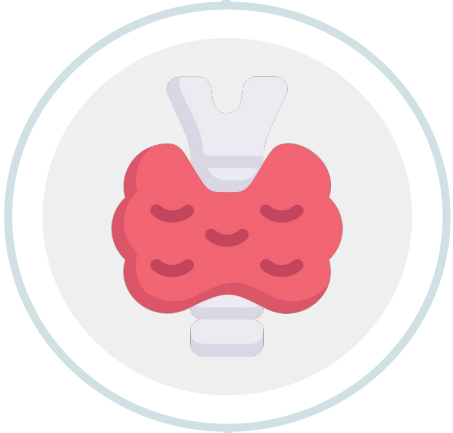
Adrenal Disorders



Objectives :

- ★ Understand anatomy, physiology and biochemistry of adrenal glands
- ★ Understand the different hormonal functions of the adrenal glands
- ★ Differentiate between different hypo-functioning and hyper-functioning states
- ★ Understand clinical approach and management of adrenal disorders, function, hyper and hypo-secretion.

Editing file

Color index

Original text
Females slides
Males slides
Doctor's notes 438
Doctor's notes 439
Text book
Important
Golden notes
Extra

Male's dr "my slides are enough for the exams"

There is a big difference between Male's and Female's slide content (female's slide is way more), here in the teamwork we combined the two.

Lecture Outline:

★ Basics review of adrenal glands

- Anatomy of the adrenal glands
- Physiology of the adrenal glands
- Biochemistry of the adrenal glands

★ Intro

- Regulation of Secretion
- Circulation of Cortisol & Adrenal Androgens
- Adrenal Disorders

★ Primary adrenocortical insufficiency (Addison's disease)

- state of inadequate cortisol and/or aldosterone production by the adrenal glands

★ Secondary/ Tertiary adrenal insufficiency

- inadequate pituitary ACTH secretion

	Primary AI (Addison's or Acute AI)	Secondary AI
Skin and Mucosa	Dark (palmar crease, extensor surface)	Pale
Potassium	High	Normal
Sodium	Low	Normal or Low
Metabolic Acidosis	Present	Absent
Associated Diseases	Primary hypothyroidism, type 1 DM, vitiligo, neurological deficits	Central hypogonadism or hypothyroidism, growth hormone deficiency, DI, headaches, visual abnormalities
Associated Symptoms	Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia GI: N/V, abdominal pain, diarrhea	Same except: No salt craving GI less common
Diagnostic Test	Insulin tolerance test Cosyntropin Stimulation Test High morning plasma ACTH	Insulin tolerance test Cosyntropin Stimulation Test Low morning plasma ACTH

★ Treatment of Adrenocortical Insufficiency

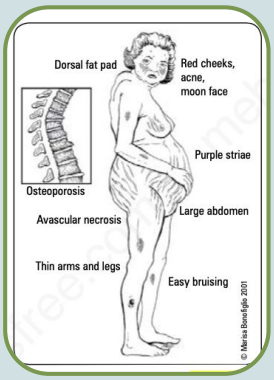
★ Acute Adrenal Crisis

- A state of acute adrenocortical insufficiency occurring in patients with Addison's disease who are exposed to the stress of infection, trauma, surgery or dehydration.

★ Congenital Adrenal Hyperplasia

★ Hypercortisolism (Cushing Syndrome)

- Results from chronic glucocorticoid excess (endogenous or exogenous sources)



★ Conn's Syndrome

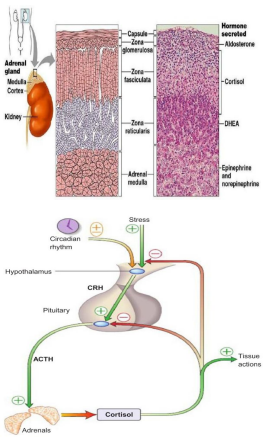
★ Pheochromocytoma

- is a nonmalignant lesion of the adrenal medulla autonomously overproducing catecholamines despite a high blood pressure

Basic Review of Adrenal Gland

◄ Anatomy of the adrenal glands:

- The two structures of the adrenal glands arise from two different germ layers: the adrenal cortex from the mesoderm and the adrenal medulla from ectoderm neural cells
- The adult adrenal glands weighs 8-10 gm and lie in the **retroperitoneum** above and medial to the upper poles of the kidneys.
- A fibrous capsule surrounds the gland. The **yellowish outer cortex** comprises **90%** of the adrenal weight and the **inner medulla** about **10%**.
- **The outer cortex has three zones: GFR**
  - **Zona glomerulosa**
  - **Zone fasciculata**
  - **Zona reticularis**
- The inner two zones function as one unit, **both producing cortisol and androgens** while the **zona glomerulosa produces mineralocorticoids.**
- The zona fasciculata and reticularis are **regulated by ACTH**, **excess** or **deficiency** of this hormone alters the structure and function of the zones i.e. both zones **atrophy** when ACTH is deficient and when ACTH is present in excess, **hyperplasia** and hypertrophy of these zones occur.

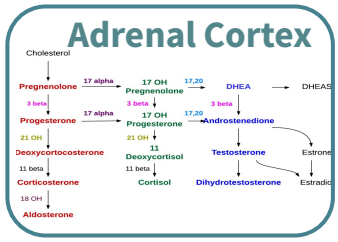


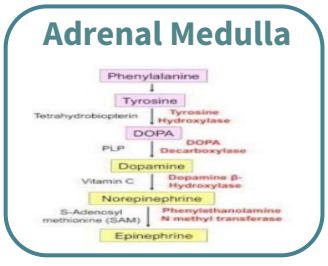
◄ Physiology of the adrenal glands:

Tissue Area	Hormones	Effect	Regulation
Zona Glomerulosa	**S**alt **Mineralocorticoids** **(aldosterone)**	**Kidney: Maintain intravascular volume and electrolytes by:** - increase reabsorption of Na+ and water	angiotensin II, (RAAS), ACTH, K+ ↑Na+
Zona Fasciculata	**S**weet **Glucocorticoids** **(cortisol)**	- Lipolysis, Increase blood sugar - One of the most important hormone in the body if there is no cortisol it will lead to hypotension if not treated lead to death.	ACTH (from pituitary gland)
Zona Reticularis	**S**ex **Androgens**	It is the main source of androgen in human But it is important in the disorders	
Medulla (Stress hormone fight or flight)	**Catecholamines** (Epinephrine (adrenaline),Norepinephrine (noradrenaline), Dopamine)	Most of the time activate sympathetic fibers and increase **(BP, HR, blood sugar)** But could present with activations of parasympathetic as pathologic disorders	-

◄ Biochemistry of the adrenal glands:

- **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**, others include ACTH and Neural Components of the adrenergic and dopaminergic systems.
- **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** (lipid)
- All adrenal **medulla** hormones are **originating from amino acid Tyrosine** (protein)





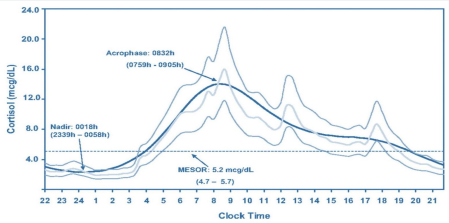
Introduction

◄ Regulation of Secretion:

1) Circadian Rhythm: Affected by psychological or physiological factors.

- Regulates both the magnitude and the number of CRH and ACTH secretary episodes.
- Cortisol secretion is low in the late evening when we go to sleep and high in the early morning where we need it the most.
- **This rhythm is changed by:**

Changes in Sleep pattern[1]	**Light-dark exposure**	**Feeding times**	**Psychological stress**	**CNS and pituitary disorders**
Cushing syndrome	**Liver disease[2]**	**Chronic renal failure[2]**	**Alcoholism**	**Certain Drugs e.g. cyproheptadine**



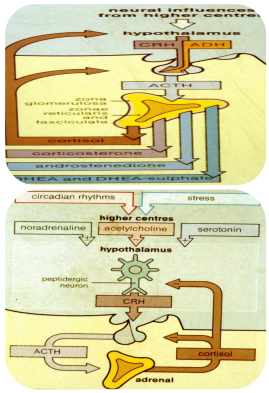
Physiological cortisol circadian rhythm

The circadian rhythm of cortisol secretion could help you in diagnosis of abnormal hormone levels, **Cortisol reaches peak levels in the early morning (8 or 10 am), and the lowest level is at night (12am).**

- If a patient has some clinical features of adrenal disorder and we **measured his cortisol level at 12PM and was very high then this is abnormal**, but if it's high in the morning then this is the normal
- **If we measure cortisol in the morning and it was very low then this is abnormal**

2) Stress:

- e.g**. surgery and hypoglycemia. It causes ACTH and cortisol** (cortisol is a very sensitive hormone to **any** form of stress) **to be secreted** within minutes of the onset of stress and this is mediated by increased CRH secretion.
- This is abolished by prior high dose glucocorticoid administration and in Cushing's syndrome.



