary HTN:** **important**
  - Young age < 40
  - 3 anti-HTN medications
  - Resistant HTN
  - Accelerated HTN

- If there's any adrenal mass in image: **adrenal incidentaloma** You should rule out:
  - pheochromocytoma
  - Cushing
  - and if there is HTN ,you should R/O hyperaldosteronism also

  By measuring all adrenal hormone levels (cortisol, aldosterone, catecholamines, RAAS)

B: Biochemical

- 24 hr urine collection of Metanephrines (2X) (if levels doubled)
- Plasma Metanephrines

- Make sure about medications that affect the result of the test (false positive)

A: anatomical

- CT scan = MRI
- MIBG: if
  - Paraganglioma
  - Young
  - large size
  - or malignant features
- Genetic Tests:

N.B: 30-40% of Pheochromocytoma and Paraganglioma Have positive genetic test. (not 10 %)

Management

- Control HTN:
  - α-blocker then B-Blocker (10-14 days before operation)
  - Ca-blockers: can be used
- Salt loading the only case where sodium is given for HTN, because if you remove the tumor there will be vasodilation and this will lead to hypovolemia
  - Oral NaCl: 3 days
  - Or IVF 0.9% saline 1-2 days before surgery
- Surgical removal (only if unilateral. Make sure to control HTN before surgery)

Blood vessels have both alpha and beta adrenergic receptor. However alpha is more prominent. **Alpha blockers should be given before beta blockers** because if beta blockers are given it would divert all the catecholamines to activate alpha receptor. Which will precipitate the symptoms of pheochromocytoma

Summary:

Adrenal Disorders

Hypofunction

Primary adrenal insufficiency (Addison disease)	Secondary adrenal insufficiency
Causes: Autoimmune (most common),TB **Clinical features** • Hypotension • Hyperpigmentation (only in primary!!!), due to MSH not ACTH • Weakness, fatigue, hypoglycemia...	**Causes** Panhypopituitarism Withdrawal from glucocorticoid therapy Surgical removal of the pituitary glands **Pathophysiology:** ACTH deficiency leads to: 1-Decrease cortisol & androgen secretion. 2-Aldosterone secretion remains normal
Biochemical: 1-Measure plasma cortisol level 2-Measure ACTH, renin & aldosterone levels 3-ACTH stimulation test (definitive diagnosis) -failure to secrete cortisol → primary insufficiency -increase in cortisol → secondary insufficiency	
Treatment: replace both: -Glucocorticoids (hydrocortisone) -Mineralocorticoids (fludrocortisone)	**Treatment:** Replace glucocorticoids (hydrocortisone only)

Congenital Adrenal Hyperplasia

Caused by: 21-OH deficiency **Clinical features:** -Ambiguous genitalia in female -Dehydration & shock **Treatment:** - Glucocorticoids (hydrocortisone) -Mineralocorticoids (fludrocortisone) -Surgery(for females)	**Diagnosis:** - Electrolytes imbalance (hyponatremia, hyperkalemia, hypoglycemia) - High 17-OHD - High androgens

Summary:

Hyperfunction	
Hypercortisolism (cushing syndrome)	**Hyperaldosteronism (conn's syndrome)**
Causes: -ACTH dependant: pituitary tumor (cushing disease) or ectopic -ACTH independent **Clinical features:** -Moon face -Truncal obesity -Purple striae -Osteoporosis	**Causes:** - Adenoma - Hyperplasia **Clinical features:** - Secondary HTN - High Na, low K, high cl - Alkalosis
Biochemical: -24h urine free cortisol (high) -1mg DST (no suppression) -Midnight salivary cortisol (high) -ACTH measurements to know the cause	**Biochemical:** -Initial(screening) test: aldosterone/renin ratio -Confirmatory test: saline infusion test -Imaging tests:CT
Treatment: -surgical	**Treatment:** -adenoma = surgical -hyperplasia = spironolactone
pheochromocytoma	
Caused by: Tumor of adrenal medulla produces catecholamines **Clinical features:** -secondary HTN -episodic(spells): sweating, palpitation, headache **Diagnosis** -24h urine collection of metanephrines	**Management:** 1-a-blocker then B-blocker (10-14 days before operation) 2-oral NaCl (3 days before surgery) 3-surgical removal (definitive treatment)

Questions:

1. **A 21 years old male presented to the clinic with abdominal pain. blood pressure 135/85, Heart rate:100 respiratory rate:20 he was suspected to have appendicitis, so the doctor ordered a CT scan, which confirmed appendicitis which was managed but the CT showed a benign looking adrenal mass (incidentaloma).**
   which of the following is the appropriate next step in evaluation of such a mass?
   a. Fine needle biopsy of the adrenal mass for histopathology
   b. Complete Clinical evaluation for any adrenal signs or symptoms
   c. Biochemical assessment of the adrenal gland
   d. Repeat the CT scan for further evaluation

2. **A 65 years old female, known case of rheumatoid arthritis presented to clinic complaining of excessive hair growth, and increase in her body weight,the physical exam showed purple abdominal striae and several bruises,here vital signs were stable, but she had blood pressure of 150/90, the doctor ordered a 24hr urine cortisol free test, which was significantly high, but her ACTH was markedly low, what is the most likely diagnosis?**
   a. Secondary hyperparathyroidism
   b. Cushing disease
   c. Ectopic ACTH
   d. Ectopic glucocorticoids

3. **75 old male who's not known to have any chronic diseases, presented to the clinic in a regular follow up, which showed an elevated blood pressure, he was told to come later to confirm the blood pressure reading, in the next visit the blood pressure was 150/90 confirming Hypertension, the patient was completely asymptomatic,**
   which of the following choices is the most likely following step?
   a. Anti-hypertensive medication and if he shows no improvement do further evaluation
   b. Sending him for CT for cushing syndrome evaluation
   c. Doing an ACTH stimulation for adrenal insufficiency
   d. Doing an MRI for the pituitary to assess pituitary masses

4. **A 35 years old male presented to the clinic with nausea and ,fatigue. He has hypotensive and hypoglycemic and his electrolytes levels are shown below:**
   K:5.5 (normal range 3.5-5 mEq/L)
   Na:130 (normal range 136-145 mEq/L)
   And after further evaluation, his cortisol level were low even after ACTH stimulation test. Choose the best lifelong treatment for this patient?
   a. Intravenous Hydrocortisone
   b. Fludrocortisone to replace the mineralocorticoids
   c. ACTH analogues
   d. Hydrocortisone and fludrocortisone

1-b
2-d
3-a
4-d