Endocrine system   11

Clinical

Principles of endocrine testing

The endocrine system is the mechanism by which information is communicated around the body using chemical messengers (hormones). These messengers are secreted by glands and may be transported through the bloodstream to a distant target organ (endocrine activity) or may act directly on local tissue (paracrine activity). Hormones are of various types including peptides, glycoproteins, steroids or amines such as catecholamines.

- Peptide, glycoprotein and amine hormones act by binding to cell surface receptors, which initiate a cascade of intracellular signalling molecules. These hormones may be synthesised and stored as inactive precursors (prohormones).
- Steroid hormones and thyroid hormones circulate freely and bound to plasma proteins. It is only the unbound (free) hormone that is biologically active. The bound hormone acts as a buffer against rapid changes in hormone levels. Steroid hormones act via intracellular receptors, which travel to the cell nucleus and regulate DNA transcription and hence protein synthesis.

The sensitivity of target organs to a hormone is dependent on the level of receptor expression. Prolonged exposure to a hormone often results in receptor downregulation, whereas absent or minimal hormone exposure leads to receptor upregulation.

Hormones may act on glands to cause the secretion of other hormones and may also act to downregulate their own production (negative feedback), for example the action of thyroid hormones on the anterior pituitary (see Fig. 11.1).

Endocrine dysfunction generally results in over or under functioning of a gland. Reduced function may result from a number of mechanisms. For example, hypothyroidism may result from a failure of the anterior pituitary gland or a failure of the thyroid gland. Endocrine testing is used to both identify the lack of hormone and to elucidate the underlying cause. For example,

- measurement of thyroid hormones is used to detect hypothyroidism
- measurement of thyroid stimulating hormone (TSH) helps to identify the cause. A low TSH signifies failure of the anterior pituitary (secondary hypothyroidism). A high TSH signifies failure of the thyroid gland (primary hypothyroidism).

Clinical features of apparent hormone deficiency may also result from a failure of response at the target organs.

Some hormones have cyclical or pulsatile secretion. In these cases a single random hormone sample will not determine whether the level is high or low. In such instances either testing at specific times of day (e.g. early morning cortisol levels) or dynamic endocrine testing is required. Dynamic endocrine testing uses techniques to stimulate or suppress hormone secretion. For example, cortisol is secreted from the adrenal glands in response to adrenocorticotrophin hormone (ACTH). Administering a synthetic ACTH (Synacthen) allows the response of the adrenal glands to be assessed.
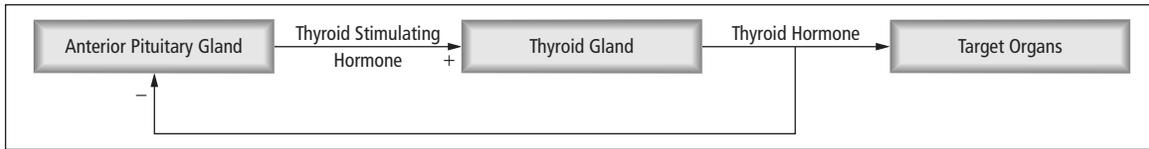
Figure 11.1 An example of negative feedback control.

The hypothalamus and pituitary

Introduction to the hypothalamus and pituitary

The pituitary gland lies in the sella turcica, which is a tightly enclosed bony space at the base of the cranium, roofed by a reflection of the dura. The optic chiasm lies just above the pituitary fossa and the cavernous sinuses run lateral to it. These structures may be affected by expansion of the pituitary gland. It consists of two lobes:

- The posterior lobe is a physical and functional extension of the ventral hypothalamus. The nerve endings within the posterior pituitary contain and secrete oxytocin and vasopression (antidiuretic hormone).
- The anterior lobe originates from Rathke's pouch. Although the anterior lobe is of separate origin to the hypothalamus, it is under its close control. Hypothalamic hormones reach the anterior pituitary in high concentrations via hypophyseal–pituitary portal veins.

The hypothalamus lies just above the pituitary, and has centres for appetite (the satiety centre), thirst, temperature control and the sleep–wake cycle. The hypothalamus secretes polypeptide hormones that regulate anterior pituitary hormone secretion, mostly by stimulation. They are secreted episodically and some, e.g. corticotrophin-releasing hormone and thyrotrophin–releasing hormone have an important circadian (*circa*-about, *dia* - day) rhythm.

The hypothalamus and pituitary form the basis of the central control of various endocrine axes, which are vital to everyday function (see Fig. 11.2). Disorders of the hypothalamus itself are very rare; however, disorders of the pituitary are common.

Pituitary adenomas

Definition
Pituitary adenomas are benign slow growing tumours arising from the anterior pituitary.

