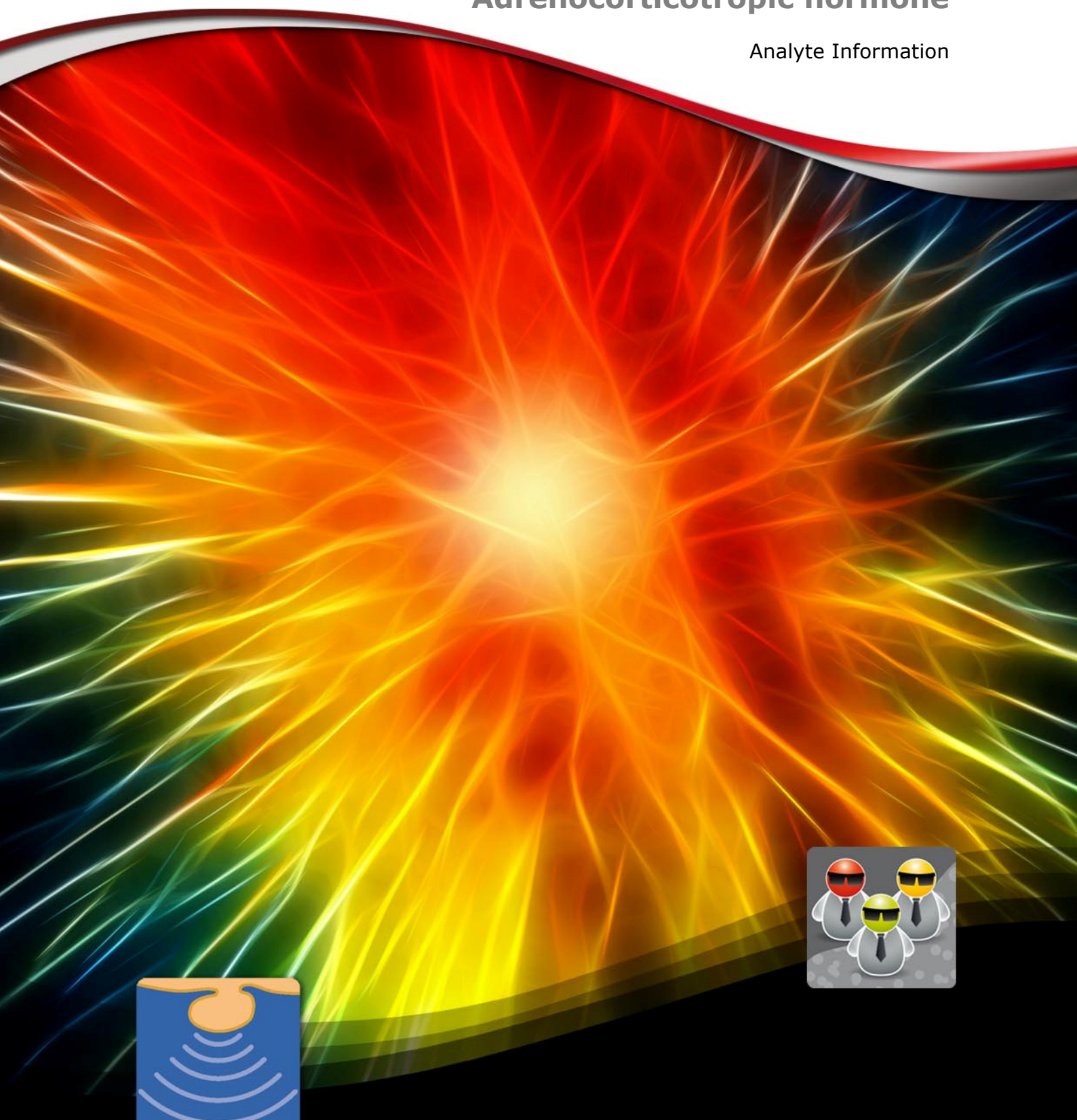




# Adrenal Function

## Adrenocorticotrophic hormone

Analyte Information





## Adrenocorticotrophic hormone

### Introduction

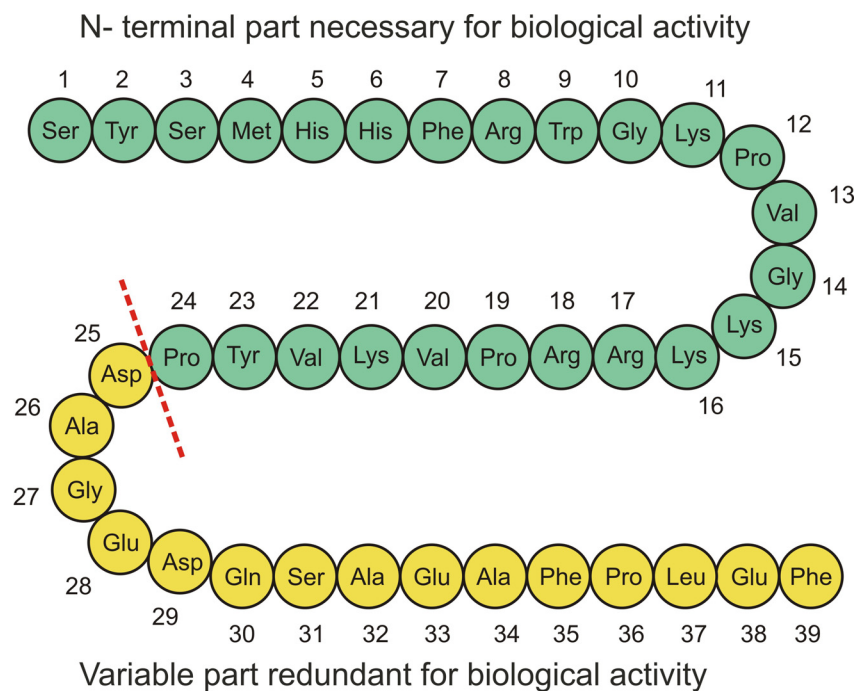
Adrenocorticotrophic hormone (ACTH) is a polypeptide tropic hormone produced and secreted by the anterior pituitary gland.

Adrenocorticotrophic hormone, as its name implies, stimulates the adrenal cortex. More specifically, it stimulates secretion of glucocorticoids such as cortisol, and it also has certain effects on the secretion of aldosterone. ACTH also partially regulates adrenal androgen production of both dehydroepiandrosterone (DHEA) and androstenedione.

ACTH has a molecular weight of 4.54 Da.

ACTH is single chain polypeptide composed of 39 amino acids. Twenty-four N-terminal amino acids are necessary for the biological activity of ACTH and are the same across all species, whereas 15-C terminal amino acids are very variable (Fig. 1).

