- Cushing's disease It is associated with bilateral adrenal hyperplasia, often secondary to a basophil adenoma of the anterior pituitary gland.
- 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.

- The patient may have weight loss with general illness. One metabolic complication is a hypokalaemic alkalosis.

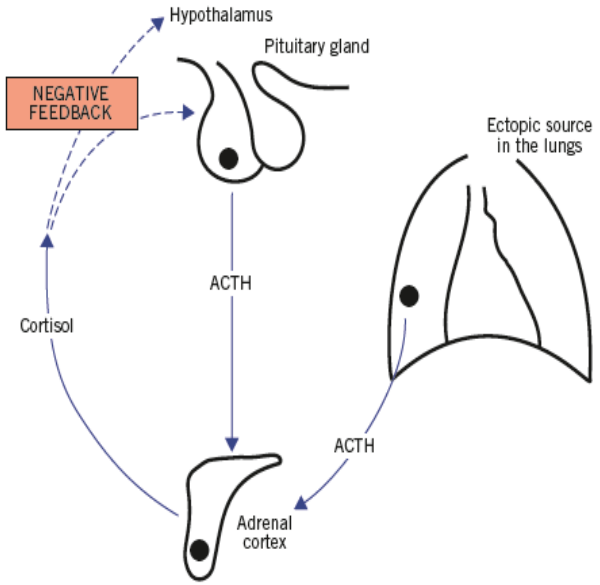


Figure 8.4 Cushing's disease, indicating excess cortisol production caused either by hyperstimulation of the adrenal gland by adrenocorticotrophic hormone (ACTH), from either the pituitary or an ectopic source, or by autonomous hormone secretion from an adrenal tumour.

- 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 do not normally secrete aldosterone, which is produced in the zona glomerulosa layer of the adrenal cortex.
- Benign adenomas occur and also carcinomas.
- The latter secrete a variety of steroids,including androgens, and thus may cause hirsutism or virilization.
- In these cases plasma ACTH is suppressed by the excess glucocorticoids.

Basis of investigation of suspected Cushing's syndrome

- The following questions should be asked:

  Is there abnormal cortisol secretion?

  If so, does the patient have any other condition that may cause it?

  If Cushing's syndrome is confirmed, what is the cause?

- Is there abnormal cortisol secretion?

Plasma cortisol concentrations reflect ACTH activity at that moment and, because of the episodic nature of cortisol secretion, such isolated values may be misleading. infact, cyclical Cushing's syndrome may require repeated investigation.

The level of cortisol measured in a 24-h urine sample reflects the overall daily secretion.

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.

However, it is not a diagnostic finding because it can also be caused by, for example, stress and endogenous depression.

The assessment of diurnal rhythm is not a practical outpatient procedure.

Out-patient screening tests therefore may include the following.

- Estimation of 24-h urinary free cortisol Only the unbound fraction of cortisol in plasma is filtered at the glomeruli and excreted in the urine (urinary ‘free’ cortiso).

- 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.
- Plasma and urinary cortisol concentrations are usually much higher when Cushing’s syndrome is due to adrenocortical carcinoma or overt ectopic ACTH secretion.
- Determinations of 24-h urinary free cortisol have about a 5%per cent false-negative rate, but if three separate determinations are normal, Cushing’s syndrome is most unlikely.

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 h the following morning

. The overnight dexamethasone suppression test is a sensitive, but not completely specific, test for evaluating such patients.

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.

There are some problems, for example certain anticonvulsant drugs, such as phenytoin, may interfere with dexamethasone suppression tests, inducing liver enzymes that increase the rate of metabolism of the drug. Plasma concentrations may therefore be too low to suppress the feedback centre.

- Additional tests

In some cases, additional tests are needed to confirm the diagnosis of excess cortisol production.

The 48-h low dose dexamethasone suppression test may be useful as it gives fewer false-positives than the overnight low-dose dexamethasone test: 0.5 mg dexamethasone is given orally at 6-h intervals from 09:00 h on day 1 for eight doses, and then plasma cortisol is measured after 48 h at 09:00 h.

Plasma cortisol should normally suppress to less than 50 nmol/L, but not in Cushing's syndrome.