Aetiology
The cause of most pituitary adenomas is unknown. Gene mutations have been characterised in some pituitary adenomas, for example in the condition multiple endocrine neoplasia (MEN) type 1 tumours including pituitary adenomas occur due to the loss of tumour suppressor genes.

Pathophysiology
Seventy per cent of pituitary adenomas are functioning, i.e. hormone secreting. These tend to present earlier than the other 30% non-functioning tumours.
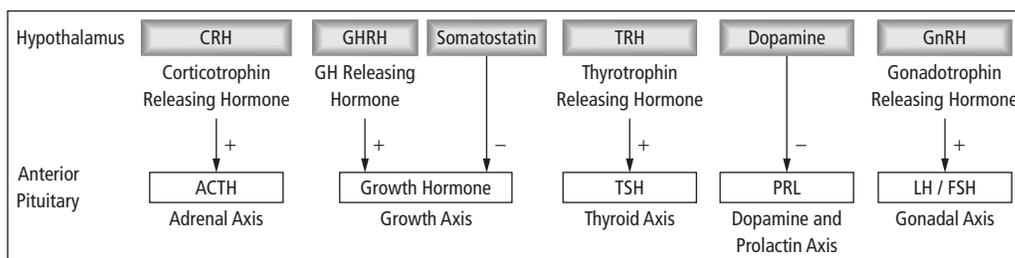

Figure 11.2 Hypothalamic and pituitary secretion.

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Table 11.1 Common hormone secreting pituitary adenomas

Hormone producing pituitary adenoma	Clinical syndrome
Prolactin (60%)	Hyperprolactinaemia (e.g. amenorrhoea and subfertility in women)
Growth hormone (20%)	Acromegaly Gigantism
Adrenocorticotrophic hormone (10%)	Cushing's disease

Clinical features

Pituitary adenomas produce symptoms through local pressure such as headache, and visual loss due to pressure on the optic chiasm (bilateral temporal heminanopia). Continuing growth disrupts other hormone secretion and can result in hypopituitarism. Symptoms may also result from the effects of hormone excess (see Table 11.1).

Macroscopy

- Tumours less than 1 cm in diameter without enlargement of, or extension outside the pituitary fossa are defined as microadenomas.
- Tumours larger than 1 cm in diameter are called macroadenomas and may cause pituitary fossa enlargement.
- Tumours $\geq$1–2 cm may extend outside the fossa towards the hypothalamus and optic chiasm, laterally into the cavernous sinus or downwards into the sphenoid sinus.

Investigations

- A mass within the sella turcica (pituitary fossa) may be identified on plain skull X-ray.
- MRI scanning using gadolinium contrast is the imaging modality of choice. Microadenomas take up less contrast and macroadenomas take up more contrast.
- If a pituitary mass is identified, hormone assays should be undertaken to identify functioning adenomas. Testing also helps identify any associated hypopituitarism, with stimulation or suppression testing where appropriate.

Management

- For prolactinomas medical treatment with a dopaminergic drug is the treatment of choice (see section on Hyperprolactinaemia, page 424).

- For other pituitary adenomas, transsphenoidal resection is the treatment of choice, with postoperative radiotherapy for patients where complete resection has not been possible. Major postoperative complications include CSF leakage, meningitis or visual impairment, which are most frequent in patients undergoing large resections. Transient diabetes insipidus or syndrome of inappropriate anti-diuretic hormone (SIADH) may also occur. Increasingly asymptomatic pituitary adenomas are found at incidental imaging. In elderly or infirm patients surgery may not be appropriate.
- All patients require regular assessment for hormone deficiencies with replacement therapy used as necessary.

Hypopituitarism

Definition

Hypopituitarism is a clinical term referring to underfunction of the pituitary gland. This may imply a deficiency of single or multiple hormones.

Aetiology

The commonest causes are pituitary or hypothalamic tumours, or secondary to pituitary surgery or cranial radiotherapy (see Table 11.2).

Pathophysiology

Hypopituitarism may be primary due to destruction of the anterior pituitary gland or secondary to a deficiency of hypothalamic stimulation (or excess of inhibition).

Clinical features

Symptoms and signs are related to the deficiency of hormones (see Table 11.3). General symptoms of panhypopituitarism include dry, pale skin with sparse body hair. On examination postural hypotension and bradycardia may be found with decreased muscle power and delayed deep tendon reflexes.

Investigations

All functions of the pituitary should be assessed using basal levels, stimulation tests and suppression testing where appropriate.