**Fig.1: The structure of human ACTH**



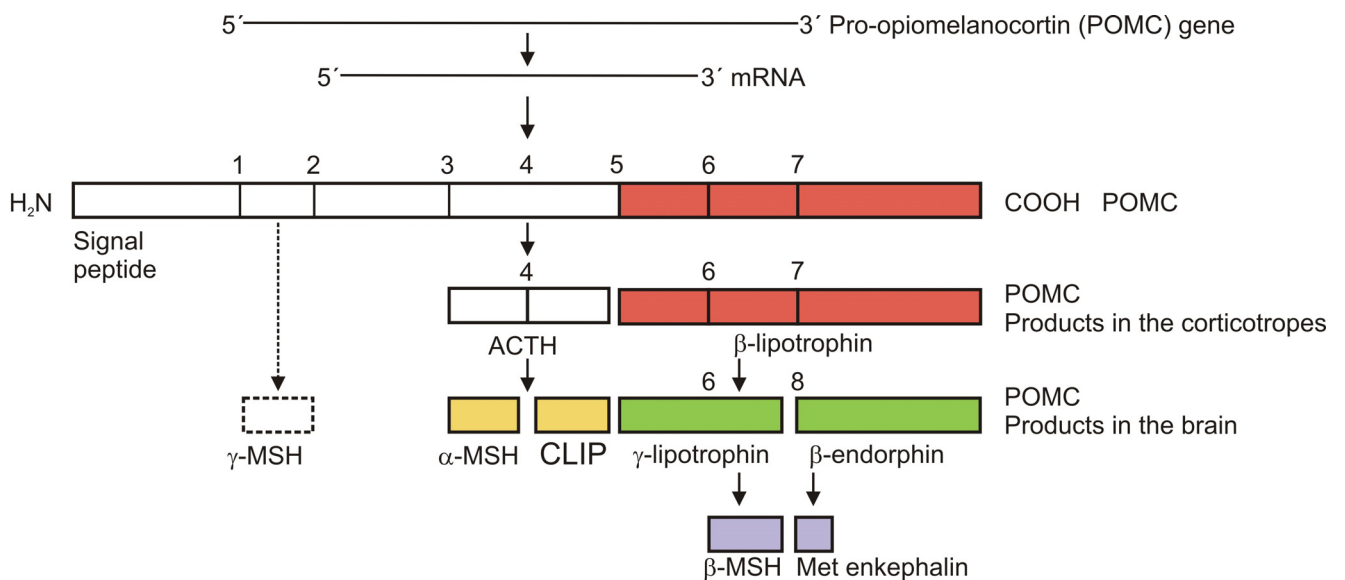
Adrenocorticotrophic hormone is also known as corticotrophin, adrenocorticotrophin and adrenocorticotrophin hormone.



## Biosynthesis and metabolism

ACTH and other related peptides originate from a large precursor molecule called pre-pro-opiomelanocortin (pre-POMC). Removal of the signal peptide during translation yields the 267-amino acid polypeptide POMC. It undergoes a series of post-translational modifications such as phosphorylation and glycosylation before it is proteolytically cleaved by endopeptidases to yield various polypeptide fragments with varying physiological activity. These fragments include ACTH,  $\beta$ -lipotropin,  $\gamma$ -lipotropin, melanocyte-stimulating hormone (MSH) and  $\beta$ -endorphin (Fig.2). POMC, ACTH and  $\beta$ -lipotropin are secreted by corticotropes in the anterior lobe of the pituitary gland in response to corticotropin-releasing hormone (CRH) released by the hypothalamus<sup>1</sup>.