- **Is there another cause for the abnormal cortisol secretion?**

Various conditions can mimic Cushing's syndrome(pseudo-Cushing's) and thus give false-positive results for screening tests.

The following non-Cushing's causes of abnormal cortisol secretion are important to remember:

- Stress over-rides the other mechanisms controlling

ACTH secretion, with loss of the normal circadian variation of plasma cortisol and a reduced feedback response.

Urinary free cortisol excretion may be increased even in relatively minor physical illness or mental stress.

Endogenous depression may be associated with sustained high plasma cortisol and ACTH concentrations that may not be suppressed even by a high dose of dexamethasone.

However, these patients often have a normal cortisol response to insulin-induced hypoglycaemia, whereas those with Cushing's syndrome do not

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.

- Severe obesity can also imitate Cushing's syndrome. ترابط حميم

- What is the cause of Cushing's syndrome?

The following biochemical investigations may help to elucidate the cause.

Table 8.2 Some biochemical test results in patients with Cushing's syndrome

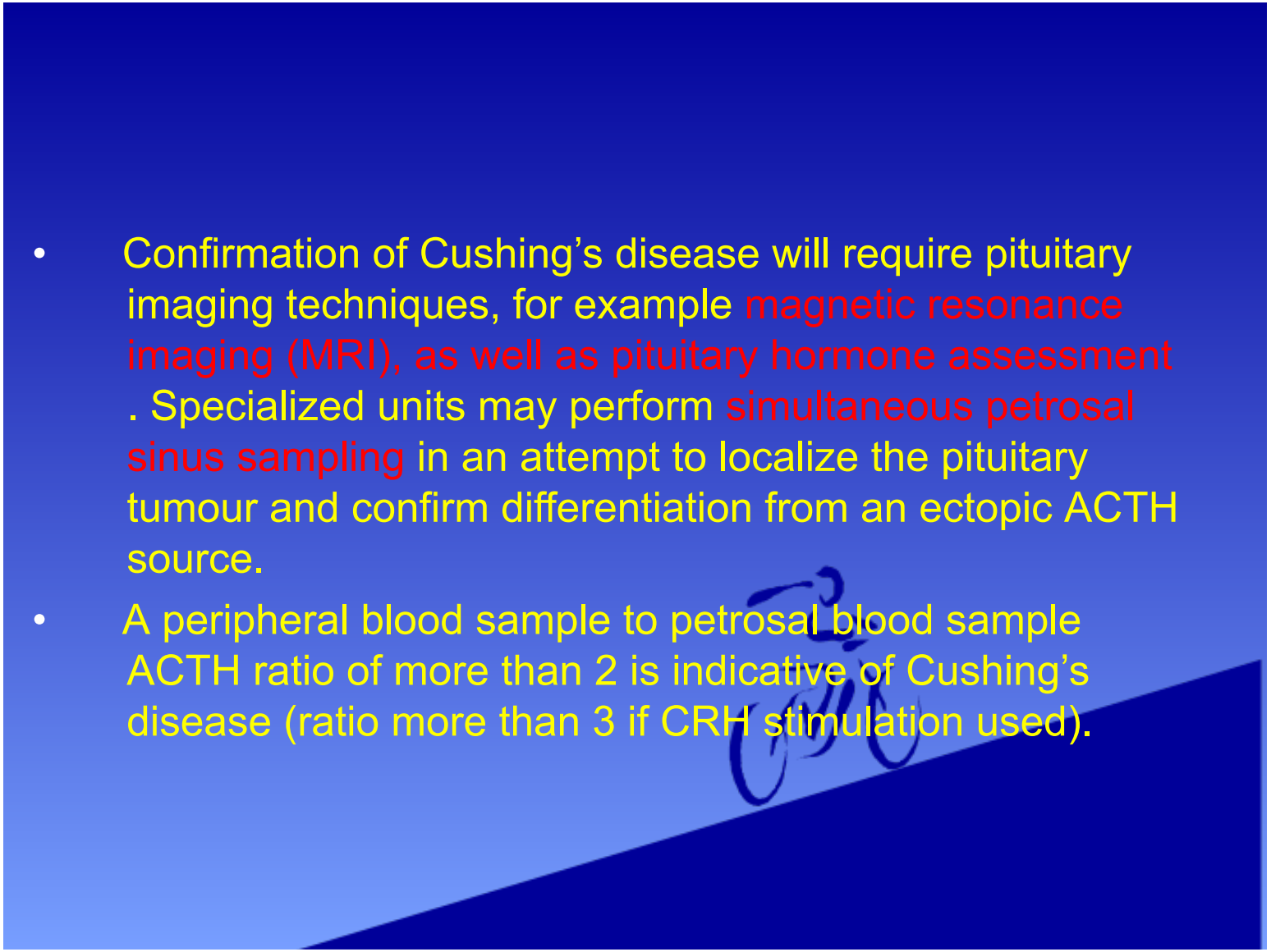
	Pituitary dependent (Cushing's disease)	Ectopic ACTH	Adrenocortical carcinoma	Adrenocortical adenoma
Plasma cortisol				
Morning	Raised or normal	Raised	Raised	Raised or normal
Evening	Raised	Raised	Raised	Raised
After low-dose dexamethasone	No suppression	No suppression	No suppression	No suppression
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