3) Feedback inhibition:

- It occurs by glucocorticoids **both** at the **pituitary** and **hypothalamus inhibiting CRH and ACTH production** and thus further synthesis of glucocorticoids

◄ Circulation of Cortisol & Adrenal Androgens:

- Cortisol and the adrenal androgens circulate **bound to plasma proteins.**
- The plasma half life of cortisol is short (70-90 min) and is determined by the extent of plasma binding and by the rate of metabolic inactivation.
- **Cortisol binds mainly to CBG (**cortisol binding globulin or transcortin **)** = 75% and to a lesser extent to albumin = 15% and about **10% of circulating cortisol is free** and it is this **biologically active** cortisol which is regulated by ACTH.
- **Androgens except for testosterone bind weakly to albumin.** However, **testosterone** is bound extensively to a specific globulin, **sex hormone binding globulin (SHBG).**
- free cortisol level measurement is not available at all hospitals, we use total cortisol instead. So it's important to know the factors that affect CBG , Because you don't know wether the increase is caused by free cortisol or CBG.

1- people who stay up late or have night shifts
2- all chronic diseases can affect the pituitary circadian rhythm.

Introduction

◄ Circulation of Cortisol & Adrenal Androgens cont.

- ❖ can be affected by physiological or psychological factors. any condition affecting total body proteins will affect CBG levels.
- ❖ **Cortisol binding globulin** increase and decrease in:

	Increase In		Decrease In
1	**Pregnancy**	1	Familial deficiency states
2	**Oral contraceptives (OCP) users**	2	**Protein deficiency states**
3	Hyperthyroidism	3	Hypothyroidism
4	Diabetes mellitus	4	Nephrotic syndrome
5	Certain hematological disorders	5	Severe liver disease
6	Genetic familial condition	-	-

◄ Adrenal Disorders

Adrenal Disorders

Function:
- ➢ Hypersecretion
- ➢ Hyposecretion

➔ Primary and Secondary

Structural:
- ➢ Adenoma
- ➢ Hyperplasia
- ➢ Bilateral vs unilateral
- ➢ Adrenal vs extra-adrenal

◄ Evaluation of Adrenal disorders:

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

Biochemical: (To prove if he has high or low levels of that hormone).
- ➢ Screening Test
- ➢ Confirmatory Test

Anatomical:
- ➢ CT or MRI adrenal if needed (adenoma, hyperplasia, uni or bilateral, adrenal , extra-adrenal, benign or malignant)

Then Treatment

◄ Adrenocortical hypofunction:

1. **Adrenal insufficiency**
2. **Congenital Adrenal Hyperplasia**

Primary adrenocortical insufficiency (Addison's disease)

◄ Causes:

No need to memorize the causes just understand that there are many reasons for adrenal gland destruction

Causes	
Major	• **Idiopathic atrophy (autoimmune) 80%:** ○ DR. Thomas Addison in 1849, TB was the commonest cause, **now autoimmune is the most common cause.** Addison's disease is more common in women 2.6:1. It is usually diagnosed in the 3rd to 5th decade. ○ Idiopathic addison's disease is **frequently accompanied by other immunological and autoimmune endocrine disorders** e.g. **hyperthyroidism**, **hypothyroidism**, **hashimoto**, **anemia** and **gonadal failure**. One or more of these disorders is usually present in **40-53%** of patients with idiopathic addison's disease. ○ Often positive adrenal antibodies ,Could be an isolated problem or associated with other autoimmune diseases (part of polyglandular disease): ■ **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%**
Other	Adrenal glands are very small therefore any diffuse pathology will affect them like: • **Infection** (fungal: Histoplasmosis, CMV, HIV, Syphilis, ..etc) • **Infiltration** (lymphoma, Hemochromatosis, Amyloidosis, Sarcoidosis, malignancy) any metastatic disease will affect them because they're very vascular • **Iatrogenic** (Surgical adrenalectomy, Anticoagulation and hemorrhage) • **Medications:** ketoconazole, rifampin, phenytoin, Phenobarbital, Mitotane (Cytotoxic drugs), Metyrapone (Enzyme inhibitor), Aminoglutethimide. • **Hereditary and Congenital diseases:** enzyme defects, hypoplasia, congenital adrenal hyperplasia,adrenal unresponsiveness to ACTH, adrenoleukodystrophy, adrenomyeloneuropathy, Refsum disease, Wolman disease) • **Miscellaneous**: ○ Triple A syndrome= Allgrove syndrome ○ Adrenal hemorrhage and infarction ○ Radiation therapy

◄ Pathophysiology:

❖ The disease progression is usually gradual (it takes months or years) and patients will present with vague nonspecific symptoms.

❖ **There's destruction of adrenal cortex (3 layers)**

❖ Gradual adreno-cortical destruction causes decrease adrenal reserve with **normal basal steroid secretion in the initial phase but failure to respond to stress.**

❖ **Acute crises can be precipitated by stresses of surgery, trauma or infection,** delivery sometimes **which require increased corticosteroid secretion.**

❖ With further loss of cortical tissue, even **basal secretion of mineralocorticoids and glucocorticoids become deficient** leading to the manifestation of chronic adrenocortical insufficiency when **more than 90% of both adrenal cortices** occur.

❖ About **25% of cases present with a crises** or an impending one at the time of diagnosis

Primary adrenocortical insufficiency (Addison's disease)

◄ Clinical features:

❖ **The chief symptoms** of chronic primary adrenocortical insufficiency are **hyperpigmentation, weakness** and **fatigue, weight loss, anorexia,** and **gastrointestinal disturbances,** postural dizziness.

Hyperpigmentation (present in 92% of patients):

- Reversible, due to secondary **increase in ACTH and BLPH** because of **decrease** negative feedback inhibition **The generalized hyperpigmentation of the skin and mucous membranes is the earliest manifestation** and is increased in sun exposed areas and accentuated over **pressure areas** (elbows, knuckles), **palmar creases, nail beds**, nipples, areolae, and peri-vaginal and peri- anal mucosae as well as **gums and buccal mucosa** (pathognomonic, you can check the oral mucosa in ethnicly dark people)
- **Scars formed after the onset of ACTH excess become hyperpigmented.**
- **Only in Primary adrenal insufficiency** due to melanocyte stimulating hormone **(MSH)** from pro-opiomelanocortin (POMC) **Not ACTH**

Abdominal Disturbances (present in 56% of patients):

- **Especially nausea and vomiting** occur in most patients.
- Abdominal pain and constipation.
- Diarrhoea is less frequent.

Hypotension (present in 88-90% of patients):

- mineralocorticoids can be normal in the beginning but eventually the whole gland is destroyed and mineralocorticoids will be lost and the patient will get vascular instability and hypotension
- BP and HR, particularly Standing and supine. **Think about Adrenal insufficiency if not respond to IVF and initial management, or when he come with typical presentation (abdominal pain, nausea, vomiting and dark pigmentation "his relatives say he became darker in color in the past week")**
- Causes **orthostatic symptoms (present in 12% of patients).**
- Can cause syncope and in severe cases shock and death.

Hypoglycemia:

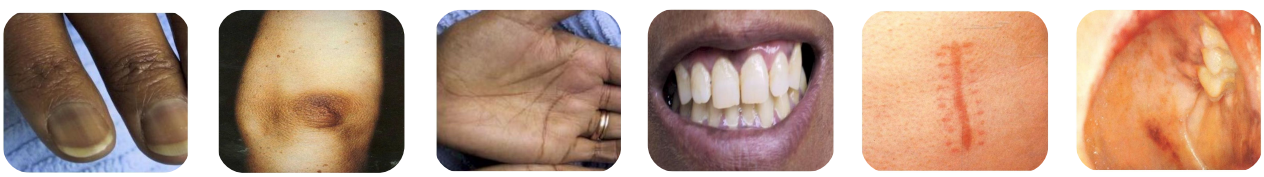
- Due to cortisol deficiency which inhibits insulin production. Severe hypoglycaemia is uncommon in adults but can be **provoked by fasting, fever, infection or nausea and vomiting.** More common in secondary.

Salt craving (present in 19% of patients):

- occurs because of sodium wasting secondary to mineralocorticoid deficiency **which can also lead to dehydration, hyponatremia, hyperkalemia, and acidosis.**

Other:

- **General weakness, fatigue, malaise, anorexia and weight loss are invariable features (present in 100% of patients).**
- **Amenorrhoea**[1] is common and can be due to weight loss and chronic illness or associated ovarian failure.
- Loss of body hair can occur secondary to deficient adrenal androgens secretion.

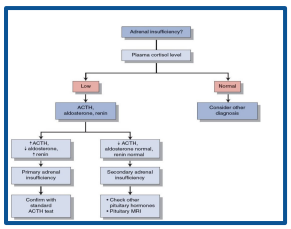


1- can be due to primary gonadal failure or secondary to chronic diseases. always ask about the regularity of the cycle since it can be affected by many conditions.

Primary adrenocortical insufficiency (Addison's disease)

◄ Laboratory Findings

- **Hyponatremia and hyperkalemia are classical in primary adrenal insufficiency,** less prominent in secondary
- There might be **normocytic anaemia** (cortisol and thyroxine are imp for normal bone marrow function and hematopoiesis), **neutropenia, eosinophilia** and relative lymphocytosis
- **Azotaemia** and increased serum creatinine is due to **volume depletion** and dehydration.
- Mild **acidosis** is frequently present because of the dehydration
- Mild to moderate **hypercalcemia**; we don't know why it happens but it's reported



◄ Biochemical Evaluation:

Measure a.m. cortisol (little value)

- ❖ **If high (>550 nmol/L) : rule out**
- ❖ **If very low : diagnosis** (random cortisol below 100 nmol/L during the day is highly suggestive)
- ❖ **If borderline result :** proceed for **confirmatory test (Rapid ACTH stimulation test):**
  - ➢ After a baseline cortisol sample is obtained a synthetic ACTH called Tetracosactrin (Synacthen) is given in a dose of 0.25mg IM. Or IV. and additional cortisol samples are obtained at 30 and 60 min following the injection.
  - ➢ **Absent or impaired cortisol response confirms the presence of hypoadrenalism** but does not differentiate Addison's disease from ACTH deficiency or iatrogenic suppression by steroid medication.
  - ➢ In hyperfunctional diseases we will try to suppress the gland while in this case we will try to stimulate it and assess it's response.