**Fig.2: Synthesis of adrenocorticotrophic hormone (ACTH) <sup>2</sup>.**

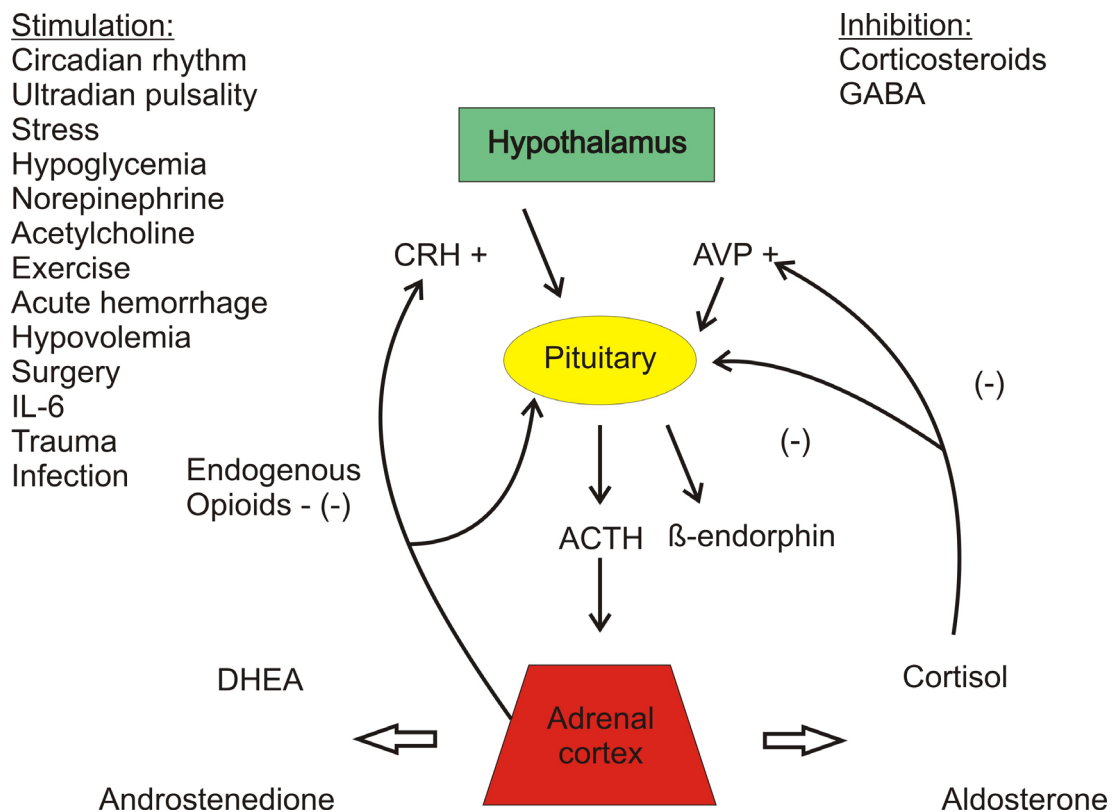


Many variables affect the secretion of ACTH, which is both pulsatile and circadian in nature; regulation of pituitary secretion of ACTH by the hypothalamus and higher centers is complex. The hypothalamic-pituitary-adrenal axis (HPA) comprises the mutual interactions of the hypothalamus, pituitary gland and adrenal glands. The HPA axis is a major part of the neuroendocrine system that controls reactions to stress and regulates many body processes, including



sexuality. Neural and others factors control pulsative and circadian secretion of corticotropin-releasing hormone. CRH and (to a lesser extent) arginine vasopressin (AVP), both produced by the hypothalamus, stimulate the release of ACTH by the anterior pituitary gland. ACTH stimulates the adrenal cortex to secrete cortisol and aldosterone as well as DHEA, DHEA-S and androstenedione. Negative feedback on CRH, AVP and ACTH production is provided mainly by cortisol, but endogenous opioids such as met-enkephalin and  $\beta$ -endorphin have a down-regulatory effect on the hypothalamic-pituitary-ACTH axis as well (Fig.3).

**Fig.3: The regulatory feedback loop of the HPA axis**



GABA: gamma amino butyric acid

The half-life of ACTH in human blood is about ten minutes.



## Physiological Function

ACTH acts through the stimulation of cell-surface ACTH receptors, which are located primarily on the adrenocortical cells of the adrenal cortex. This results in the synthesis and secretion of gluco- and mineralocorticosteroids and androgenic steroids.

The ACTH receptor is a seven-membrane-spanning G-protein-coupled receptor. Upon ligand binding, the receptor undergoes conformation changes that stimulate the enzyme adenylyl cyclase, which leads to an increase in intracellular cAMP creation and subsequent activation of the protein kinase A. This ultimately results in stimulation of steroidogenesis.

ACTH acts at several key steps to influence the steroidogenic pathway in the adrenal cortex:

- ACTH stimulates lipoprotein uptake into cortical cells. This increases the bio-availability of cholesterol in the cells of the adrenal cortex.
- ACTH increases the transport of cholesterol into the mitochondria and activates its hydrolysis.
- ACTH stimulates cholesterol side-chain-cleavage enzyme, which is responsible for the rate-limiting step in steroidogenesis<sup>3</sup>. This results in the production of pregnenolone.

