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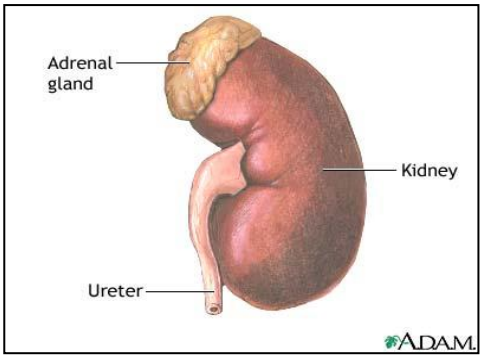


ANATOMICALLY

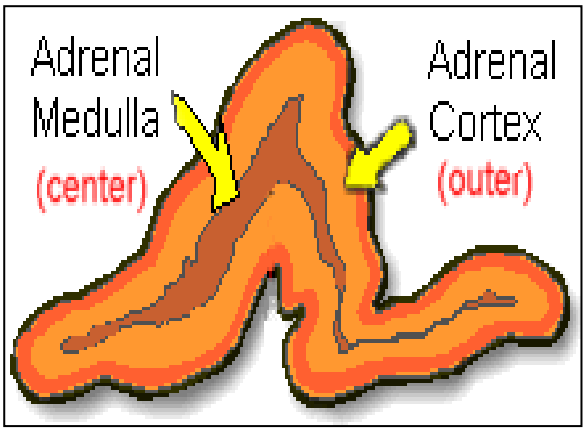
- **The adrenal gland is situated on**

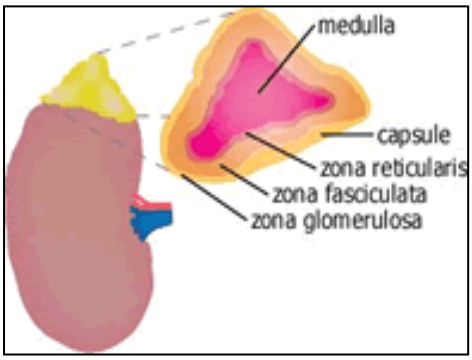
  the anteriosuperior aspect of the kidney

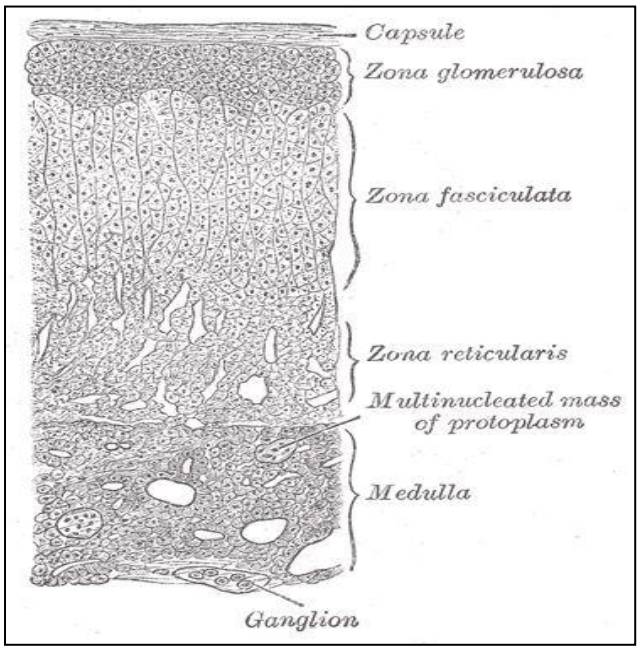
HISTOLOGICALLY:

- **The adrenal gland consists of two distinct tissues**

of different embryological origin, the outer cortex and inner medulla







The adrenal cortex comprises three zones based on cell type and function:

- **Zona glomerulosa**

  The outermost zone → aldosterone (the principal mineralocorticoid).