Measure ACTH Plasma levels:

- ❖ It **differentiates between primary** and **secondary** states being high in the primary form and low normal or low in secondary forms.

	Primary	Secondary (Pituitary problem)
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

◄ Anatomical Evaluation:

- ❖ **Adrenal insufficiency is clinical and biochemical diagnosis**
- ❖ No indications to do imaging unless clinically indicated such as:
  - ➢ **Patient on anticoagulation**
  - ➢ **Malignancy with metastasis**
  - ➢ **Other infiltrative disease**
- ❖ Abdominal radiograph (we don't do KUB anymore) reveal **adrenal calcification** in half the patients with **tuberculosis adrenilitis** and in some patients with **other invasive or hemorrhagic causes of adrenal insufficiency**

Secondary/ Tertiary adrenal insufficiency

◄ Causes:

- **The commonest cause of ACTH deficiency is exogenous glucocorticoid administration.**
  Prolonged use of steroids suppresses the adrenal glands)
- **Pituitary/hypothalamic tumors are the most common causes of naturally occurring pituitary ACTH hyposecretion.**
- Panhypopituitarism (congenital / acquired):
  - Tumors, surgery, radiation therapy
  - Hypothalamic / pituitary disorders
- Isolated ACTH deficiency
- Inadequate glucocorticoid replacement
- Infant born to steroid-treated mother
- Surgical removal of ACTH-producing adenoma of the pituitary gland (Cushing's disease)
- Withdrawal from glucocorticoid therapy

◄ Pathophysiology of Secondary Adrenocortical Insufficiency:

- **ACTH deficiency is the primary event** and leads to decrease cortisol and adrenal androgen secretion.
  Aldosterone secretion remains normal[1] except in few cases
- **Basal ACTH and cortisol may be normal but ACTH reserve is impaired and the response to stress is subnormal.**

- With chronicity there is atrophy of zona fasciculata and reticularis and therefore **basal cortisol secretion is decreased.**
- **At this stage, the pituitary adrenal axis is impaired and will not respond to stress and to exogenous ACTH.**

◄ Clinical features:

The clinical features may be non-specific initially unless an acute crisis occur in an undiagnosed patient, **Hypoglycemia is occasionally the presenting feature.**

The hyperpigmentation is absent because of deficient ACTH and beta lipotropic hormone (BLPH) **and** the **mineralocorticoid secretion is usually normal**, Otherwise the symptoms may be similar to primary.

- Electrolytes abnormalities are usually **absent**
- Hypotension is usually **not present** except in acute presentations.

Hyponatremia may occur **because of water retention** and inability to excrete a water load with **no hyperkalaemia.**

1- Zona glomerulosa is spared and stimulated by RAAS.

Treatment of Adrenocortical Insufficiency

◄ Treatment of Adrenocortical Insufficiency:

- Once Addison's disease is suspected, investigation is urgent. **If the patient is seriously ill or hypotensive, hydrocortisone 100 mg should be given intravenously or intramuscularly together with intravenous 0.9% saline.** Ideally this should be done immediately after a blood sample is taken for later measurement of plasma cortisol.
- Full investigation should be delayed until emergency treatment has improved the patient's condition.
- **IVF: dextrose and salt** for rehydration and to restore intravascular volume, especially if it comes as an emergency case
- **Electrolytes replacement**

Patients with Addison's disease require life long therapy usually with both glucocorticoids and mineralocorticoids.

- Ask the patient to wear bracelet or card that indicat he has AI

Steroid Replacement	

Primary Adrenocortical Insufficiency	• **Glucocorticoids (by hydrocortisone)**
	  ○ a dose of 25-30 mg/d. It is usually given as twice per day but can be given once daily or three times daily as suitable for the well being and normal energy level for each patient.
	• **Mineralocorticoids (by Fludrocortisone)**
	  ○ Fludrocortisone is the mineralocorticoid of choice. Given in 0.05-0.1 mg/day dose in the morning

secondary Adrenocortical Insufficiency	• **Glucocorticoids (by hydrocortisone only)** • In secondary hypoadrenalism fludrocortisone is rarely required.
NB: Hydrocortisone has some Mineralocorticoids activity, so if you use hydrocortisone in high IV dose, stop **Fludrocortisone.**	

Acute Adrenal Crisis

Definition

- **A state of acute adrenocortical insufficiency** occurring in patients with **Addison's disease** who are exposed to the **stress of infection, trauma**, **surgery** or **dehydration**.
- **Shock** and **coma** may rapidly **lead to death in untreated patients**

◀ Clinical Features

1	Weakness, apathy	**5**	Nausea, vomiting, anorexia
2	Hypotension and shock vascular collapse	**6**	Fever
3	Abdominal Pain	**7**	depressed mentation
4	Hypoglycemia	**8**	Dehydration and volume depletion

◀ Treatment

- It should be started as soon as possible once diagnosis suspected.
- If oral therapy cannot be taken because of vomiting or diarrhea, then medical assistance should be sought for parenteral therapy.
- The patient should be informed about life-long therapy and the need to **increase the dose of steroids during illness (should be at least doubled for minor illnesses)** and if symptoms continue, a physician should be called.
- Whenever they are under stress they should double the dose, this may include : acute viral illness.They can increase the dose for 3-5 days until the stress is gone then go back to usual dose.
- **Parenteral cortisol** is commonly used and it has sufficient mineralocorticoid activity so additional treatment is not required.
- The dose is 100 mg every 6 hrs, and the dose is gradually tapered when condition is stable.
- Maintenance therapy with oral cortisol with or without a mineralocorticoid is then given.
- **Intravenous fluids** **including glucose and saline are required to correct volume depletion**, hypotension and hypoglycemia as well as the acidosis and hyperkalemia but the shock may not respond to vasopressors unless glucocorticoids are administered.

The **5 S**'s of adrenal crisis treatment are **Salt** (0.9% saline), **Sugar** (50% dextrose), **Steroids** (100 mg hydrocortisone IV once, then 200 mg over 24 hours), **Support** (normal saline to correct hypotension and electrolyte abnormalities), and **Search** (for the underlying disorder).

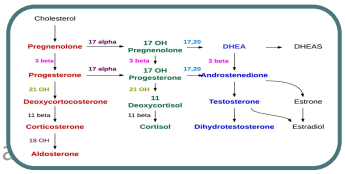
◀ Prevention

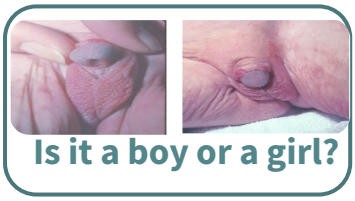
- Adrenal crisis **can be prevented** in an already diagnosed patient **by proper education** on dosage of drugs during illness.

Congenital Adrenal Hyperplasia

◄ Congenital Adrenal Hyperplasia

- Classic CAH (congenital adrenal hyperplasia) is an autosomal recessive disorder with an incidence of 1 in 7,000-15,000
- Non-Classic CAH is less severe and effects 1 in 500-1000 individuals
- 90–95% of CAH cases are caused by **deficiency of 21-hydroxylase enzyme**, which catalyses the synthesis of **cortisol** and **aldosterone** from cholesterol
- **Ambiguous genitalia (Female);** Males might go undiagnosed until they present with a salt- wasting crisis within one to three weeks of age which can lead to death
- Failure to thrive
- **Dehydration & Shock (usually male)**
- Salt-loss presentations with electrolytes imbalance:
  - **Hyponatremia, Hyperkalemia, Hypoglycemia.**
- **Hyperpigmentation**





◄ Diagnosis:

❖ **Clinical severity depends on degree of 21-hydroxylase deficiency, good genotype phenotype correlations.**

Clinical	• History and examination (B.P)
	• **Classical CAH:**
	  ○ **Simple Virilising:** Ambiguous genitalia in females
	  ○ **Salt Wasting:** Dehydration, vomiting and diarrhoea. If untreated can prove fatal
	• **Non-classical CAH:**
	  ○ Milder than classical CAH – Androgen excess can **cause precocious puberty in either sex, Males are often undiagnosed/asymptomatic,** can be easily confused with PCOS

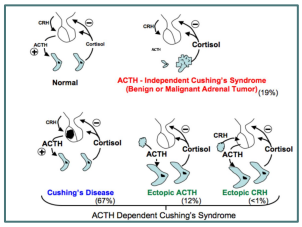
Biochemical	• Serum electrolytes & glucose:
	  ○ Low Na & high K, Fasting hypoglycemia
	  ○ Elevated serum urea due to associated dehydration
	• Elevated plasma Renin & ACTH levels
	• Low Cortisol
	• **High 17 – OHP**
	• **High androgens** especially testosterone level
	• Low Aldosterone (in salt losing types only)

◄ Management:

❖ **Hydrocortisone**: 10-20 mg/m2/day divided into three doses. Adult usually 10-5-5 mg
  ➢ Glucocorticoids which suppress ACTH, are used to reduce the levels of adrenal sex steroids in the blood
❖ **Fludrocortisone** 0.05 - 0.2 mg/day
  ➢ Individuals with salt wasting CAH also require mineralocorticoids and sodium chloride supplements
❖ **During adrenal crisis** intravenous hydrocortisone 50-100 mg Q 6-8 hrs
❖ **IVF** D5 0.9% saline
❖ **During fever or sickness 2-3 fold increment in hydrocortisone dose,** also the patient should have a card or a bracelet indicating that he have adrenal insufficiency,
❖ **In vomiting or diarrhea**, parental therapy is indicated
❖ **Medical Alert:** bracelet
❖ Surgery on virilised females, Growth monitoring to detect over and under treatment.
❖ Dexamethasone can be used to prevent/reduce prenatal virilisation. Side effects for the mother include weight gain, irritability and oedema

Adrenocortical Hyperfunction

◄ Adrenocortical Hyperfunction:



A. Hypercortisolism (Cushing syndrome):

❖ Chronic glucocorticoid excess whatever the cause leads to a constellation of symptoms and physical features known as Cushing's syndrome, first described by Cushing in 1932.

