



College of Pharmacy

Fifth Stage

Clinical Chemistry

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Lecture 2

The Adrenal Gland

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The adrenal glands are divided into two functionally distinct parts. The **adrenal cortex** is part of the hypothalamic-pituitary-adrenal endocrine system. The **adrenal medulla** is part of the sympathetic nervous system. The adult adrenal cortex consists of three layers that secrete steroid hormones. The outer thin layer (zona glomerulosa) secretes only **aldosterone**. The inner two layers (zona fasciculata and zona reticularis) form a functional unit and secrete **cortisol** and **androgens**. Steroid hormones are derived from the lipid **cholesterol** as appeared in Figure (1).

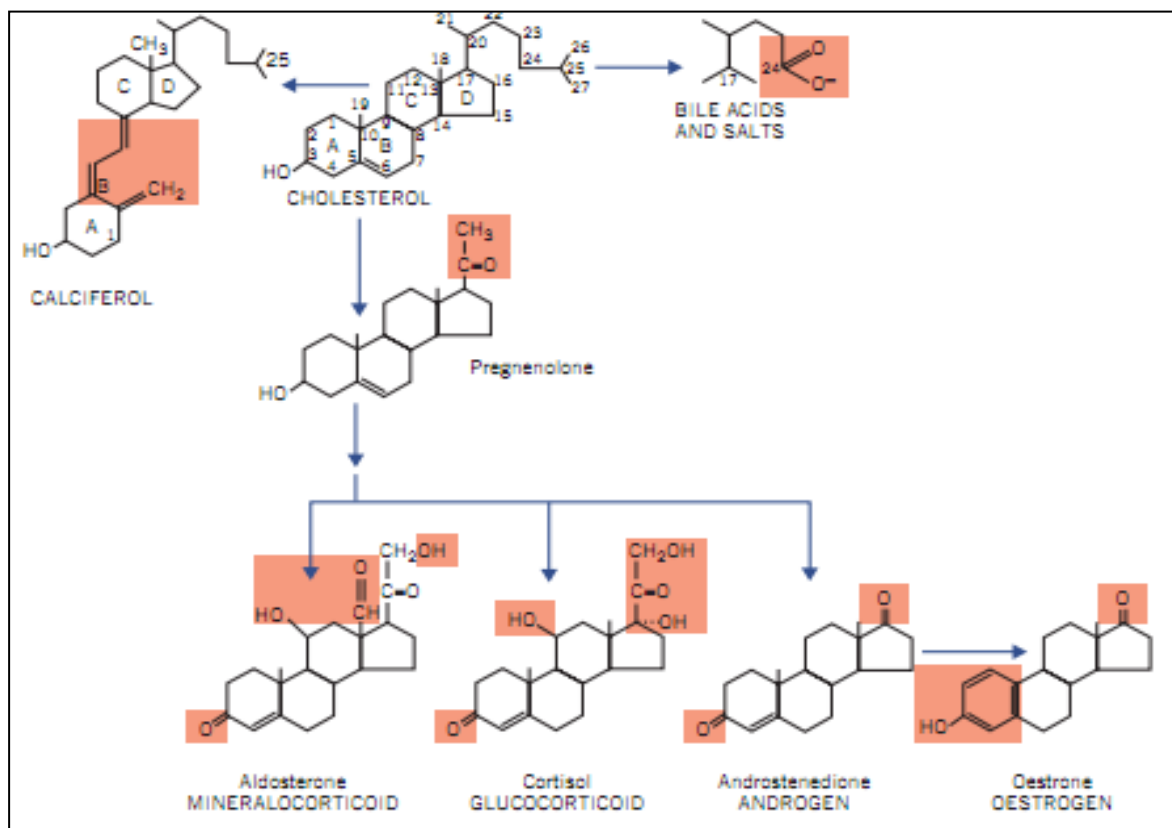


Figure (1) Synthetic pathway of steroid hormones from cholesterol

The hypothalamic-pituitary-adrenal axis

The hypothalamus, anterior pituitary gland and adrenal cortex form a functional unit. The hypothalamic-pituitary-adrenal axis illustrated in Figure (2). **Cortisol** is synthesized and secreted in response to ACTH released from the anterior pituitary gland. The secretion of ACTH is dependent on corticotrophin releasing hormone

(CRH), released from the hypothalamus. High plasma **free** cortisol concentrations suppress CRH secretion (negative feedback) and alter the ACTH response to CRH, thus acting on **both** the hypothalamus and the anterior pituitary gland.