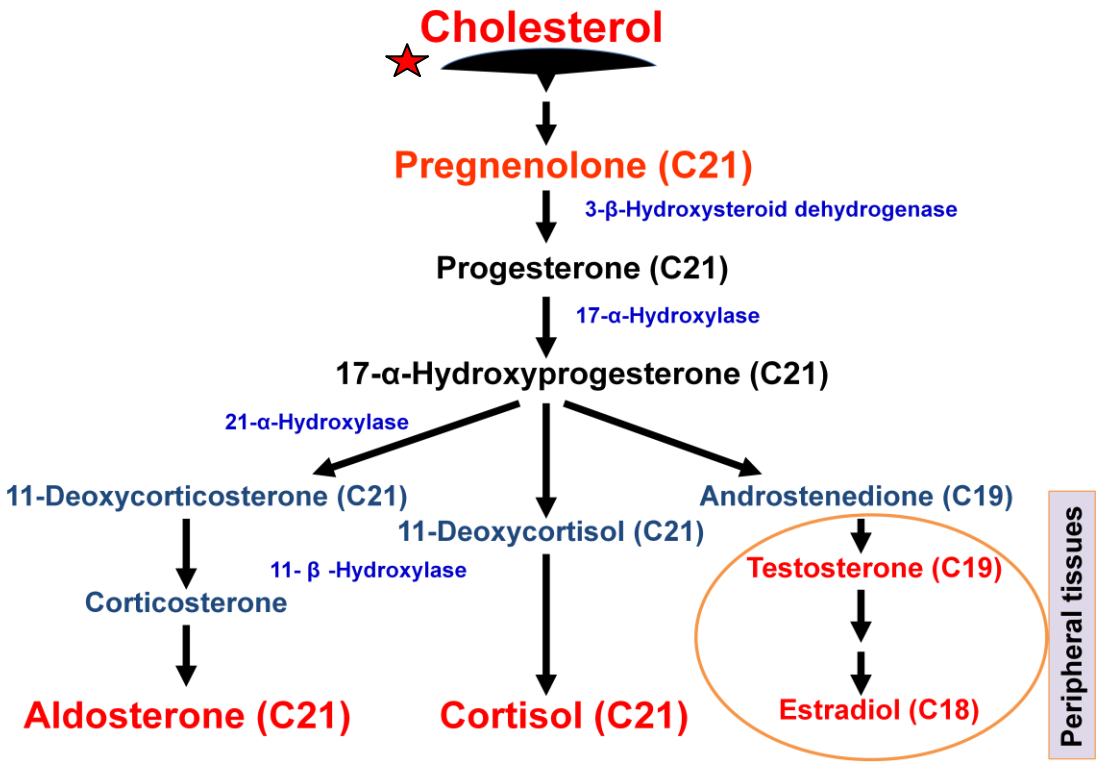
  The deeper layers of the cortex:

- **Zona fasciculata**

  → glucocorticoids – mainly cortisol (95%)

- **Zona reticularis**

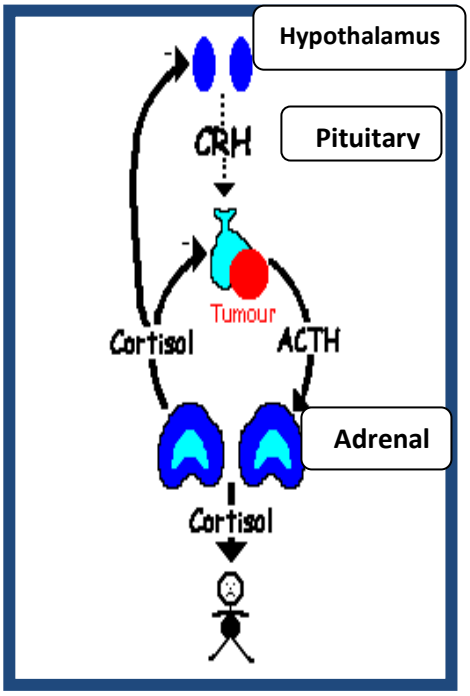
  → Sex hormones



The imp thing here just know the precursor of Aldosteron , cortisol and adrenal androgen **is cholesterol** .