★ The most common cause is iatrogenic i.e. secondary to chronic steroid ingestion.

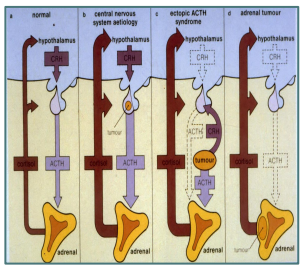
Others causes are:

- ACTH dependent (↑ACTH): (Cushing's disease 68% or Ectopic ACTH syndrome 15%)
- ACTH independent (↓ACTH due to –ve feedback): (Iatrogenic, adrenal adenoma 9% or carcinoma 8%)

B. Hyperaldosteronism

Hypercortisolism (Cushing Syndrome)

◄ introduction



Cushing's disease:

- Is defined as the specific type of Cushing's syndrome due to excessive pituitary ACTH secretion and loss of the normal feedback mechanism of the HPA axis (commonly secondary to an adenoma)
- Women to men ratio is 8:1 and the age of diagnosis is usually between 20-40 yrs.

Ectopic ACTH syndrome:

- **Non-pituitary tumors secrete biologically active ACTH**. It is more common in men, female to male ratio is 1:3 with the peak incidence at the age of 40-60 years, usually malignant. **It is most common with oat-cell carcinoma of the lung** (50% of the cases) but other tumors, e.g. **pancreatic cell tumors, carcinoid tumors**, etc. can cause it.

Glucocorticoid producing adrenal adenomas and carcinomas (very rarely)**:**

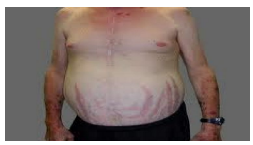
- Arise spontaneously and they are autonomous and not under pituitary hypothalamic control.

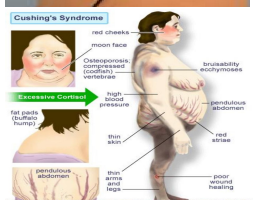
Hypercortisolism due to other causes (also referred to as pseudo-Cushing's syndrome)

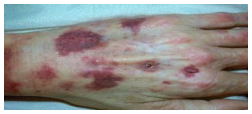
- Alcohol excess (biochemical and clinical features)
- Major depressive illness (biochemical features only, some clinical overlap)
- Primary obesity (mild biochemical features, some clinical overlap)

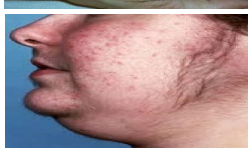
★ Signs & Symptoms:

Obesity	• **The most common manifestation** and is classically **central (truncal) affecting mainly the face (moon faced)** with a plethoric appearance, neck, trunk, and abdomen with relative sparing of the extremities; distal extremities and fingers are slender • supraclavicular and dorsal cervical fat pads "**buffalo hump**"
Skin Changes	• There is **thinning of the skin** (pathognomonic) because of atrophy of the epidermis and underlying connective tissue and facial plethora. • They also have **striae which are classically,** dark, **red to purple** and large > 2 cm may appear on the abdomen and are due to loss of connective tissue support as well as **easy bruising.** • **Minor wound heal slowly** and they have frequent mucocutaneous fungal infections. • **Hyperpigmentation is common in the ectopic ACTH:** while ACTH-secreting pituitary tumours retain some negative feedback sensitivity to cortisol, this is absent in tumours that produce ectopic ACTH, typically resulting in higher levels of both ACTH and cortisol than are observed in pituitary-driven disease.









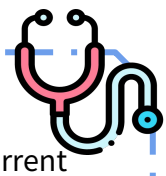
Hypercortisolism (Cushing Syndrome)

◄ Signs & Symptoms Cont.

Hirsutism	• **Facial hirsutism** is most common but it can occur anywhere in the body. • **It is due to the hypersecretion of adrenal androgens.** • **Acne** and seborrhea usually accompany the hirsutism. • Virilism is rare and occur in adrenal carcinoma.
Hyper-tension	• It is a classical feature in Cushing's syndrome and its complications contribute greatly to the morbidity and mortality in the disease; excess cortisol at the renal level works as a mineralocorticoid which causes high Na an low K
Gonadal Dysfunction	• This is very common as a result of elevated androgens and cortisol, e.g. **amenorrhoea**, infertility, decreased libido.
Psychological Disturbances	• Symptoms range from mild irritability to anxiety, depression, poor memory and concentration to euphoria and mania as well as sleep disorders. • Severe depression and psychosis as well as hallucinations and paranoia can occur.
Muscle wasting and weakness	• **Commonly proximal** and more prominent in the lower limbs. • Distal extremities and fingers are slender
Osteoporosis	• A common complication presenting with back pain, and pathological fractures can occur in severe cases; cortisol causes osteoclast activation
Renal Calculi	• Occur secondary to hypercalciuria and renal colic may occasionally be a presenting complaint.
Thirst and Polyuria	• Occur secondary to development of diabetes mellitus but **asymptomatic glucose intolerance is much more common.** mainly because of the electrolyte abnormality

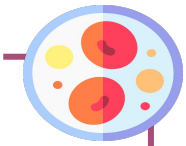
◄ Diagnosis

Clinical:



- Function : Hirsutism, acne, easy bruising, DM, HTN, irregular period, proximal weakness, recurrent infections, depression, fractures
- O/E: hirsutism, acne, moon face, central obesity, stria, proximal weakness, supraclavicular fat pad.

Laboratory:



- **High normal hemoglobin and hematocrit** are usual with lymphocytopenia and depressed eosinophils count.
- **Hypokalemic alkalosis may occur in the setting of ectopic ACTH production.** Most patients have secondary
- **Hyperinsulinism and abnormal glucose tolerance tests while some have fasting hyperglycemia or clinical diabetes mellitus**

Hypercortisolism (Cushing Syndrome)

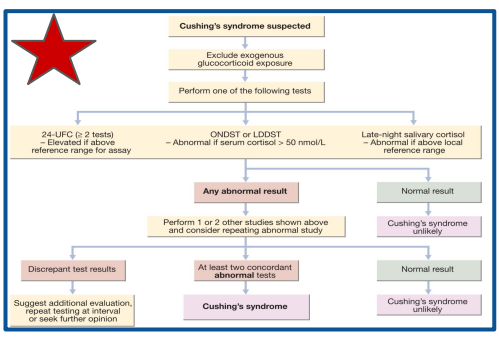
◄ Diagnosis Cont.

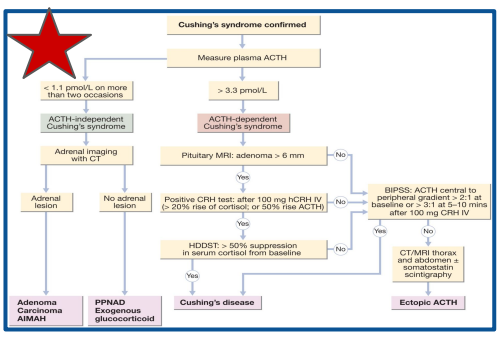
Biochemical:

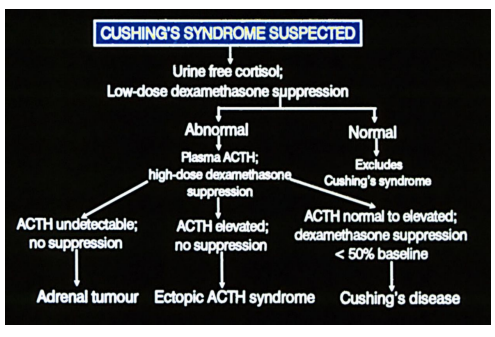
Cortisol & ACTH	• **High cortisol** which is random and episodic with loss of normal circadian rhythm . • **High ACTH** (ACTH dependent) and low if (non-ACTH dependent). • **In Cushing's disease, ACTH is normal or modestly elevated while in the ectopic syndrome, it is markedly elevated. In adrenal tumors, ACTH is undetectable.**
24- hour urinary free cortisol (UFC)	• a very sensitive test and **Is an excellent method for diagnosis of Cushing's syndrome** and in differentiating it from other forms of hypercortisolism, e.g. obesity.
Midnight salivary cortisol	High cortisol level at night
Dexamethasone Suppression Tests (1MG DST) **(establish the presence of a Cushing's syndrome regardless of the cause. It assesses feedback inhibition of the hypothalamic pituitary adrenal axis which is abnormal in Cushing's syndrome).**	**Overnight 1 MG Dexamethasone suppression test (A screening test):** • If the test is positive in the absence of conditions causing false positive results (pseudo-cushing's). e.g. **alcoholism**, **depression**, and **drugs**, then the diagnosis should be confirmed by other tests.
	LOW DOSE TEST: • Dexamethasone 0.5 mg is given every 6 hours for two days. Plasma cortisol level should suppress after the last dose
	Overnight high dose Dexamethasone suppression test: • A simple fast test – The AM cortisol after 8 mg of Dexamethasone given the night before should reduce to less than 50% of the baseline value
	TWO-DAY HIGH DOSE TEST: • Dexamethasone 2 mg every 6 hours is given for two days Serum and urine cortisol should suppress to less than 50% the baseline values.