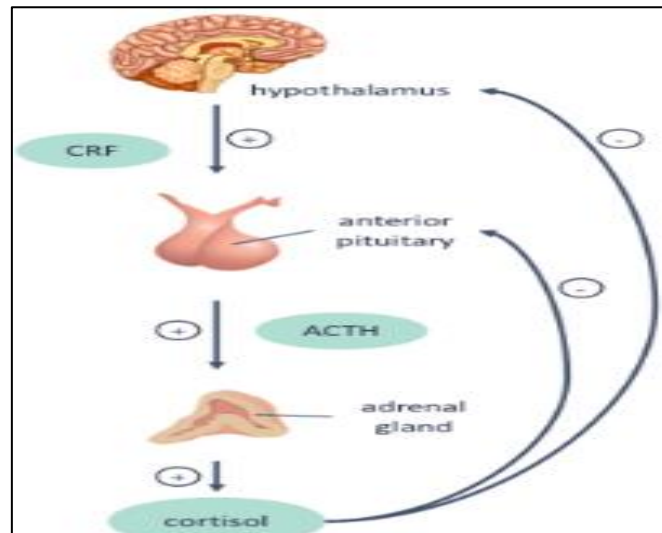


Figure (2) The hypothalamic-pituitary-adrenal axis

Glucocorticoids

Cortisol and **corticosterone** are naturally occurring glucocorticoids. They stimulate gluconeogenesis and the breakdown of protein and fat, that is, they antagonize some of insulin's action. Glucocorticoids in excess may impair glucose tolerance and alter the distribution of adipose tissue. **Cortisol** helps maintain the extracellular fluid volume and normal blood pressure. Circulating cortisol is bound to cortisol-binding globulin (**CBG; transcortin**) and to albumin. At normal concentrations, only about 5 per cent of the total is unbound and physiologically active. **Cortisone** is not secreted in significant amounts by the adrenal cortex. It is biologically inactive until it has been converted in vivo to **cortisol** (hydrocortisone). Glucocorticoids are **conjugated** with glucuronate and sulphate in the liver to form **inactive metabolites**, which because they are more water soluble than the mainly protein-bound parent hormones, can be excreted in the urine.

Mineralocorticoids (Aldosterone)

The aldosterone is secreted from zona glomerulosa of adrenal cortex. Synthesis of the **aldosterone** is **controlled by** the **renin-angiotensin system** and **not normally by**

ACTH. Although ACTH is important for maintaining growth of the zona glomerulosa, deficiency of ACTH **does not** significantly reduce output of aldosterone. In contrast to other steroids, aldosterone is not transported in plasma bound to specific proteins. Aldosterone stimulates the exchange of sodium for potassium and hydrogen ions across cell membranes and its renal action is especially important for sodium and water homeostasis. Like the glucocorticoids, it is **inactivated** by hepatic **conjugation** and is excreted in the urine.

Adrenal androgens

The main **adrenal androgens** are **dehydroepiandrosterone (DHEA)** and **androstenedione**. They promote protein synthesis. **Testosterone**, the most powerful androgen, is synthesized in the **testes** or **ovaries** but **not** in the adrenal cortex. Most circulating androgens, like cortisol, are protein bound, mainly to sex-hormone-binding globulin (SHBG) and albumin. There is extensive peripheral interconversion of adrenal and gonadal androgens and then conjugated in the liver and excreted as glucuronides and sulphates in the urine.

Control of cortisol hormone secretion

1. Feedback control

2. Inherent rhythms (circadian rhythm): ACTH is secreted episodically, each pulse being followed 5-10 minutes later by cortisol secretion. Plasma cortisol concentrations are usually highest between about 07.00 and 09.00 hour and lowest between 23.00 and 04.00 hour.