Hypothalamic-Pituitary-Adrenal (HPA) Axis:

- **The hypothalamus secretes corticotrophin-releasing hormone (CRH) which stimulates the anterior pituitary gland to release ACTH.**
- **ACTH acts on the zona fasiculata cells → release of glucocorticoids (*Cortisol*).**



Regulation of ACTH and Cortisol Secretion:

1. Negative feedback control:

- **ACTH release from the anterior pituitary is stimulated by hypothalamic secretion of corticotrophin releasing hormone (CRH).**

- CRH → ↑ ACTH → ↑[Cortisol]

↑[Cortisol] or synthetic steroid suppress CRH & ACTH secretion

synthetic steroid
ex: drugs of asthmatic pt.

2. Stress (e.g. major surgery, emotional stress)

- **Stress → ↑↑ CRH & ACTH → ↑↑ Cortisol**

that why we let pt 30 min wating before doing the test
To avoid stress and the false (+)

3. The diurnal rhythm of plasma cortisol:

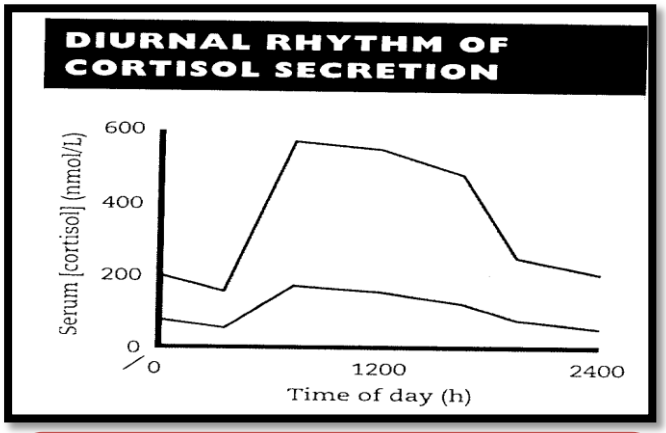
- **Highest Cortisol level:**

  in the morning (8 - 9 AM).

- **Lowest Cortisol level**:

  in the late afternoon and evening (8 - 9 PM).

There is one normal peak in the morning every day



The diurnal rhythm of cortisol secretion; the area between the curves represents values that lie within the reference range

Plasma [CBG] :

b/c **glucocorticoids** is fat soluble need careir protein =CBG
what we measurement in the lab is the **total cortisol**

- **In the circulation, glucocorticoids are mainly protein-bound (about 90%), <u>chiefly to cortisol-binding globulin</u> (CBG or transcortin).**
  - **↑↑ in pregnancy and with estrogen treatment (e.g. oral contraceptives).**
  - **↓↓ in hypoproteinemic states (e.g. nephrotic syndrome).**
- **The biologically active fraction of cortisol in plasma is the free (unbound) component.**

Cortisol and ACTH measurements:

venous stasis: tie around the arm that increase protein accumulation so CBG high cause high false total protein

Serum [cortisol] and plasma [ACTH]:

- Serum measurement is preferred for cortisol and Plasma for ACTH.
- Samples must be collected (without venous stasis) between 8 a.m. and 9 a.m. and between 10 p.m. and 12 p.m. because of the diurnal rhythm.
- Temporary ↑↑ in these hormones may be observed as a response to emotional stress.

24 hours sample very difficult to collected if the first difficult we use **Cortisol / Creatinine ratio**

Urinary cortisol excretion :

- Cortisol is removed from plasma by the liver → metabolically inactive compounds → excreted in urine mainly as conjugated metabolites (e.g. glucuronides).
- A small amount of cortisol is excreted unchanged in the urine (UFC).imp
- In normal individuals:
  - Urinary free cortisol (UFC) is < 250 nmol/24 h.
  - Cortisol / Creatinine ratio in an early morning specimen of urine is < 25 µmol cortisol / mol creatinine.