## Levels

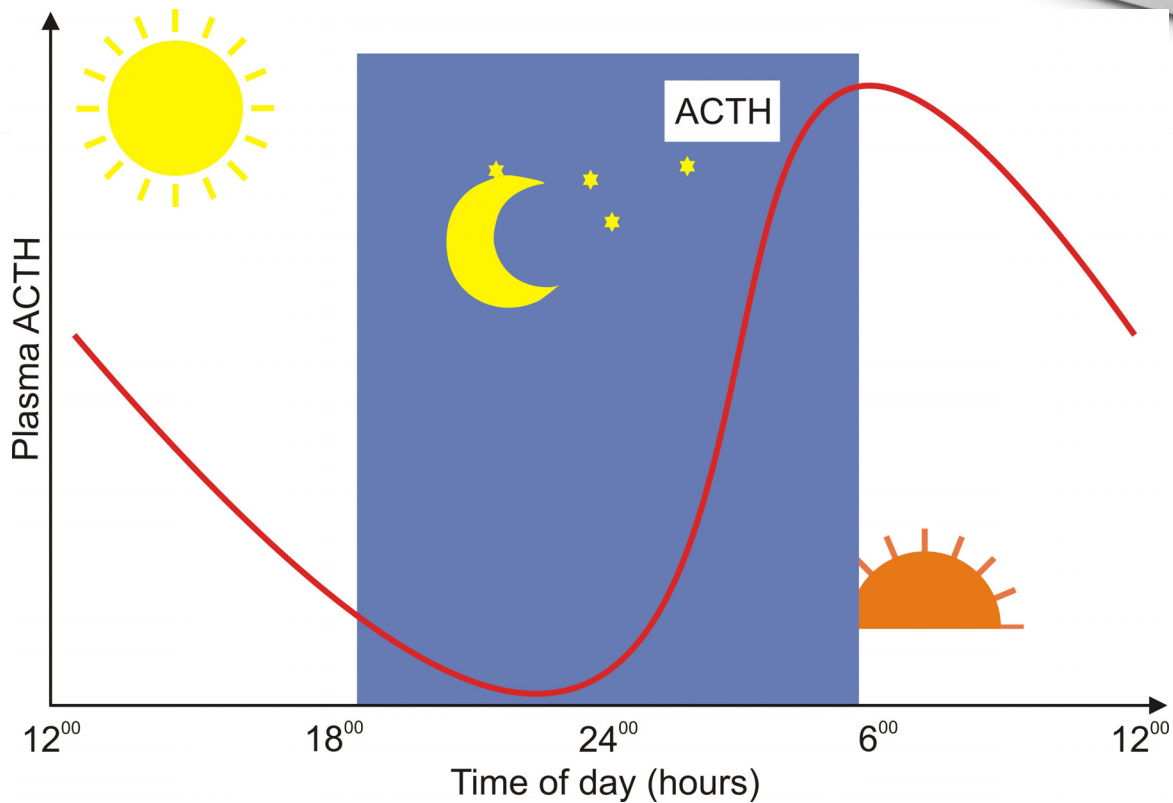
ACTH secretion does not change significantly with age.

ACTH and cortisol levels exhibit peaks (6-8 a.m. – soon after rising) and nadirs (11 p.m. – on retiring to bed), although there may be significant oscillation throughout the day. Periodicity is absent in all types of hypercortisolism except in occasional cases of adrenal tumors.

Pregnancy, menstrual cycle, and stress increase ACTH secretion.



**Fig.4: Diurnal rhythm of ACTH levels<sup>4</sup>**



Typical ACTH levels in plasma of children and adults are given in Table 1.

For each assay, the relevant values are shown in the appropriate Instruction for Use (IFU).

**Table 1: typical ACTH levels in plasma<sup>5</sup>**

<b>Specimen (plasma)</b>	<b>Reference interval (pg/mL)</b>
Cord blood:	50 - 570
Newborn (1 day)	10 - 185
Adults	
8:00 a.m. (unrestricted activity)	< 120
4:00 – 8:00 p.m.	< 85
Hospitalized volunteers	
5:00 – 7:00 a.m. (supine)	8 - 30
12:00 a.m. (supine)	< 10



Pediatric reference values are the same as those for adults, as confirmed by reviewed literature.

ACTH is unstable in blood, and proper handling of the specimen is important.