3. Physical or mental stress, may over-ride the other mechanisms and cause sustained ACTH secretion.

Adrenocortical hyperfunction

Cushing's syndrome

Cushing's syndrome is mainly caused by an **excess** of circulating cortisol but also other steroids such as androgens. The clinical and metabolic features may include the following:

1. **Obesity**, involving the trunk and face, and a characteristic round, red face.
2. **Impaired glucose tolerance and hyperglycaemia**. Cortisol has the opposite action to that of insulin, causing increased gluconeogenesis, and some patients may have diabetes mellitus.
3. **Increased protein catabolism**, which also increases urinary protein loss. Thus, there is a negative nitrogen balance associated with proximal muscle wasting with weakness, thinning of the skin and osteoporosis. The tendency to bruising and the purple striae.
4. **Hypertension**, caused by urinary retention of sodium and therefore of water, which are due to the mineralocorticoid effect of cortisol. Increased urinary potassium loss may cause **hypokalaemia** and **alkalosis**.
5. **Androgen excess**, which may account for the common findings of greasy skin with acne vulgaris and hirsutism, and menstrual disturbances in women.
6. **Psychiatric disturbances**, such as depression.

Causes of Cushing's syndrome

1. One of the most common causes of Cushing's syndrome is iatrogenic and related to excessive steroid treatment.
2. Increased **endogenous** cortisol production may be due to hyperstimulation of the adrenal gland by ACTH, either from the **pituitary** gland or from an **ectopic source** (increase glucocorticoids and ACTH). The secretion of ACTH is increased in the following conditions:
 - A. **Cushing's disease**: It is associated with bilateral adrenal hyperplasia, often secondary to a basophil **adenoma of the anterior pituitary gland**.
 - B. **Ectopic ACTH secretion**: In this condition, usually from a small-cell carcinoma of the bronchus, ACTH concentrations may be high enough to cause skin pigmentation.

3. Tumours of the adrenal cortex. (Increase glucocorticoids and decrease ACTH)

The secretion of ACTH is appropriately suppressed in primary cortisol secreting **tumours** of the adrenal cortex. The tumours may be **benign** or **malignant** and are usually derived from the zona fasciculata/zona reticularis of the adrenal cortex. These glucocorticoid secreting tumours (**benign adenomas** or **carcinomas**) **do not** normally secrete **aldosterone**, which is produced in the zona glomerulosa layer of the adrenal cortex. The **carcinomas** secrete a variety of steroids, including androgens, and thus may cause hirsutism or virilization.