★ CAUSES OF ADRENOCORTICAL HYPERFUNCTION: CUSHING'S SYNDROME

- ACTH - dependent :

1. ↑ Pituitary ACTH 70% (Cushing's disease). imp
2. Ectopic ACTH by neoplasms 10%.
3. ACTH therapy.

- ACTH - independent :

1. Adrenal tumor 20% (adenoma or carcinoma)
2. Glucocorticoid therapy.

★ Ectopic ACTH by neoplasm : not from the ACTH axis mostly from tumors in the broncos.

ACTH therapy :

The most common medication from steroid

We should know the different b/w Cushing disease or syndrome :

When the problem in the ↑ Pituitary ACTH "tumors"

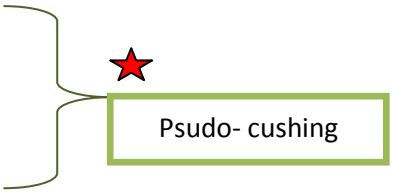
Cushing disease is apart of Cushing syndrome

- When we stop the cortisol should be gradual to avoid crisis" to adapt stimulation secretion "

Causes of elevated serum cortisol concentrations:

1. Increased cortisol secretion:

- **Cushing's syndrome**
- **Exercise**
- **Stress, Anxiety, Depression**
- **Obesity**
- **Alcohol abuse**
- **Chronic renal failure**



2. Increased cortisol binding globulin (CBG): because it decreases – feedback from free cortisol on ACTH

- **Congenital**
- **Estrogen therapy**
- **Pregnancy**

Glucocorticoid functions

- **Glucocorticoids have widespread metabolic effects on carbohydrate, fat and protein metabolism.**
- **Upon binding to its target, CORTISOL enhances metabolism in several ways:**
  - **In the liver, Cortisol is an insulin antagonist and has a weak mineralocorticoid action →**
    - **↑↑ Gluconeogenesis → production of glucose from newly-released amino acids and lipids**
    - **↑↑ Amino acid uptake and degradation**
    - **↑↑ Ketogenesis.**
    - **In the adipose tissue:**

      Cortisol → ↑↑ Lipolysis through breakdown of fat .
    - **In the muscles:**

      Cortisol →↑↑ proteolysis and amino acid release.
    - **Conserving glucose: by inhibiting uptake into muscle and fat cells.**

Cortisol is an insulin antagonist : anti- insuline action so,

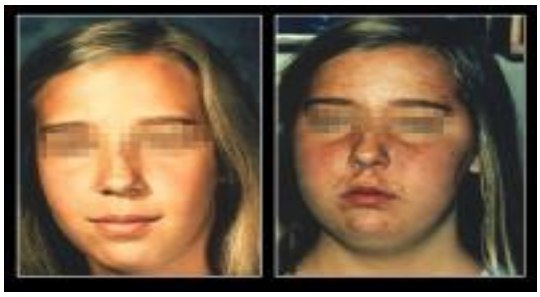
we stimulate it secretion by hypo -glycemia
lipolysis:↑↑ Ketogenesis

so, it called "catabolic hormones"

Cushing's Syndrome

Symptoms:

- **Weight gain: trunk and face with sparing of the limbs (central obesity) "**around the viscera"
- **Buffalo's hump. "**Depostion of fat **"**
- **Moon face**
- **Excessive sweating**
- **Atrophy of the skin and mucous membranes**
- **Purple striae on the trunk and legs**
- **Proximal muscle weakness (hips, shoulders)**
- **Hirsuitism**



Proximal muscle : b/c it the big ms which begins the movement

- **The excess cortisol may also affect other endocrine systems → ↓ libido, amenorrhoea and infertility**
- **Patients frequently suffer various psychological disturbances ranging from euphoria to frank psychosis**

Signs:

- **Loss of diurnal rhythm of cortisol and ACTH.**
- **Hypertension (due to the aldosterone - like effects)**
- **Hyperglycemia or diabetes due to insulin resistance.**
- **Hypokalemic alkalosis**
- **↑ protein metabolism.**
- **Impaired immunity**."b/c it cause immunosupressn**"**

Loss of diurnal rhythm of cortisol and "ACTH

When we measures the cortisol in the morning the another time in the night .. Then the lab result come the same that indicate problem

Can see it in Cushing and psudo-Cushing

Hypokalemic alkalosis

due to more proton excreation : ex:k+

Hypertension (due to the aldosterone - like effects)

which increase NA reabsorption " together with water "

And execration of k.