**Equation for the conversion of units: 1 pg/mL = 0.22 pmol/L**

### **Diagnostic utility – prospects and possibilities**

Blood ACTH levels help detect, diagnose and monitor conditions associated with excessive or deficient cortisol levels. ACTH determination helps identify causes of hypercortisolism and hypocortisolism.

Elevated cortisol levels and lack of diurnal variation have been identified in patients with Cushing's disease and also in patients with adrenal tumors. Low cortisol levels are found in cases of primary adrenal insufficiency (Addison's disease, congenital adrenal hyperplasia) and in ACTH deficiency. Due to normal circadian variation of cortisol levels, distinguishing normal and abnormally low cortisol levels can be difficult. Measuring both ACTH and cortisol can help to differentiate among some of these conditions. Additionally, various functional tests have been performed to evaluate the pituitary-adrenal axis (ACTH-cortisol), including insulin-induced hypoglycaemia, ACTH stimulation, CRF stimulation and artificial blockage of cortisol synthesis with metyrapone.

Relative ACTH and cortisol levels under different conditions are shown in Table 2.

**Table 2: ACTH and Cortisol levels in different conditions**

		Plasma ACTH	
		↓	↑
Plasma Cortisol	↑	Primary hypercortisolism (Cushing's syndrome)	Secondary hypercortisolism (pituitary or ectopic tumor, Cushing's disease, pseudo-Cushing's syndrome)
	↓	Secondary hypocortisolism (pituitary tumor, Sheehan's syndrome)	Primary hypocortisolism (Addison's disease, Nelson's syndrome)



Hypercortisolism is often (70% of cases<sup>6</sup>) caused by stimulation of adrenal cortex by increased ACTH production as a result of basophil adenoma of the anterior pituitary – known as Cushing’s disease. This disease affects women five times more often than men. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made.

Hypercortisolism may also be caused by ectopic ACTH syndrome. In such cases benign or (more often) cancerous tumors outside of the pituitary gland produce ACTH. Lung tumors make up more than half of these cases, and men are affected three times more often than women.

In rare cases, an abnormality of the adrenal glands, most often an adrenal tumor, may cause Cushing’s syndrome. Adrenal tumors are five times more common in women than in men, and the average age of onset is about 40.

The most common signs of hypercortisolism are obesity, moon face, high blood pressure, increased blood glucose concentrations, fragile skin, acne, osteoporosis and hirsutism.

Adrenal insufficiency is an endocrine disorder that occurs when the adrenal glands do not produce enough of certain hormones. Adrenal insufficiency can be primary or secondary.

Primary adrenal insufficiency, also called Addison’s disease, occurs when the adrenal glands are damaged and cannot produce sufficient quantities of cortisol and/or aldosterone. Addison’s disease affects one to four of every 100,000 people in all age groups and both sexes.<sup>7</sup>

Secondary adrenal insufficiency occurs when the pituitary gland fails to produce enough ACTH. If ACTH output is too low, cortisol production drops. Eventually, the adrenal glands can shrink due to lack of ACTH stimulation.

Elevated ACTH levels are associated with the following disorders:

- Addison’s disease (primary adrenal insufficiency)
- congenital adrenal hyperplasia
- pituitary-dependent Cushing’s disease
- ectopic ACTH-producing tumors
- Nelson’s syndrome (rapid enlargement of a pituitary adenoma after bilateral adrenalectomy)







Decreased ACTH levels are associated with the following disorders:

- secondary adrenocortical insufficiency
- adrenal carcinoma
- adrenal adenoma
- hypopituitarism



## **Diagnostic utility – Practical applications**

### **Discrimination between primary and secondary adrenal insufficiency**

In a patient with hypocortisolism, elevated ACTH levels indicate primary adrenal insufficiency, whereas non-elevated levels are consistent with secondary adrenal insufficiency of pituitary or hypothalamic origin.