Anatomical:

- **If ACTH:**
  - **high: MRI pituitary**
  - **low: history then CT adrenals**
- CT scanning will help in localizing pituitary and adrenal tumors and in some instances, ectopic ACTH production.
- Small tumors may be difficult to detect and selective venous sampling may be needed. In some cases, more detailed isotope scanning and **arteriography or venography may be needed.**







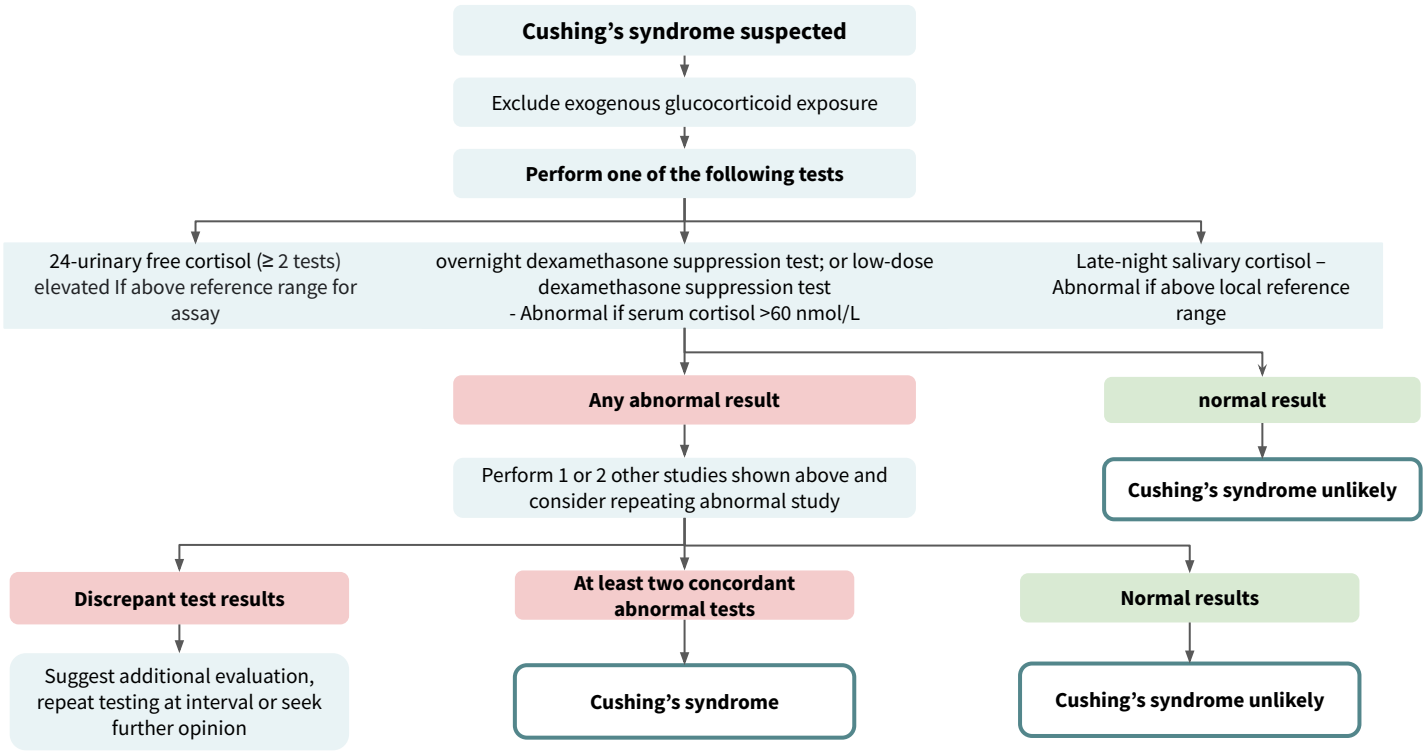
Hypercortisolism (Cushing Syndrome)

◀ Diagnosis Cont.

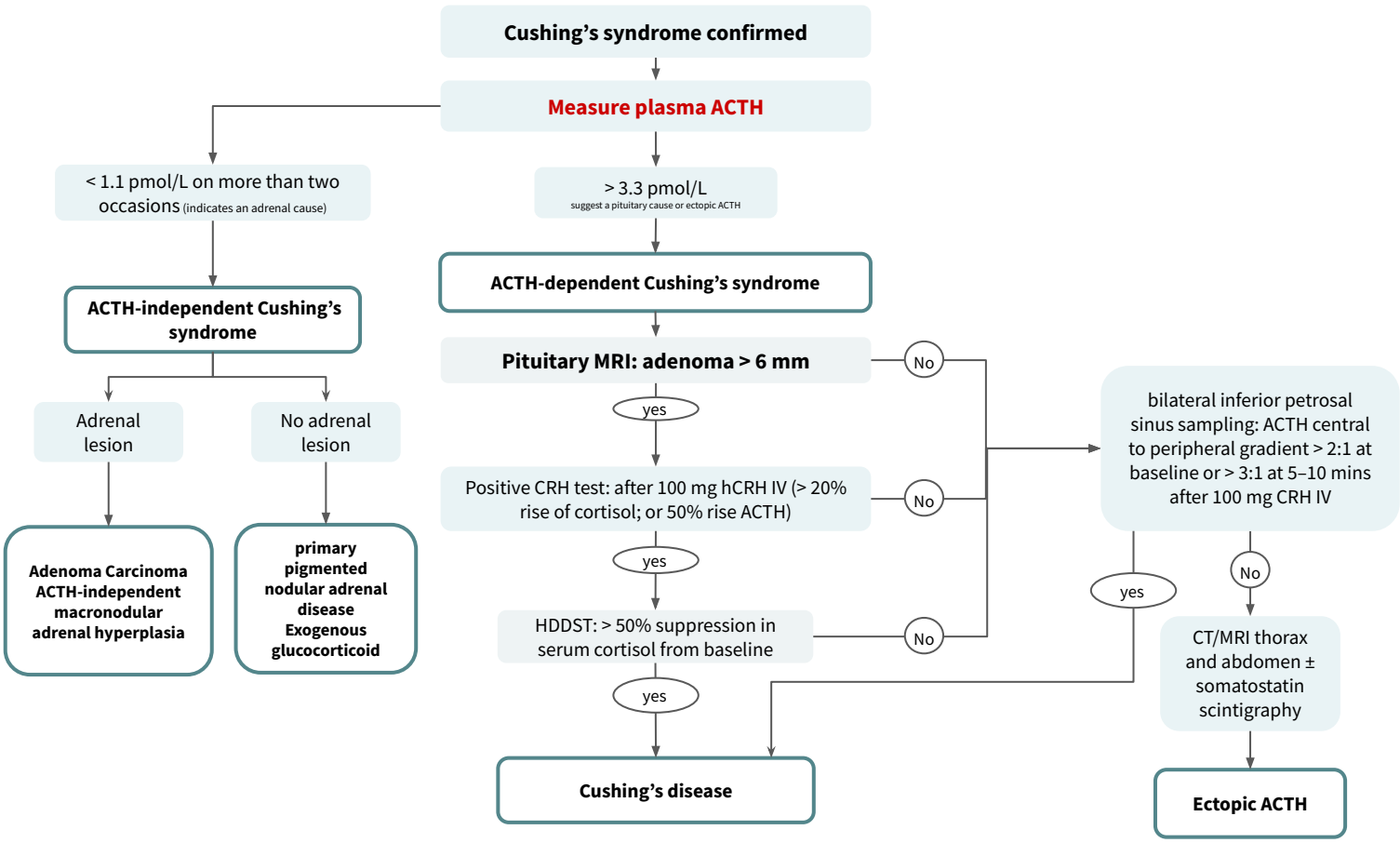
Check MedEds High-Yield Summary for a simplified version

Testing for Cushing's syndrome should be avoided under conditions of stress, such as an acute illness, because this activates the HPA axis, causing potentially spurious results. The diagnosis of Cushing's is a two-step process:

1. **to establish whether the patient has Cushing's syndrome**



2. **to define its cause**



Hypercortisolism (Cushing Syndrome)

◄ Treatment:

Surgical:

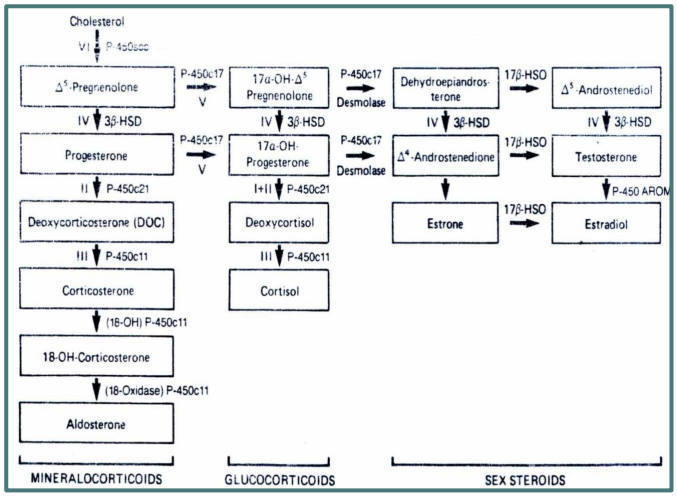
Hypercortisolism has a lot of complications and can be fatal if left untreated.