Investigations of suspected adrenocortical hyperfunction

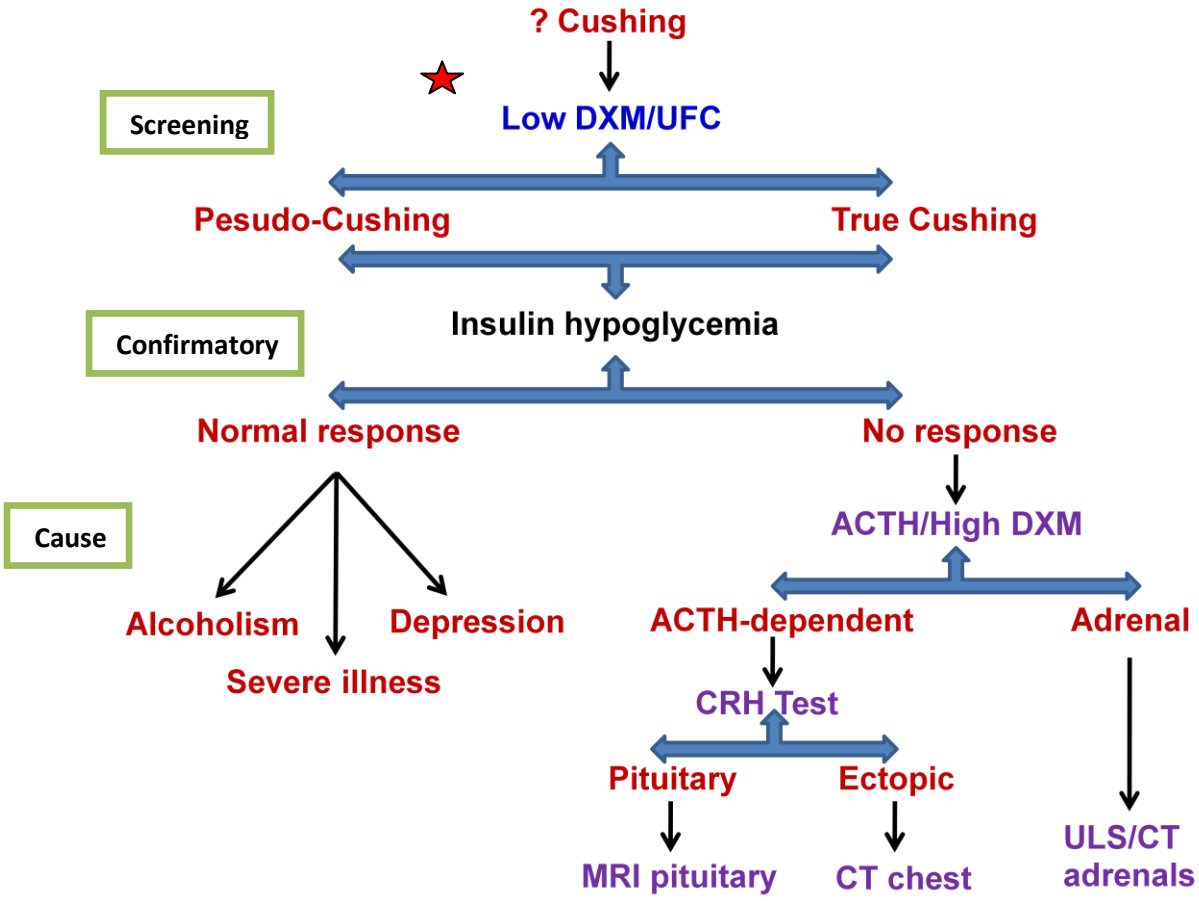
A. **Screening tests (out-patient):**
to assess the clinical diagnosis of adrenocortical hyperfunction.