When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value (or the 24-hour urinary free cortisol value) is lower than expected, further tests are needed to establish the diagnosis. First, the basal plasma ACTH concentration should be measured, followed by the short ACTH stimulation test. Other frequently used tests are the metyrapone and insulin-induced hypoglycemia test.

#### **ACTH stimulation test**

The ACTH stimulation test is the most commonly used test for diagnosing adrenal insufficiency. In this test, blood cortisol, urine cortisol or both are measured before and after injection of a synthetic form of ACTH. The normal response after an ACTH injection is a rise in blood and urine cortisol levels: people with Addison's disease or long-standing secondary adrenal insufficiency have little or no increase in cortisol levels.

#### **Metyrapone test**

This test helps to distinguish between primary and secondary hypercortisolism. Metyrapone inhibits 11- $\beta$ -hydroxylase secretion and thus reduces the conversion of 11-deoxycortisol to cortisol. ACTH secretion is stimulated by cortisol declines; increased ACTH production increases 11-deoxycortisol, but it cannot be metabolized to cortisol. Elevated 11-deoxycortisol levels indicate primary adrenal insufficiency, whereas



decreased levels (due to decreased ACTH production) indicate secondary adrenal insufficiency.

### **CRH stimulation test**

When the response to the ACTH test is abnormal, a CRH stimulation test can help determine the cause of adrenal insufficiency. In this test, synthetic CRH is injected intravenously and blood cortisol levels are measured both before and at 30-minute intervals for two hours after the injection. People with Addison's disease respond by producing high levels of ACTH but no cortisol. People with secondary adrenal insufficiency have absent or delayed ACTH responses. CRH will not stimulate ACTH secretion if the pituitary is damaged, so an absence of ACTH response points to the pituitary as the cause. A delayed ACTH response points to the hypothalamus as the cause.

### **Diagnosis during an emergency**

In patients suspected of having an Addisonian crisis, treatment must begin with injections of salt, glucose-containing fluids, and glucocorticoid hormones immediately. Although a reliable diagnosis is not possible during crisis treatment, measurement of blood ACTH and cortisol during the crisis—before glucocorticoids are given—is enough to make a preliminary diagnosis. Low blood sodium, low blood glucose, and high blood potassium are also usually present at the time of an adrenal crisis. Once the crisis is controlled, an ACTH stimulation test can be performed to obtain the specific diagnosis.

### **Discrimination between primary and secondary adrenal hypercortisolism**

In a patient with hypercortisolism (Cushing's syndrome), decreased ACTH levels are consistent with a cortisol-producing adrenal adenoma or carcinoma, primary adrenal micronodular hyperplasia, or exogenous corticosteroid use.

Normal or elevated ACTH in a patient with Cushing's syndrome puts the patient in the ACTH-dependent Cushing's syndrome category. This is due either to an ACTH-producing pituitary adenoma or to ectopic production of ACTH (bronchial carcinoid, small cell lung cancer, others). Further diagnostic studies such as dexamethasone suppression testing, CRH



stimulation testing, petrosal sinus sampling and imaging studies are usually necessary to determine the source of the excess ACTH.

### **Dexamethasone-corticotropin-releasing hormone (dexamethasone-CRH) test**

Some subjects exhibit high cortisol levels but do not develop the progressive effects of Cushing's syndrome, such as muscle weakness, fractures and thinning of the skin. These people may have pseudo-Cushing's syndrome, a condition sometimes found in people who have depression or anxiety disorders drink excess alcohol, have poorly controlled diabetes, or are severely obese. Pseudo-Cushing's does not have the same long-term effects on health as Cushing's syndrome and does not require direct treatment of the endocrine glands.

The dexamethasone-CRH test rapidly distinguishes pseudo-Cushing's from mild cases of Cushing's. This test combines the LDDST (low-dose dexamethasone suppression test) and a CRH stimulation test. In the CRH stimulation test, an injection of CRH causes the pituitary to secrete ACTH. Pre-treatment with dexamethasone prevents CRH from causing an increase in cortisol in people with pseudo-Cushing's. Elevations of cortisol during this test suggest Cushing's syndrome.

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