- **Adrenal tumours:**
  - **Adenomas are successfully treated by adrenalectomy** while this treatment for carcinoma is usually unsuccessful and medical therapy can control hypercortisolism in these patients
- **Ectopic ACTH syndrome:**
  - **Therapy is directed at removal of the tumour which is only successful in the benign tumours** otherwise drugs that block steroid synthesis can be used, e.g. **Metyrapone** and **mitotane** with steroid replacement if necessary.
- **Cushing's disease:**
  - Treatment is directed at control of ACTH hypersecretion by the pituitary and available methods include:
    - Microsurgery -**Trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice.**
    - Radiotherapy
    - Pharmacological inhibition of ACTH secretion

Medical:

Drug	Mechanism Of Action
Mitotane	acts by inhibiting cortisol synthesis through inhibiting the **P450 enzyme responsible for 11B hydroxylation.**
Metyrapone	The usual drug , also blocks cortisol synthesis by **inhibiting 11B hydroxylase action and also the cholesterol side-chain cleavage.**
Ketoconazole	is a potent **inhibition of the P450 enzymes** with a **principle effect on the 17-20 lyase enzymes but it also inhibits 11B hydroxylase, 18 hydroxylase and cholesterol side-chain cleavage.**

- **When hypercortisolism cannot be cured with surgery, give mifepristone.** Mifepristone inhibits cortisol receptors throughout the body.
- **When adrenal cancer cannot be fully resected or there is metastatic disease that can't be identified, give mitotane.**



Hyperaldosteronism

◀ Causes of mineralocorticoid excess:

Cause	Renin	Aldosterone	Example
Primary hyperaldosteronism	Low	High	**Conn's syndrome**, Idiopathic bilateral adrenal hyperplasia
Secondary hyperaldosteronism	High	High	Inadequate renal perfusion (diuretic therapy, cardiac failure, liver failure, nephrotic syndrome, renal artery stenosis)
Non-aldosterone-dependent activation of mineralocorticoid pathway	Low	Low	Ectopic ACTH syndrome

Conn's Syndrome

◀ Causes:

Primary hyperaldosteronism

- Adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex
- rarely, adrenal carcinoma
- Bilateral adrenal hyperplasia; idiopathic AH
- Indeterminate hyperaldosteronism, Dexamethasone suppressible hyperaldosteronism.

◀ Clinical Features:

1

- The clinical picture may mimic CAH from of 11 α-hydroxylase deficiency
- Expansion of the extracellular fluid volume and **Secondary HTN**

2

- Patient usually come to medical attention because of symptoms of **hypokalemia or detection of previously unsuspected hypertension.**

3

- If potassium depletion is severe with **alkalosis**, there is increased thirst and polyuria and maybe paresthesia, (secondary to hypokalemia).
- Headache is a frequent complaint.

4

- There are no characteristic symptoms and often nonspecific complaints, e.g. **tiredness, lethargy, weakness, nocturia and symptoms of potassium depletion.**

5

- Blood pressure can range from borderline to severe hypertensive levels.

Cases from doctor notes:

- 80 year old came to the hospital and he has a BP of 150/100, must likely he has essential HTN.
- if a 20 year old has high BP then i must rule out secondary causes of HTN e.g. hyperaldosteronism
- ★ if a 70 year old has HTN and **didn't respond to multiple medications** then i must rule out secondary causes of HTN e.g. hyperaldosteronism.

Conn's Syndrome

◄ Clinical Features Cont.

6

Accelerated/malignant hypertension is rare and a postural fall in blood pressure without reflex tachycardia is observed in severe potassium depletion because of blunting of the baroreceptors.

7

- **A positive trousseau or chevostek sign may suggest alkalosis with severe potassium depletion;** alkalosis causes pseudohypocalcemia

8

- **Retinopathy** is mild with hemorrhages being rare.
- The ECG shows signs of modest LVH and potassium depletion.

◄ Laboratory Findings:

- Because aldosterone biosynthesis is intensified, the entire biosynthetic pathway becomes activated and precursors like DOC, corticosterone, and 18-hydroxycorticosterone are present in increased amount in person with an aldosterone producing tumor.
- **There is no abnormalities in cortisol production, plasma cortisol levels or cortisol metabolism.**
- **Diuretics should be stopped three weeks prior to potassium measurement.**
- **A high serum sodium** in the presence of reduced haematocrit value (due to increased extracellular fluid and plasma volume from sodium retention).
- **There is also failure to concentrate urine.**
- High Chloride
- **Alkalosis**

★ **High Aldosterone.**

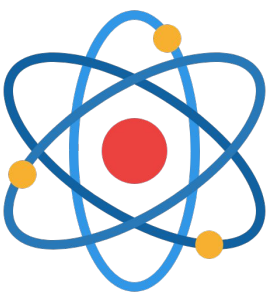
- Increased total body sodium content that leads to **suppression of renin production.**

Potassium depletion occur decreasing the total body and plasma concentration of potassium and **producing alkalosis.**

low K (episodic weakness, Paresthesias, transient paralysis, tetany, nephropathy with polyuria and polydipsia)

With moderate potassium depletion. There is decreased carbohydrate tolerance and **resistance to antidiuretic hormone.**

If **hypokalemia** is documented, **the next step** is to **assess the renin angiotensin system** by doing a **random plasma renin activity** level and if normal or high in the absence of diuretics therapy, then primary aldosteronism is very unlikely **but if it is suppressed**, then **primary aldosteronism** is a likely diagnosis.



Conn's Syndrome

◄ Laboratory Findings Cont.

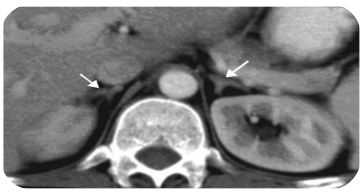
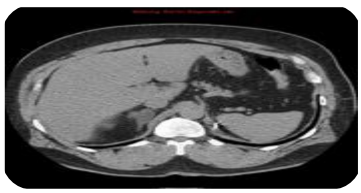
Screening test	Confirmatory test

• **aldosterone/renin ratio**
  ○ If high: do confirmatory test
  ○ If low: look for secondary causes
	• **Saline infusion test** (elevated aldosterone confirms the diagnosis)
	• **Oral salt loading test**
	• **Captopril test**
	• **Fludrocortisone suppression test**

Measurement of Aldosterone (both plasma and urinary): Very sensitive

- ❖ Aldosterone measurement should be performed while the patient is taking a high salt diet with sodium chloride supplementation.
- ❖ Assessment of aldosterone production can be best done by **measurement of urinary aldosterone excretion over 24 hour period and it is superior to plasma aldosterone measurement in detecting abnormal production of aldosterone but cannot discriminate between adenoma and hyperplasia. While the plasma levels can differentiate between the two conditions in most cases.**

◄ Radiological Findings:

Localization of Adenoma/Carcinoma	Anatomical (CT Adrenal)
• **Scanning** using I.V. Administered 1^3 iodocholesterol locates tumour in 80% of the cases depending on the size of the tumour. • **NP59 scan** is another scan which consumes less time. • **CT** scanning is also useful with less radiation hazard. • **MRI** • Other methods include **adrenal venography**, adrenal vein catheterization and bilateral sampling of blood for aldosterone measurements.	 Mercedes sign or inverted Y-shape  Tumor in the adrenal gland (adenoma secreting aldosterone and we will do surgery for it)

◄ Treatment:

- **Adrenal hyperplasia (if bilateral) → Spironolactone**
  - antihypertensive medication should be given as surgery will not ameliorate the hypertension.
- **Adenoma (if unilateral) → unilateral adrenalectomy**
  - **Adequate potassium replacement and adequate extracellular volume expansion** with adequate control of BP before surgery all of which can be achieved by spironolactone with or without other medications which should be given for some time before surgery.
  - The surgical cure of hypertension associated with adenoma is excellent as is reported to be over 50% in many series with reduction of hypertension in the remainder.

Pheochromocytoma

Definition

- Pheochromocytomas are tumors arising from the **chromaffin cells** in the sympathetic nervous system.
- **They release epinephrine or norepinephrine (or both) and in some cases, dopamine into the circulation.**

◄ Characteristics:

- Adenoma of adrenal **medulla** and activates sympathetic nervous system.
- **50%** are silent. (NO symptoms)
- Pheochromocytoma may occur as a heritable disorder either alone or in combination with other endocrine tumours, e.g. MEN type II A – hyperparathyroidism, pituitary adenoma and medullary thyroid carcinoma or MEN Type II B – pheochromocytoma with mucosal neuroma.
- **Secondary HTN**
- Only 0.1% of hypertensive patients have pheochromocytoma but recognition is important because it can be fatal during delivery or surgery if unrecognized and not properly treated.
- **Episodic (spells): sweating, palpitation, headache**

◄ The role of 10:

- 10% **bilateral**
- 10% **Familial**
- 10% **Malignant**
- 10% **Extra adrenal**

❖ **Common extra adrenal sites and near the kidneys and the organ of Zuckerkandl.**
❖ **They can also occur in the posterior mediastinal region.**

◄ When you should think about Pheochromocytoma ?

