

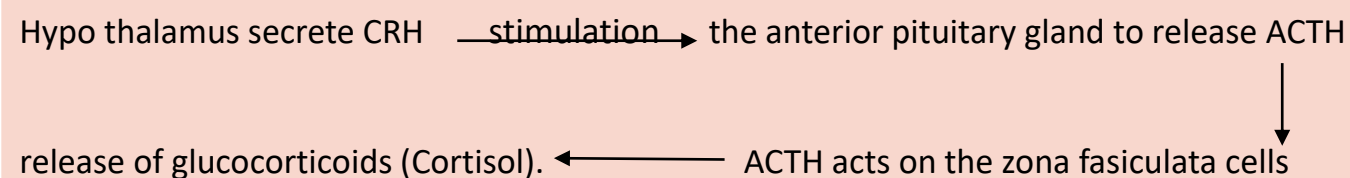
# Adrenal gland

<p><b>Anatomy</b> The adrenal gland is situated on the anteriosuperior aspect of the kidney.</p>	<p><b>Histology</b> The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla</p>
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The adrenal cortex comprises three zones based on cell type and function

Zona glomerulosa	Zona fasciculata	Zona reticularis
<p><u>The outermost zone . produces aldosterone</u></p>	<p>deeper layers of the cortex</p>	
	<p><b>Produces glucocorticoids mainly cortisol (95%)</b></p>	<p><b>Produces sex hormone</b></p>

## Hypothalamic-Pituitary-Adrenal (HPA) Axis



## Regulation of ACTH and Cortisol Secretion

1- Negative feedback	2- stress
<p><u>ACTH IS stimulated by CRH which released from the hypothalamus</u></p> <p>CRH → ↑ ACTH → ↑ [Cortisol]</p> <p>→ ↑ [Cortisol] or synthetic steroid suppress CRH &amp; ACTH secretion</p>	<p>e.g. major surgery, emotional stress</p> <p>Stress → ↑ CRH &amp; ACTH → ↑ Cortisol</p> <p>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 )</p>

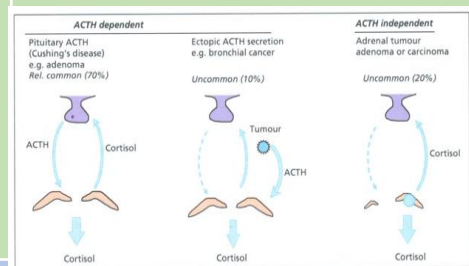
## Plasma [CBG]

CBG= cortisol binding globulin

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

<b>Roles</b>	<b>CAUSES OF ADRENOCORTICAL HYPERFUNCTION: CUSHING'S SYNDROME</b>	
<p>1- Serum measurement is preferred for cortisol and Plasma for ACTH</p> <p>2- Samples must be collected between 8 a.m. and 9 a.m. and between 10 p.m. and 12 p.m. because of the diurnal rhythm.</p> <p>3- Temporary increase in these hormones may be observed as a response to emotional stress.</p>	<b>ACTH – dependent</b>	<b>ACTH – independent</b>
	<ol style="list-style-type: none"> <li>↑ Pituitary ACTH 70% (Cushing's disease).</li> <li>Ectopic ACTH by neoplasms 10%.</li> <li>ACTH therapy.</li> </ol>	<ol style="list-style-type: none"> <li>Adrenal tumor 20% (adenoma or carcinoma)</li> <li>Glucocorticoid therapy.</li> </ol>



**Urinary cortisol excretion**  
 Cortisol is removed from plasma by the liver → metabolically inactive compounds → excreted in urine mainly as conjugated metabolites (e.g. glucuronides), But A small amount of cortisol is excreted unchanged in the urine.

**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. (no need to memorize the numbers)

**Glucocorticoid Functions**

Glucocorticoids have widespread metabolic effects on carbohydrate, fat and protein metabolism.

Conserving glucose: by inhibiting uptake into muscle and fat cells.

CORTISOL enhances metabolism in several ways

**In the muscles** : Cortisol ↑ **proteolysis** and amino acid release

**In the adipose** : tissue: Cortisol ↑ **Lipolysis** through breakdown of fat

**In the liver** : Cortisol is an insulin antagonist and has a weak mineralocorticoid action →

- ↑ Gluconeogenesis
- ↑ Amino acid uptake and degradation
- ↑ Ketogenesis.

## Cushing's Syndrome

**Signs**

- Loss of diurnal rhythm of cortisol and ACTH.
- Hypertension
- Hyperglycemia or diabetes due to insulin resistance.
- Hypokalemic alkalosis
- ↓ protein metabolism.
- Impaired immunity

**Symptoms**

- Weight gain: (central obesity)
- Buffalo's hump.
- Moon face
- Excessive sweating
- Atrophy of the skin and mucous membranes
- Purple striae on the trunk and legs
- Proximal muscle weakness (hips, shoulders)
- Hirsutism
- Patients frequently suffer various psychological disturbances

# Investigations Of Suspected Adrenocortical Hyperfunction

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

Effective screening tests **need to be sensitive** but do not have to be highly specific.

Interpretation

**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

## 1- Low-dose dexamethasone (DXM) suppression test

**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 . 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

## to confirm or exclude the provisional diagnosis

### Insulin-induced hypoglycemia

<p>Pseudo-Cushing patients show abnormal diurnal rhythm of S. cortisol, but, with Insulin-induced hypoglycemia → ↑ CRH, ACTH and cortisol blood levels</p>	<p>True Cushing patients: No response to hypoglycemia</p>
<p>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  <b>Contraindicated in: epilepsy or heart disease.</b></p>	<p>Interpretation of the results:                  Normally:                  Basal serum cortisol: at least 145 nmol/L                  At 60 - 90 minutes: the level &gt; 425 nmol/L</p> <p>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.</p>

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

<p>To differentiate ACTH-dependant from ACTH-independent: Plasma ACTH (Diurnal rhythm)                  Plasma [ACTH] should be measured on blood specimens collected at 8-9 a.m. and 8-9 p.m.</p>	<p>To distinguish between ACTH-dependent causes (Pituitary Vs Lung):                  1-High-dose DST.  <b>It is used to distinguish Cushing's disease from ectopic ACTH secretion</b>                  2-CRH stimulation test                  Measures the ACTH and cortisol levels basally and 60 minutes after injection of 100 µg CRH.</p>				
<p>Undetectabl</p>	<p>↑ ACTH</p>	<p>↑ ↑ ↑ ACTH</p>	<p>1- high dose DST                  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.</p>		
<p>Functional adrenal tumor</p>	<p>Cushing's disease (pituitary-dependent)</p>	<p>Ectopic (non-endocrine) origin of ACTH</p>	<p>2-CRH stimulation test</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> <p>Ectopic ACTH &amp; adrenal tumors                              No response                              False-positive responses are unusual</p> </td> <td style="width: 50%; padding: 5px;"> <p>Cushing's disease ↑↑ ACTH &amp; cortisol above basal at 60 min                              10% of patients fail to respond</p> </td> </tr> </table>	<p>Ectopic ACTH &amp; adrenal tumors                              No response                              False-positive responses are unusual</p>	<p>Cushing's disease ↑↑ ACTH &amp; cortisol above basal at 60 min                              10% of patients fail to respond</p>
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<p>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</p>					