ACTH, adrenocorticotrophic hormone.

- Plasma ACTH is raised only in ACTH-dependent Cushing's syndrome, and plasma concentrations are low in patients with secreting adrenocortica tumours. Conversely, plasma ACTH concentrations are markedly raised in patients with 'ectopic' ACTH production.
- The high-dose dexamethasone suppression test may be useful. pituitary-dependent Cushing's disease (this occurs in about 90% of cases). Plasma cortisol concentration suppression. In the other two categories, ectopic ACTH production or adrenal tumours, will usually have no effect, although there may be some suppression in some cases of 'ectopic' ACTH secretion.
- If there is virilization, measure plasma androgens as testosterone, DHEA and DHEAS. High concentrations suggest an adrenocortical carcinoma

- In cases of Cushing's syndrome with raised plasma ACTH concentration, the intravenous CRH test (100 µg in adults or 1 µg/kg body weight in children) has gained popularity.
- In Cushing's disease)pituitary disorder), an increase in baseline plasma cortisol concentration of about 25% occurs in 90% of patients, whereas patients with ectopic ACTH, for example with lung carcinoma, usually fail to show this rise.
- 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.

- Confirmation of Cushing's disease will require pituitary imaging techniques, for example magnetic resonance imaging (MRI), as well as pituitary hormone assessment . Specialized units may perform simultaneous petrosal sinus sampling in an attempt to localize the pituitary tumour and confirm differentiation from an ectopic ACTH source.
- A peripheral blood sample to petrosal blood sample ACTH ratio of more than 2 is indicative of Cushing's disease (ratio more than 3 if CRH stimulation used).



- In cases of ectopic ACTH secretion, imaging techniques are important to try to locate the tumour, such as thin-slice MRI of the chest and abdomen
- . 70% of these tumours co-secrete other peptide hormones such as glucagon, somatostatin, calcitonin and bombesin.
- Ectopic ACTH-induced Cushing's syndrome is more likely to present with hypokalaemia, skin pigmentation, short clinical history and severe myopathy.
- Plasma ACTH concentrations are also often much higher than those found in Cushing's disease.
- Abdominal imaging, for example CT scanning, may locate an adrenal tumour. Here, plasma ACTH is usually low and the tumour may also secrete androgens.

Treatment of Cushing's syndrome

- The treatment of depends upon the cause.
- Surgery is usually the treatment of choice. In Cushing's disease, pituitary removal by trans-sphenoidal surgery with pituitary radiation as an adjunct may be necessary. Adrenal tumours also usually require surgery, although the prognosis may be poor with carcinoma.
- Bilateral adrenal removal can lead to skin pigmentation due to pituitary ACTH release – Nelson's syndrome. Similarly, if the source of ectopic ACTH is found, surgery may be indicated to remove the tumour, for example lung carcinoma.
- cortisol-inhibiting drugs are used such as ketoconazole, mitotane and metyrapone, which inhibit steroid 11-b-hydroxylase .