❖ **Typical symptoms (tachycardia, palpitations, sweating, headache and high blood pressure)**
❖ **Secondary HTN:**
  ➢ **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
  ➢ If there is HTN ,you should R/O hyperaldosteronism also

Pheochromocytoma

◄ Clinical Manifestation:

General	• Most patients have symptoms that vary in intensity and are perceived to be mainly **episodic or paroxysmal** by about half the patients. • Patients with persistently secreting tumors and chronic symptoms usually experience the symptoms complex in response to transient increases in the release of catecholamines. • In addition, they have **increased metabolic rate** with **heat intolerance, increased sweating** with **weight loss. There is also hyperglycemia and glucose intolerance.**
Frequency of attacks	• **The attacks in pheochromocytoma in those patients with paroxysmal symptoms** occur several times a week or oftener and last 15 minutes or less but they may occur at intervals of months or as often as 25 times a day and may last minutes to days. With time the attacks usually increase in frequency but do not change much in character.
Precipitating factors	• They are usually precipitated by activities that compress the tumor, e.g. changes in position, exercise lifting, defecation or eating and by emotional distress or anxiety, even coughing or sneezing or abdominal examination.
Hypertension	• Most patients with persistent hypertension also have **superimposed paroxysms** and only few patients are entirely free of symptoms and hypertension between attacks and give no evidence of catecholamine excess during these intervals.

◄ Symptoms during or following paroxysms:

- **In the attack the symptoms resemble those produced by injection of epinephrine or norepinephrine.**

1	Fatigue or exhaustion	**7**	Forceful heartbeat with or without tachycardia
2	Tremor	**8**	Sweating
3	Visual disturbances	**9**	Cold hands and feet
4	Abdominal or chest pain	**10**	Anxiety or fear of impending death
5	Headache	**11**	Nausea and vomiting
6	Increased sweating	**12**	weight loss, constipation

Pheochromocytoma

◀ Symptoms Between paroxysms:

1

When there's a metabolic derangement like diabetes and hypertension you should suspect secondary cause and look for hormonal disturbance including hypercortisolism , pheochromocytoma or conn's disease.

2

The intense alpha-recepto-mediated peripheral vasoconstriction **causes cool, moist hands** and feet and facial pallor.
This combination of increased cardiac output and vasoconstriction causes marked **elevation of the blood pressure**. The decreased heat loss and increased metabolism cause a **rise in temperature** and **flushing** and leads to **reflex sweating** which may be profuse and usually follows the cardiovascular effects.

3

- The increased **glycolysis** and **alpha receptor mediated inhibition of insulin** release cause an increase in blood sugar levels.
- **Hypertension is usually present and characteristically there is wide fluctuations and an episode of marked hypertension might be followed by hypotension and shock.**

4

- **The blood pressure typically does not respond to commonly used antihypertensive medications.**
- Chronic constriction of the arterial and venous beds leads to reduction in plasma volume and the inability to further constrict the bed upon arising causes the **postural hypotension** that is characteristically observed.

5

Patients with persistent symptoms and hypertension may develop **hypertensive retinopathy or nephropathy** as well as the other sequelae of hypertension.

6

A mass is felt in the neck or abdomen and palpation may produce a typical paroxysm.

7

CVA, CCF and MI are all observed. A significant number were found to have myocarditis post partum.

◀ Other causes of increased sympathetic activity

- **Other causes of increased sympathetic activity must be thought of:**

1	**Angina** due to coronary vasospasm	4	Severe anxiety state
2	Hypertension, Thyrotoxicosis	5	Menopausal hot flushes
3	Hypertensive crises associated with: Paraplegia, Tabesansalis, Lead poisoning, Acute porphyria		

Pheochromocytoma

◄ Diagnosis

The diagnosis of pheochromocytoma should be considered in the following patients:

A. **Patients with paroxysmal symptoms**
B. **Children with hypertension**
C. **Adults with severe hypertension not responding to therapy.**
D. Hypertensive patients **with diabetes or hyper-metabolism.**
E. Hypertensive patients with symptoms resembling the **symptom complex** described above or can be **evoked by exercise position change** .. ect. or certain antihypertensive medications.
F. Patients who become severely hypertensive or go into shock during anesthesia, surgery or obstetric delivery,
G. Patients who have disorders sometimes associated with pheochromocytoma, e.g. **neurofibromatosis, mucosal adenomes, medullary carcinoma of thyroid** or those who have first degree relatives who have pheochromocytomas or other manifestations of MEN.

➢ Ganglioneuromas and neuroblastomas can produce catecholamines with dopamine being the major product leading to a similar picture resembling pheochromocytoma.

◄ Laboratory Diagnostic Test:

- In patients with continuous hypertension or symptoms, levels of plasma or urinary **catecholamines and their metabolites** are usually clearly increased, the difficulty arises in patients having brief and infrequent paroxysms with symptom-free intervals and in such cases, **sampling of blood or urine should be done during a carefully observed episode to confirm the diagnosis.**

COMPOUND	Characteristic
Metanephrin Normetanephrin (Blood /Urine)	• **The best initial test is the level of free metanephrines in plasma.** • 24 hr urine collection of Metanephrines(2X) **(Confirmatory Test).** • Make sure about medications that affect the result of the test (false positive) • Increased by catecholamines, MAOI and others. • **high levels are diagnostic for pheochromocytoma**
Vanilly Mandelic Acid (VMA) (Urine)	• Increased by catecholamines and food that contain vanillin or L-dopa. Decreased by Clofibrale and MAOI.
Catecholamines (Blood/Urine)	-
Epinephrine Norepinephrine Dopamine (Urine)	• May be increased with highly fluorescent compounds, e.g. tetracycline, quinidine as well as food and drugs containing catecholamines, e.g. bananas and other drugs, e.g. methyldopa, ethanol. Make sure about medications that affect the result of the test (false positive)

Pheochromocytoma

◄ Anatomical Evaluation:

- **Once the diagnosis has been established, the tumor must be located prior to surgical removal.**
- **CT scanning** gives better results than sonography or other radiological tests. (CT scan = MRI).
- **MRI is evolving as very specific and excellent technique for detecting pheochromocytomas.**
- Analysis of blood samples obtained for venous drainage can be of great value in locating small tumours in unusual locations.
- **MIBG (meta-iodo-benzyl-guanidine)** can detect even the smallest tumour but not all pheochromocytomas produce detectable images and other tumors e.g. neuroblastoma give positive images, MIBG if:
  - Paraganglioma
  - Young
  - Large size
  - malignant features
- Genetic Tests:
  - N.B: 30-40% of Pheochromocytoma and Paraganglioma Have positive genetic test. (not 10%)

◄ Treatment

❖ Treatment is directed toward:

1. **Reduction of symptoms**
2. **Lowering of BP**
3. **Amelioration of paroxysms**

- **Therapy with alpha adrenergic antagonists should be instituted.** Such treatment will allow expansion of the vascular bed and plasma volume.
- Agents commonly used include **phentolamine** and **phenoxybenzamine**, small doses of **propranolol** maybe required for marked tachycardia or arrhythmia prior or during surgery.
- Therapy with **phenoxybenzamine can be used as a diagnostic test** in the occasional patient in whom the chemical tests are inconclusive. A good response in the nature and frequency of attacks as well as on BP indicates the need for re-evaluation of the patient with a strong suspicion for pheochromocytoma.

❖ Surgery

- Patients should be fully prepared medically prior to surgery to avoid intra and postoperative complications.
- **Once the tumor is removed, the blood pressure usually falls and I.V. fluids and / or blood might be needed to restore circulatory volume.**
- Persistence of high BP after surgery should alert physician to look for other causes, e.g. renal vascular hypertension.

- **Before the patient goes to surgery we need to:**

Control HTN:
  - ➢ **α-blocker[2] then B-Blocker** (10-14 days before operation)
  - ➢ Ca-blockers: can be used

Salt loading[1]:
  - ➢ Oral NaCl: 3 days
  - ➢ Or IVF 0.9% saline 1-2 days before surgery

- **Surgical removal**
  - ➢ **Surgical tumor resection** with early ligation of venous drainage is the **treatment of choice.**
  - ➢ Ligation lowers the possibility of catecholamine release/crisis by tying off drainage.

1- 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
2- Phenoxybenzamine is an alpha blocker that is the **best initial therapy of pheochromocytoma**. Calcium channel blocker and beta blockers are used afterward.

Extra

◀ Case study 1

A 32-year-old Caucasian woman was seen because of a 40 pound weight gain over the last two years. Patient has been having headaches and has been emotionally labile. She complained of generalized weakness, irregular and infrequent menstrual periods and has noticed some hair growth
BP= 160/100 mm/Hg. Generalized obesity with slight centripetal distribution. Height= 5'6", weight = 185 pounds.

- Face slightly rounded and plethoric, dark hair present on the chin, upper lip and legs, acne marks present.
- Abdomen - obese with violaceous striae on the lower abdomen and in the axillary region.
- CNS - Depressed mood, some muscle wasting.
- Extremities - some ecchymoses on arms and thighs.