Table 11.2 Causes of hypopituitarism

Type	Causes
Invasive	Large pituitary adenoma
	Craniopharyngioma or primary CNS tumour
	Metastasic tumour (esp. breast)
Infarction	Postpartum necrosis (Sheehan's syndrome)
	Pituitary apoplexy (haemorrhagic infarction of pituitary tumour)
Infiltration	Sarcoidosis, haemochromatosis, histiocytosis X
Injury	Head trauma
Immunologic	Organ-specific autoimmune disease
Iatrogenic	Surgery, irradiation
Infectious	Mycoses, TB, syphilis
Idiopathic	Familial
Isolated	
GH	Dwarfism, emotional deprivation
LH, FSH	Kallmann's syndrome, weight loss, sickle cell anaemia
TSH	Chronic renal failure, pseudohypoparathyroidism
ACTH-LPH	Lymphocytic hypophysitis, familial
PRL	Pseudohypoparathyroidism

Management

Treatment of the underlying cause may be required. Hormone replacement depends on the results of pituitary function testing:

- In ACTH deficiency, lifelong glucocorticoid replacement is essential.
- In TSH deficiency, oral thyroxine is given and titrated according to free T_4. Thyroxine replacement may aggravate any partial adrenal insufficiency, if present, by increasing cortisol clearance.
- Gonadotrophin deficiency in women may be treated with cyclical oestrogen replacement to maintain secondary sexual characteristics and prevent osteoporosis. Progestagen is used to induce bleeding and prevent endometrial hyperplasia. In men testosterone replacement restores libido and potency, maintains beard growth and muscle power, prevents osteoporosis and improves sense of well-being. In adolescent males testosterone induces epiphyseal closure, so replacement therapy should be delayed as long as possible. Treatment of associated infertility requires complex hormone replacement to stimulate ovulation/spermatogenesis.
- Growth hormone deficiency is treated with recombinant human growth hormone.

Dopamine and prolactin axis

Dopamine from the hypothalamus acts to inhibit prolactin secretion from the pituitary (see Fig. 11.3).

- If the hypothalamic pituitary connection is disrupted, e.g. by stalk section or hypothalamic lesions then pituitary prolactin (PRL) secretion is uncontrolled.
- PRL release is stimulated by drugs that block dopamine receptors (e.g. metoclopramide) or cause a reduction in hypothalamic dopamine (e.g. methyldopa). Stress, sleep and nipple stimulation increase PRL.
- Oestrogens during pregnancy increase PRL secretion but also suppress milk production. As oestrogens fall postpartum, milk production accelerates.
- Administration of dopamine or levodopa inhibits PRL release. Pituitary haemorrhage causing death of the lactotrophs results in failure of lactation (Sheehan's syndrome).

Table 11.3 Features of pituitary hormone deficiency in order of frequency

| Hormone	Clinical features
Growth hormone deficiency	Changes in body composition, osteopenia and insulin resistance
	Reduced growth in childhood
Gonadotrophins (LH, FSH) deficiency	Amenorrhoea in women
	Decreased libido, impotence in men
Thyroid stimulating hormone deficiency	Hypothyroidism
Adrenocorticotrophic hormone deficiency	Adrenocortical insufficiency, but less severe than primary adrenal failure. The zona glomerulosa and aldosterone secretion usually remains relatively intact, so Addisonian crisis is rare. Symptoms are more common at times of stress, such as illness.
	Reduced adrenal androgens causes loss of body hair
Prolactin deficiency	Failure to lactate after giving birth

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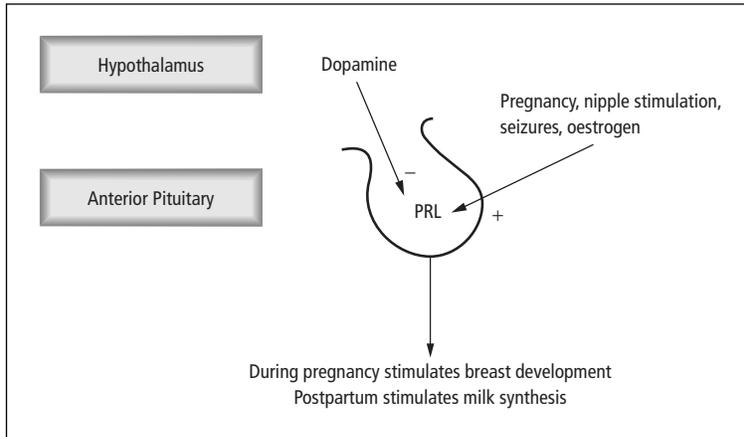
Figure 11.3 Factors affecting prolactin secretion.