B. **Confirmatory tests (in-patient):**
to confirm or exclude the provisional diagnosis

C. **Tests to determine the cause: to ascertain:**

1. The site of the pathological lesion
(adrenal cortex, pituitary or elsewhere)
2. The nature of the pathological lesion.

Nature: if it cancerogenic or benign



A. Screening tests:

Effective screening tests need to be sensitive but do not have to be highly specific.
It includes:

1. **Low-dose dexamethasone suppression test:**
   (Overnight suppression test)

   Dexamethasone → ↓ CRH → ↓ ACTH → ↓ cortisol

2. **24-hour urinary free cortisol**

(Extra information not imp)

- The **sensitivity** of a test refers to how many cases of a disease a particular test can find. A very sensitive test is likely to give a fair number of false- positive results, but almost no true positives will be missed .it means the true +

Ex: in pregnancy test : when we have 100 pregnant then we do forthem senstive test the result show 90 (+) and 10(-)

That means the test is 90% sensitive and 10% not!

. **Numerically**, sensitivity is the number of true positive results (TP) divided by the sum of true positive and false negative (FN) results, i.e., sensitivity = TP/(TP + FN). X 100 %

- The **specificity** of a test refers to how accurately it diagnoses a particular disease without giving false-positive results..

Good enough to detect pt do not have the disease true negative

Ex: in pregnancy test : when we have 100 non pregnant women then we do for them specific test the result show 90 (-) and 10(+)

That means the test is 90% specific and 10% not!

Numerically, specificity is the number of true negative results (TN) divided by the sum of true negative and false positive (FP) results, i.e., specificity = TN/(TN + FP).x100 %

1. **Low-dose dexamethasone (DXM) suppression test: (outpatient procedure)**

Procedure:

One mg DXM administered at 11-12 PM the night before attending the clinic.

serum cortisol is measured at 8-9 AM.

★ Result:

Cortisol < 50 nmol/L (suppression)→ exclude Cushing's disease

Precautions:

Drugs that induce hepatic microsomal enzymes (Phenobarbitone & phenytoin) → ↑ DXM metabolism and ↓ DXM blood level to achieve CRH suppression (false diagnosis of Cushing)

2. **24- hour urinary free cortisol:**

★ Result:

Cortisol < 250 nmol/day → exclude Cushing's disease.

Disadvantage:

incomplete collection of urine → a false-negative result

- An alternative is to determine the urinary cortisol : creatinine ratio on an early morning specimen

★ Interpretation of screening tests:

- **The screening tests serve to:**

distinguish simple non-endocrine obesity from obesity due to Cushing's syndrome.

- **Confirmatory tests (in-patient basis) are required to rule out pseudo-Cushing's syndrome**

★ • **Pseudo-Cushing's syndrome:**

  - **Depressed or extremely anxious patients**
  - **Severe intercurrent illness**
  - **Alcoholism**

★ B. Confirmatory tests: (Inpatient)

Insulin-induced hypoglycemia
should be avoided in cardiac pt

- ➢ **Insulin-induced hypoglycemia**
- ✓ **Pseudo-Cushing patients show abnormal diurnal rhythm of S. cortisol, but, with Insulin-induced hypoglycemia → ↑ CRH, ACTH and cortisol blood levels**
- ✓ **True Cushing patients:**
  - **No response to hypoglycemia**

- **Insulin-induced hypoglycemia:**

✓ **Hypoglycemia →↑ CRH →↑ ACTH →↑ cortisol**
✓ **To test the integrity of the hypothalamic-pituitary-adrenal (HPA) axis.**
✓ **To distinguish true Cushing's syndrome from pseudo-Cushing's syndrome**
✓ **Contraindicated in: epilepsy or heart disease.**