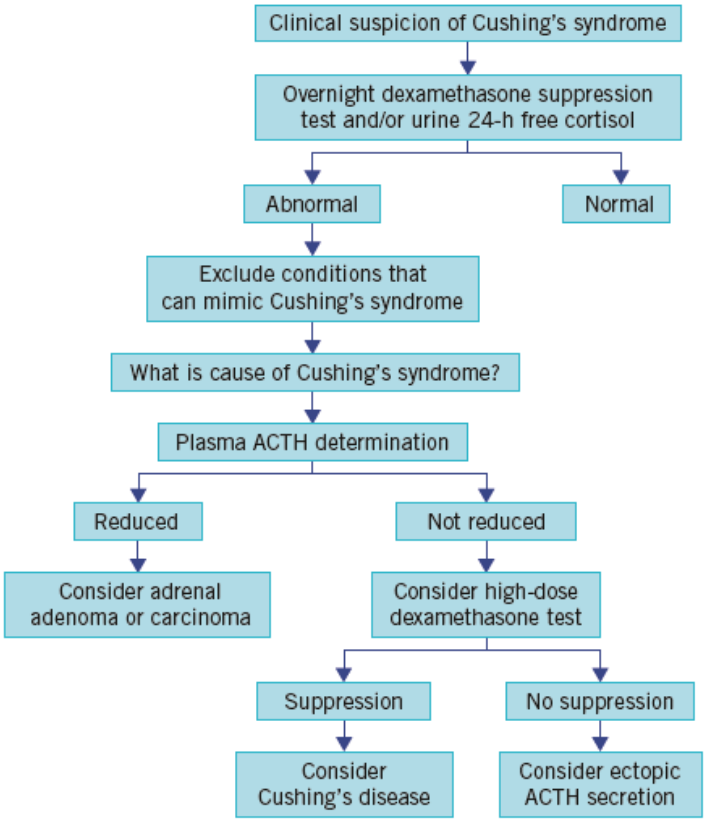


Figure 8.5 Algorithm for the investigation of Cushing's syndrome. ACTH, adrenocorticotrophic hormone.

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.
- The association of Addison's disease with hypo PTH and mucocutaneous candidiasis is described as polyglandular autoimmune syndrome type 1 and has autosomal recessive inheritance.
- Polyglandular autoimmune syndrome type 2 occurs when Addison's disease is associated with type 1 diabetes mellitus and autoimmune thyroid disease, either Hashimoto's thyroiditis or Graves' disease, .
- Tuberculosis affecting the adrenal glands is an important cause in countries where this disease is common.
- Other causes of bilateral destruction of the adrenal glands include amyloidosis, mycotic infections, (AIDS) and secondary deposits often originating from a bronchial carcinoma

An important cause of acute adrenal crisis is bilateral adrenal haemorrhage, which can occur on warfarin therapy or in patients with meningococcus septicaemia,

Certain drugs can inhibit glucocorticoid synthesis, including ketoconazole, aminoglutethimide, methadone and etomidate.

Glucocorticoid deficiency contributes to the hypotension and hypoglycaemia may be a presenting feature

. The clinical presentation of Addison's disease depends on the degree of adrenal destruction.

In cases of massive haemorrhagic adrenal destruction as in meningococcaemia, the patient may be shocked, with volume depletion; this adrenal crisis should be treated as a matter of urgency.

Conversely, sometimes the tiredness, weight loss, mild hypotension and pigmentation of the skin and buccal mucosa may occur.

The cause of these vague symptoms may only become evident if an Addisonian crisis is precipitated by the stress of some other, perhaps mild, illness or surgery.

- 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 is due to the high circulating levels of ACTH.
- Patients with primary adrenal insufficiency, as in Addison's disease due to autoimmune disease, may also show vitiligo.
- Patients with acute cortisol deficiency may present with nausea, vomiting and hypotension.
- Dilutional hyponatraemia may be present because cortisol is needed for sodium-free water excretion by the kidneys.

Other causes of hypoadrenalism

- Hypoaldosteronism hyporeninism is associated with type 2 diabetes mellitus and type IV renal tubular acidosis.
- Abnormalities of b-oxidation of very long-chain fatty acids (VLCFAs) are X-linked recessive defects in which VLCFAs accumulate in the tissues, including the adrenal glands.
- Another, rarer, cause of hypoadrenalism is Allgrove's syndrome due to congenital adrenocortical unresponsiveness to ACTH.