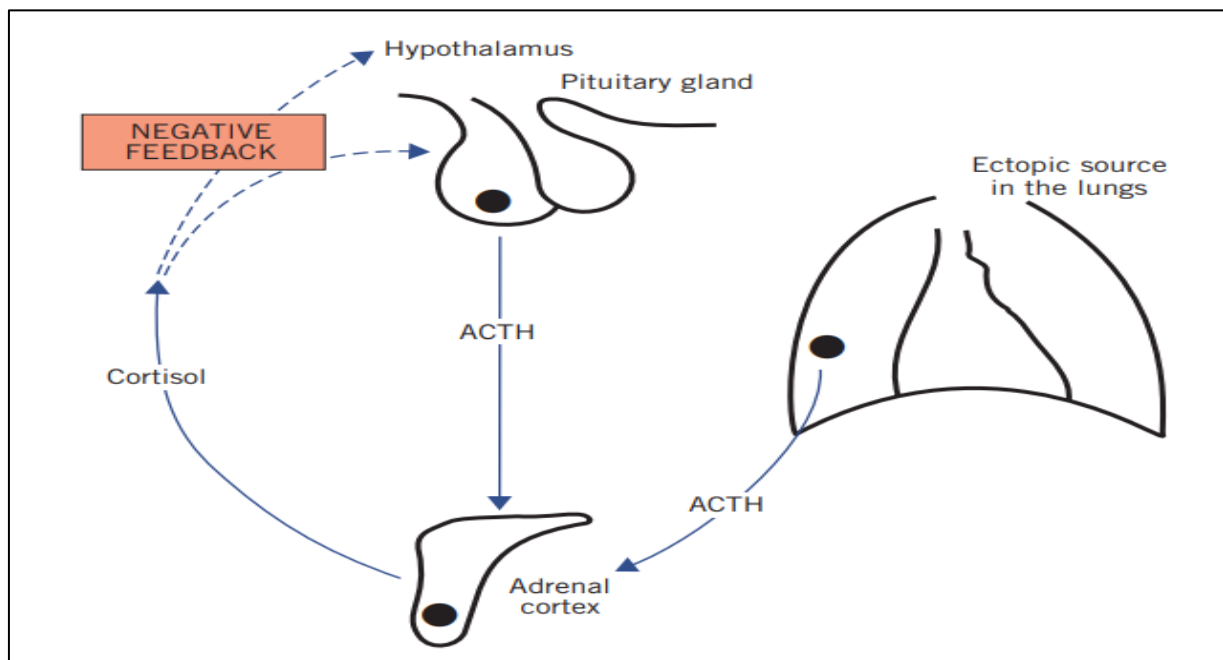


Figure (3) Excess cortisol production caused either by hyperstimulation of the adrenal gland by adrenocorticotrophic hormone (ACTH), from either the pituitary or an ectopic source, or by autonomous hormone secretion from an adrenal tumour.

4. Pseudo-Cushing's

Various conditions can **mimic** Cushing's syndrome and thus give **false-positive** results for screening tests. The following non-Cushing's causes of abnormal cortisol secretion are important to remember:

A. Stress over-rides the other mechanisms controlling ACTH secretion, with loss of the normal circadian variation of plasma cortisol and a reduced feedback response.

- B.** Endogenous depression may be associated with sustained high plasma cortisol and ACTH concentrations.
- C.** Severe alcohol abuse can cause hypersecretion of cortisol that mimics Cushing's syndrome clinically and biochemically. The abnormal findings revert to normal when alcohol is stopped.
- D.** Severe obesity.

Investigation of Cushing's syndrome (Table 1)

1. Plasma cortisol concentrations (morning and evening)

One of the earliest features of Cushing's syndrome is the **loss** of the diurnal variation in cortisol secretion, with **high** concentrations in the **late evening**, when secretion is normally at a minimum.

2. Estimation of 24-hours urinary free cortisol

Only the unbound fraction of cortisol in plasma is filtered at the glomeruli and excreted in the urine (urinary free cortisol). In Cushing's syndrome, because of the loss of circadian rhythm, raised plasma values are present for longer than normal and daily **urinary cortisol** excretion is further **increased**.

3. Low-dose overnight dexamethasone suppression test

A small dose, for example 1 mg, of this synthetic steroid inhibits ACTH, and thereby cortisol secretion by negative feedback. This is usually given at midnight and blood is taken for cortisol assay at 09.00 hour the following morning. A normal fall in plasma cortisol concentrations makes the diagnosis of Cushing's syndrome very unlikely, but failure to suppress plasma cortisol to less than 50 nmol/L does not confirm it with certainty.

4. Plasma ACTH concentrations

Plasma ACTH is detectable only in ACTH-dependent Cushing's syndrome (**Cushing's disease and ectopic ACTH**), and plasma concentrations are suppressed in patients with secreting adrenocortical tumours.

5. The high-dose dexamethasone suppression test

The high-dose dexamethasone suppression test may be useful. The principle of this test is the same as that of the low-dose test described above, but a higher dose (2 mg) given over 48 h at 6-h intervals **may suppress** the relatively insensitive feedback centre of pituitary dependent **Cushing's disease** (this occurs in **about 90 per cent** of cases). Plasma cortisol concentration suppression by about 50 per cent is usual. In the other two categories, **ectopic ACTH** production or **adrenal tumours**, when pituitary ACTH is already suppressed, even this high dose will usually have **no effect**.

6. If there is virilization, measure plasma androgens such as testosterone and DHEA. High concentrations suggest an adrenocortical carcinoma while benign adenomas is a glucocorticoid-secreting tumours only.

7. The insulin tolerance or insulin stimulation test

The insulin tolerance test may be appropriate. Elevated plasma cortisol concentrations suppress the stress response to hypoglycaemia, and this test may be of value in differentiating Cushing's syndrome from pseudo-Cushing's syndrome due to depression or obesity. This test is not without hazards due to severe hypoglycaemia.