Procedure: (not imp)- for read

- **Insulin I.V. (0.15 U/kg) to lower blood glucose to 2.2 mmol/L or less .**
- **Samples for simultaneous measurement of serum glucose and cortisol levels are taken basally (before insulin injection) and at 30, 45, 60 and 90 min after I.V. insulin injection.**
- **Failure to achieve a glucose level of 2.2 mmol/L invalidates the test and should be repeated with increment in step of 0.05U/kg.**

★ **Interpretation of the results:**

★Normally:

- **Basal serum cortisol: at least 145 nmol/L**
- **At 60 - 90 minutes: the level > 425 nmol/L**

★Patients with Cushing's syndrome:

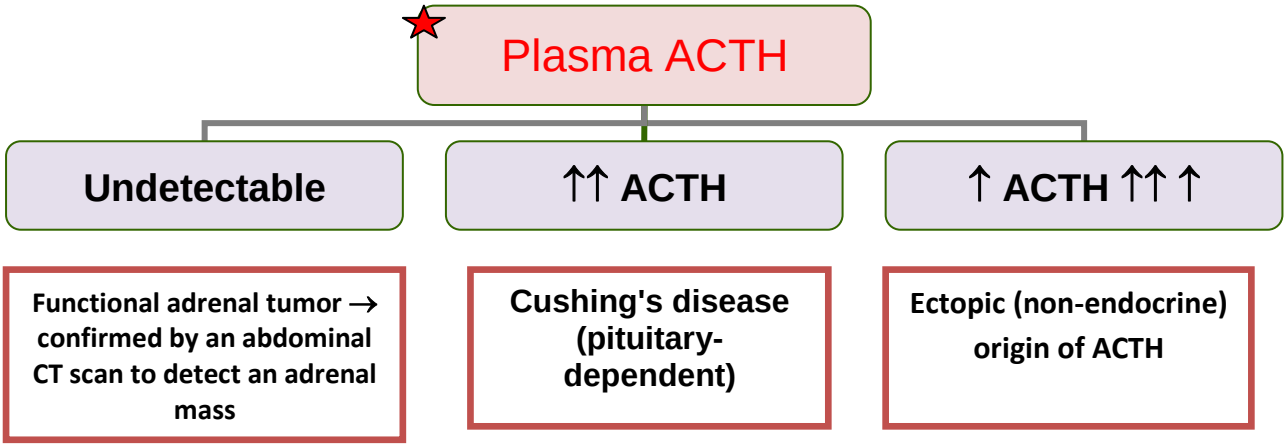
- **Whatever the cause, do not respond normally to insulin-induced hypoglycemia.**
  - **High basal serum cortisol than normal .**
  - **At 60 - 90 minutes: no increase in S. cortisol, despite the production of an adequate degree of hypoglycemia.**

★ C. Tests used to determine the cause of Cushing's syndrome:

1. **Plasma ACTH (Diurnal rhythm)**
2. **High-dose dexamethasone suppression test**
3. **CRH stimulation test**
4. **Radiological tests: MRI of pituitary and ultrasound or CT of adrenals**

★ 1. Plasma [ACTH]: to detect the site " adrenal ,piutatry ,or ectopic "

Plasma [ACTH] should be measured on blood specimens collected at 8-9 a.m. and 8-9 p.m.



2. High-dose dexamethasone suppression test:

It is used to distinguish Cushing's disease from ectopic ACTH secretion.

- 2 mg dexamethasone six-hourly for 48 hours to suppress cortisol secretion.
- Basal (pre-dexamethasone) serum cortisol or 24-hour urine free cortisol is compared with the results at the end of the 48-hour period.

low-dose dexamethasone:
To diffrencation if it Cushing or not to exculde cushing disease
High-dose dexamethasone :
To distinguish Cushing's disease from ectopic ACTH secretion

- Suppression is defined as a fall to less than 50 % of basal value.
- About 90 % of patients with Cushing's disease show suppression of cortisol output.
- In contrast, only 10% of patients with ectopic ACTH production (or with adrenal tumors) show suppression.