Sodium = 140 mM/L (n = 136-146), potassium = 3.5 mM/L (n = 3.5-5.3), chloride = 98 mM/L (n = 98-108), glucose = 214 mg/dl (n = 70-110).

1. **What is the clinical diagnosis? What clinical manifestations help to determine this diagnosis?**
   - Cushing's syndrome. weight gain (with centripetal fat distribution in the subcutaneous tissues of face and neck, mediastinum, peritoneum,) depression, mild hirsutism,muscle weakness , hypertension, hyperglycemia, skin changes
2. **What initial test(s) can be done to assess this condition?**
   - **24-hour urine free cortisol (UFC)** which assesses the integrated plasma free cortisol centrations during a 24-hour period that is filtered by the kidney. Normal is less than 100 mcg/24 hours (although in assays of greater specificity it is less than 50 mcg/24 hours). .
   - **Overnight 1 mg Dexamethasone suppression test** whereby 1 mg DEXA given p.o. at 11 p.m. and an 8 a.m. plasma cortisol > 5 mcg/dl suggests Cushing's syndrome.
3. **What is the differential diagnosis after the screening test(s) has confirmed your clinical diagnosis**
   - ACTH dependent Cushing's syndrome.
   - ACTH independent Cushing's syndrome.
   - Pseudo Cushing's syndrome

◀ Case study 2

a 21 year old Caucasian male who lives with his parents, reports ta gradual onset of weakness and fatigue,. he complained of unusual frequent diarrhea, a craving of salty foods, decreased appetite, joint pain, and that his tan was lasting longer than usual.He reported a slight decrease in his weight and not being hungry nearly as often. He states his parents are worried because he is quick to become irritated with them and rarely comes out of his room when at home.

1. **What is the clinical diagnosis?**
   - Adrenal insufficiency
2. **What initial test(s) can be done to assess this condition?**
   - Measure a.m. cortisol
3. **What therapeutic strategy would you recommend?**
   - Replacement doses of glucocorticoid
   - Patients with primary adrenal insufficiency will also require mineralocorticoid e.g., fludrocortisone
   - Medic Alert bracelet/chain.
   - Regular physician follow up.
4. **How do you differentiate between primary and secondary adrenal insufficiency**
   - Cosyntropin Test

Summary

<table>
<tr><th colspan="4">Primary adrenocortical insufficiency (Addison’s disease)</th></tr>
<tr><td>Causes</td><td colspan="3">Major:
● Autoimmune (The most common cause)
○ 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
Minor:
● Infection, Infiltration, Iatrogenic, Medications, Hereditary, Miscellaneous.</td></tr>
<tr><td rowspan="2">Evaluation</td><td>Clinical</td><td>Biochemical</td><td>Anatomical</td></tr>
<tr><td>Weakness, Tiredness, Fatigue. Nausea, Vomiting, Constipation, Abdominal pain, Diarrhea and weight loss, Hyperpigmentation, Fasting hypoglycemia, Hypotension, Shock and death.</td><td>Measure a.m. cortisol:
● If high: rule out
● If very low : diagnosis
● If borderline result : proceed for confirmatory test (ACTH stimulation test)</td><td>No indications to do imaging unless clinically indicated such as:
● Patient on anticoagulation
● Malignancy with metastasis
● Other infiltrative disease</td></tr>
<tr><td>Treatment</td><td>● IVF: dextrose and salt
● Electrolytes replacement</td><td>Steroid replacement for primary adrenocortical insufficiency:
● hydrocortisone
● Fludrocortisone</td><td>Steroid replacement for secondary adrenocortical insufficiency:
● hydrocortisone only</td></tr>
<tr><th colspan="4">Secondary/ Tertiary adrenal insufficiency</th></tr>
<tr><td>Causes</td><td colspan="3">Panhypopituitarism (congenital / acquired), 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.</td></tr>
<tr><th colspan="4">Congenital Adrenal Hyperplasia</th></tr>
<tr><td>Clinical Features</td><td colspan="2">● 90–95% of CAH cases are caused by 21- OHD
● Ambiguous genitalia (Female)
● Failure to thrive
● Dehydration & Shock (usually male)</td><td>● Salt-loss presentations with electrolytes imbalance:
○ Hyponatremia
○ Hyperkalemia
○ Hypoglycemia
● Hyperpigmentation</td></tr>
<tr><td>Diagnosis</td><td colspan="3">Clinical:
● History and examination (B.P)
Biochemical:
● Low Na & high K, fasting hypoglycemia, elevated serum urea, elevated plasma Renin & ACTH levels, low Cortisol, <u>High 17 – OHP, High androgens</u> especially testosterone level, Low Aldosterone (in salt losing types only).</td></tr>
<tr><td>Treatment</td><td colspan="3">Hydrocortisone, Fludrocortisone, During adrenal crisis (intravenous hydrocortisone), IVF D5 0.9% saline, In vomiting or diarrhea (parental therapy is indicated), Medical Alert: bracelet.</td></tr>
</table>

Summary

<table>
<tr><th colspan="4">Hypercortisolism (Cushing Syndrome)</th></tr>
<tr><td>Signs & Symptoms</td><td colspan="3">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 and osteoporosis.</td></tr>
<tr><td rowspan="2">Investigation</td><td>Clinical</td><td>Biochemical</td><td>Anatomical</td></tr>
<tr><td>• 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,</td><td>• High cortisol
• High ACTH (ACTH dependent) and low if (non-ACTH dependent).
• 24hrs for UFC
• 1MG DST
• Midnight salivary cortisol</td><td>If ACTH:
• high: MRI pituitary
• low: history then CT adrenals</td></tr>
<tr><td>Treatment</td><td colspan="3">Surgical or Medical</td></tr>
<tr><th colspan="4">Conn's Syndrome</th></tr>
<tr><td>Clinical Features</td><td colspan="3">• 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 and low K (episodic weakness, Paresthesias, transient paralysis, tetany, nephropathy with polyuria and polydipsia)</td></tr>
<tr><td>Biochemical Investigation</td><td colspan="2">Screening test:
• aldosterone/renin ratio
○ If high: do confirmatory test
○ If low: look for secondary causes</td><td>Confirmatory test:
• Saline infusion test
• Oral salt loading test
• Captopril test
• Fludrocortisone suppression test</td></tr>
<tr><td>Treatment</td><td colspan="2">Adenoma → Surgical resection</td><td>Adrenal hyperplasia → Spironolactone</td></tr>
<tr><th colspan="4">Pheochromocytoma</th></tr>
<tr><td>Clinical Features</td><td colspan="3">50% are silent. (NO symptoms), Isolated or part of MEN type II A or MEN type II B, Episodic (spells): sweating, palpitation, headache, Typical symptoms are (Secondary HTN, Young age < 40, 3 anti-HTN medications, Resistant HTN and Accelerated HTN.</td></tr>
<tr><td>Investigation</td><td colspan="3">• Biochemical: 24 hr urine collection of Metanephrines, Plasma Metanephrines
• Anatomical:
○ CT scan = MRI
○ MIBG if: Paraganglioma, Young, Large size, malignant features
○ Genetic Tests</td></tr>
<tr><td>Management</td><td colspan="3">• Control HTN: α-blocker2 then B-Blocker, Ca-blockers: can be used
• Salt loading: Oral NaCl for 3 days Or IVF 0.9% saline 1-2 days before surgery
• Surgical removal</td></tr>
</table>

Lecture Quiz

Q1: Which of the following conditions from the list below is not associated with cutaneous hyperpigmentation?
A- Hypopituitarism
B- Addison's disease
C- Cushing's syndrome
D- Pregnancy

Q2: A 65-year-old woman complains of panic attacks. She has recently retired as a school teacher, but 2–3 times a week she suffers extreme anxiety, becomes short of breath and sweats excessively. Elevated catecholamines are detected in the urine. The most appropriate medical treatment is:
A- Phenoxybenzamine alone
B- Prolopanolol alone
C- Phenoxybenzamine followed by propanolol
D- Sodium nitroprusside

Q3: A 28-year-old woman has noticed a change in her appearance; most notably her clothes do not fit properly and are especially tight around the waist. Her face appears flushed and more rounded than usual, despite exercising regularly and eating healthily her weight has steadily increased over the last 3 weeks. On visiting her GP, he notices her blood pressure has increased since her last visit and she has bruises on her arm. She is especially worried about a brain tumour. The most appropriate investigation would be:
A- Low-dose dexamethasone test
B- High-dose dexamethasone test
C- Computed tomography (CT) scan
D- Urinary free cortisol measurement

Q4: A 22-year-old woman complains of dizziness and feeling light-headed. She works in an office and most frequently experiences this when standing up to visit the toilet. She has never fainted. The patient has lost 5 kg, but attributes this to eating more healthily. She has noticed a recent scar on the back of her hand which has started to turn very dark. The most appropriate investigation is:
A- Synacthen test
B- Low-dose dexamethasone test
C- Cortisol measurement
D- Urinary free cortisol measurement

Q5: A 57-year-old woman, who has recently returned from a holiday in America, presents with dull grey-brown patches in her mouth and the palms of her hand which she has noticed in the last week. She has also noticed she gets very dizzy when rising from a seated position and is continually afraid of fainting.The most likely diagnosis is:
A- Addison's disease
B- SIADH
C- Conn's syndrome
D- 17-hydroxylase deficiency

Answers: Q1:A | Q2:C | Q3:D | Q4:A | Q5:A

Answers Explanation File!

GOOD LUCK !

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