Table (1) Some biochemical test results in patients with Cushing's syndrome

	Pituitary dependent (Cushing's disease)	Ectopic ACTH	Adrenocortical carcinoma	Adrenocortical adenoma
Plasma cortisol				
Morning	Raised or normal	Raised	Raised	Raised or normal
Evening	Raised	Raised	Raised	Raised
After low-dose dexamethasone	No suppression	No suppression	No suppression	No suppression
After high-dose dexamethasone	Suppressed	No suppression	No suppression	No suppression
Urinary free cortisol	Raised	Raised	Raised	Raised
Plasma ACTH	Usually raised	Raised	Low	Low

Adrenocortical hypofunction

1. Primary adrenocortical hypofunction (Addison's disease)

Addison's disease is caused by **bilateral destruction of all zones** of the adrenal cortex, usually as the result of an autoimmune process. Tuberculosis, amyloidosis, mycotic infections, acquired immunodeficiency syndrome (AIDS) and secondary deposits often originating from a bronchial carcinoma. An important cause of acute adrenal crisis is bilateral adrenal haemorrhage.

Glucocorticoid deficiency **contributes to** the hypotension and causes marked sensitivity to insulin; hypoglycaemia may be a presenting feature. Sometimes tiredness, weight loss, mild hypotension and pigmentation of the skin and buccal mucosa may occur. Androgen deficiency is **not** clinically evident because testosterone production by the testes is unimpaired in males and because androgen deficiency does not produce obvious effects in women. The **pigmentation** that develops in some cases of Addison's disease is due to the **high circulating levels of ACTH** or **related peptides** resulting from the lack of cortisol suppression of the feedback mechanism. Addison's disease is **characterized by** low **cortisol**, high **ACTH** concentration, **hypoglycaemia**, **hypotension**, **pigmentation**, **hyponatraemia** and **hyperkalaemia**.

2. Secondary adrenocortical hypofunction

The ACTH release may be impaired by **disorders** of the **hypothalamus** or the **anterior pituitary gland**, most commonly due to a tumour, infarction, infection and surgery. Corticosteroids suppress ACTH release and, if such drugs have been taken for a long time, the ACTH releasing mechanism may be slow to recover after the steroid is stopped. Patients may present with non-specific symptoms such as weight loss and tiredness. **Hypoglycaemia** may occur because of marked insulin sensitivity. Unlike primary adrenal hypofunction, **pigmentation** is **absent** because plasma ACTH concentrations are not raised. Secondary adrenal hypofunction is **characterised by** low **cortisol** and low **ACTH** concentration.

Investigation of adrenocortical hypofunction

1. Plasma cortisol concentrations

The low plasma cortisol concentrations give primary indication of adrenocortical hypofunction. It may not distinguish between primary and secondary adrenocortical hypofunction.

2. Plasma ACTH concentrations

Plasma ACTH assay may be of value when inappropriately low plasma cortisol concentrations have been found; a raised plasma ACTH concentration indicates primary insufficiency, whereas a low ACTH concentration suggests secondary insufficiency.

3. The tetracosactide (Synacthen) stimulation test

Synacthen has the same biological action as ACTH but, because it lacks the antigenic part of the molecule, there is much less danger of an allergic reaction. If the plasma cortisol concentrations are equivocal, perform a Synacthen test. Synacthen is given by intramuscular or intravenous injection. Blood is taken for cortisol assay at baseline (0), 30 and 60 min.

- **Normally** the plasma cortisol concentration increases by at least 200 nmol/L, to a concentration of at least 580 nmol/L.
- The peak is usually at 30 min, although a steady increase at 60 min may imply **secondary** adrenocortical hypofunction due to pituitary or hypothalamic disease (delay response).
- If the plasma cortisol concentration not increased when compared with baseline, **primary** adrenocortical hypofunction is more likely (no response).

4. A plasma autoantibody (adrenal antibodies), hyponatraemia, hyperkalaemia and hypoglycaemia and are compatible with an Addisonian crisis.

Primary hyperaldosteronism (Conn's syndrome)

Primary hyperaldosteronism (PH) is considered an important cause of secondary **hypertension**. The majority of cases of PH are due to adrenal aldosterone producing adenomas (**APAs**), although 45 per cent of cases may be due to bilateral idiopathic adrenal hyperplasia (**IAH**). There is also a genetic-familial variety of PH.

Hypertension and a **hypokalaemic metabolic alkalosis** in the face of **kaliuria** (urinary potassium more than 20 mmol/L) are suggestive of mineralocorticoid excess such as Conn's syndrome. A urinary potassium is thus a useful screening test. In PH, plasma **aldosterone** concentration will be raised, with suppressed **renin** levels.