3. CRH stimulation test:

Measures the ACTH and cortisol levels basally and 60 minutes after injection of 100 µg CRH.

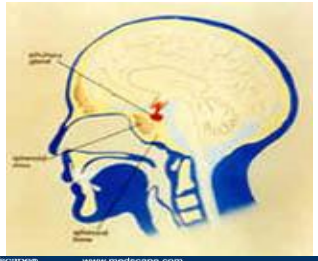
Ectopic ACTH & adrenal tumors –>
- No response
- False-positive responses are unusual

Cushing's disease –>
- ↑↑ ACTH & cortisol above basal at 60 min
- 10% of patients fail to respond

In Cushing's disease: High-dose dexamethasone suppression test + the CRH test → 100 % specificity and sensitivity.

4. Radiological Investigations: (not imp)

- Ultrasound or CT scanning of the adrenal glands
- MRI of the pituitary gland



Coronal contrast-enhanced MRI of the sella turcica in a patient with recurrent Cushing's disease

Other blood tests commonly performed for patients suspected to have Cushing's syndrome are:

- Full blood count
- Blood glucose
- Blood electrolytes and pH
- Renal function tests
- Liver function tests

Adrenal Hyperfunction

Summary of Biochemical Tests

Test	Cushing's disease	Adrenal tumor	Ectopic ACTH secreting tumor	Psudo-cushing
S. cortisol	↑	↑	↑	↑
Dexamethasone Low dose test	Not suppressed	Not suppressed	Not suppressed	Not suppressed
Urinary cortisol	↑	↑	↑	↑
Diurnal rhythm	Lost	Lost	Lost	Lost
Insulin-induced hypoglycemia	No response	No response	No response	There are response
Plasma [ACTH]	Normal or ↑	Not detectable	↑↑↑	
Dexamethasone High dose test	suppressed	Not suppressed	Not suppressed	
CRH test	↑	No response	No response	

Case study v.imp

58 years old man was admitted with weight loss and respiratory distress. He had increased pigmentation and BP was 140/80.

Lab tests

Urea	**8.6**	**(2.5-7 mmol/L)**
Sodium	**144**	**(135-145 mmol/L)**
Potassium	**2.0**	**(3.5-4.5 mmol/L)**
Cortisol	**1650**	**(150-550 nmol/L)**
Post overnight DMX	**1530**	**(<50nmol/L)**

Further investigation revealed the following

DMX suppression test	**Basal**	**after 48 h 0.5 mg qid**	**after 48h 2.0 mg qid**	
Serum cortisol	**1350**	**1420**	**1100**	**No suppression**
	8 am	**22.00 pm**		
Plasma ACTH (ng/L)	**220**	**180**		**Ref. range: 7-51**

CRH showed flat response for cortisol and ACTH

The answer: Ectopic ACTH

Take Home Message

- **Disorders of the adrenals are uncommon.**
- **Sensitive screening tests for adrenocortical functions are important.**
- **Additional confirmatory tests are required to establish the diagnosis and rule out pseudo-Cushing.**
- **Other biochemical tests and radiological investigation are required to determine the cause of Cushing's syndrome.**

Summry team note

Remember that:

1- **Ectopic ACTH** – not from the axis so, it not regulate by any affect from the axis

2-psudo-cushing : loss of diurnal rhythm **BUT** when we do insulin induce hypoglycemia test **there is response**

3- Cushing syndrome : loss of diurnal rhythm and **NO** response in insulin induce hypoglycemia

4- **in Ectopic and adrenal tumor** : **no** response to **CRH .. BUT** in Cushing there is recponce !

5- cushing have ACTH so, when there is low dose of dexamethasone can not supress ACTH **BUT in high dose of** dexamethasone there **is suppress**