Table 11.4 Factors affecting prolactin secretion

Increased prolactin (hyperprolactinaemia)	Decreased prolactin
PRL-secreting pituitary adenoma (prolactinoma)	Any cause of panhypopituitarism (see page 422)
Other pituitary tumours (reduces dopamine concentration)	Sheehan's syndrome
Hypothalamus/pituitary stalk damage	Dopamine agonists (bromocriptine/ cabergoline)
Drugs: opioids, monoamine oxidase inhibitors, cimetidine, verapamil	
Hypothyroidism (direct effect of raised TRH and TSH)	
Renal failure	
Polycystic ovarian syndrome	

- Other factors affecting PRL secretion are shown in Table 11.4.

Hyperprolactinaemia

Definition

Hyperprolactinaemia is a raised serum prolactin level causing galactorrhoea and gondadal dysfunction.

Incidence

Most common endocrine abnormality of the hypothalamic–pituitary axis.

Aetiology

Prolactin (PRL) is under the inhibitory control of dopamine released from the hypothalamus. Causes of hyperprolactinaemia are shown in Fig. 11.4 and Table 11.4.

Pathophysiology

Hyperprolactinaemia causes disturbance of the hypothalamic–pituitary–gonadal axis in both men and women, probably by a local hormonal interaction between prolactin and hypothalamic gonadotrophin-releasing hormone (GnRH) secretion.

- Gonadotrophin (luteinising hormone and follicle stimulating hormone (LH and FSH) secretion is abnormal and the mid-cycle surge in LH in women is suppressed.
- Hyperprolactinaemia in women is commonly physiological, and in men it is almost always of pathological significance.

Clinical features

In women hyperprolactinaemia causes primary or secondary amenorrhoea, oligomenorrhoea with anovulation or infertility. Galactorrhoea is variably present. Oestrogen deficiency can cause vaginal dryness and osteopenia. Hirsutism can occur, with weight gain and anxiety depression and hot flushes. In men galactorrhoea occurs occasionally, but the most common early features are decreased libido and sexual dysfunction, sometimes with impotence and infertility.
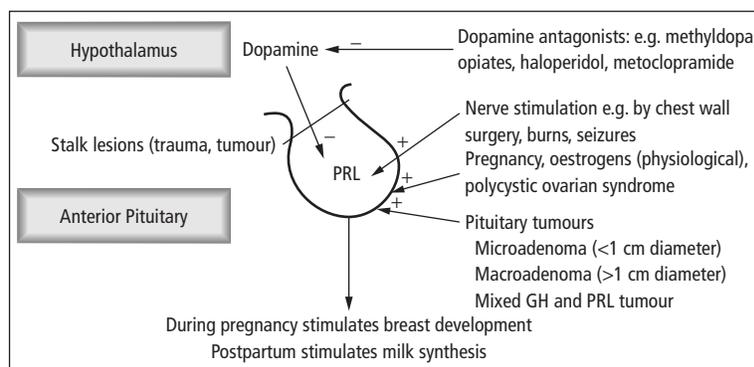
Figure 11.4 Causes of hyperprolactinaemia.

Complications
Headache, visual impairment and hypopituitarism due to local effects of the adenoma.

Investigations
Raised PRL in the absence of another cause of hyperprolactinaemia is the feature of a functioning pituitary adenoma. The serum prolactin level is in proportion to tumour size. All the pituitary hormone axes have to be tested to look for associated hypopituitarism. Plain skull X-ray is usually normal, whereas MRI will demonstrate the lesion, usually <1 cm in size.

Management
Prolactinomas are treated with dopaminergic drugs such as cabergoline. The minority of tumours that do not respond to medical treatment and hyperprolactinaemia due to stalk compression are treated surgically.

Growth axis

Growth hormone releasing hormone (GHRH or GRH) secreted from the hypothalamus in a pulsatile manner. Growth hormone (GH also called somatotrophin) promotes linear growth mainly through insulin-like growth factor (IGF-I previously known as somatomedin C), see Fig. 11.5.

Conditions that affect levels of growth hormone are shown in Table 11.5.

Acromegaly

Definition
Acromegaly is a clinical syndrome caused by growth hormone (GH)-secreting pituitary adenomas in adults.

Incidence
GH-secreting pituitary adenomas are second in frequency to prolactinomas.

Age
Can occur at any age but mean onset 40 years.

Sex
M = F

Aetiology
- 95% of cases result from growth-hormone-secreting pituitary adenoma (somatotroph). A mutation in the G_s protein leading to excessive cAMP production has been found in 40% of GH-secreting adenomas. Acromegaly may occur as part of multiple endocrine neoplasia (MEN) type I.
- In around 5% of cases there is ectopic GHRH secretion from a carcinoid tumour, GH from a pancreatic islet cell tumour, or inappropriate hypothalamic production of GRH.

Pathophysiology
Excess production of GH leads to the release of high levels of IGF-I (insulin-like growth factor) from the liver.
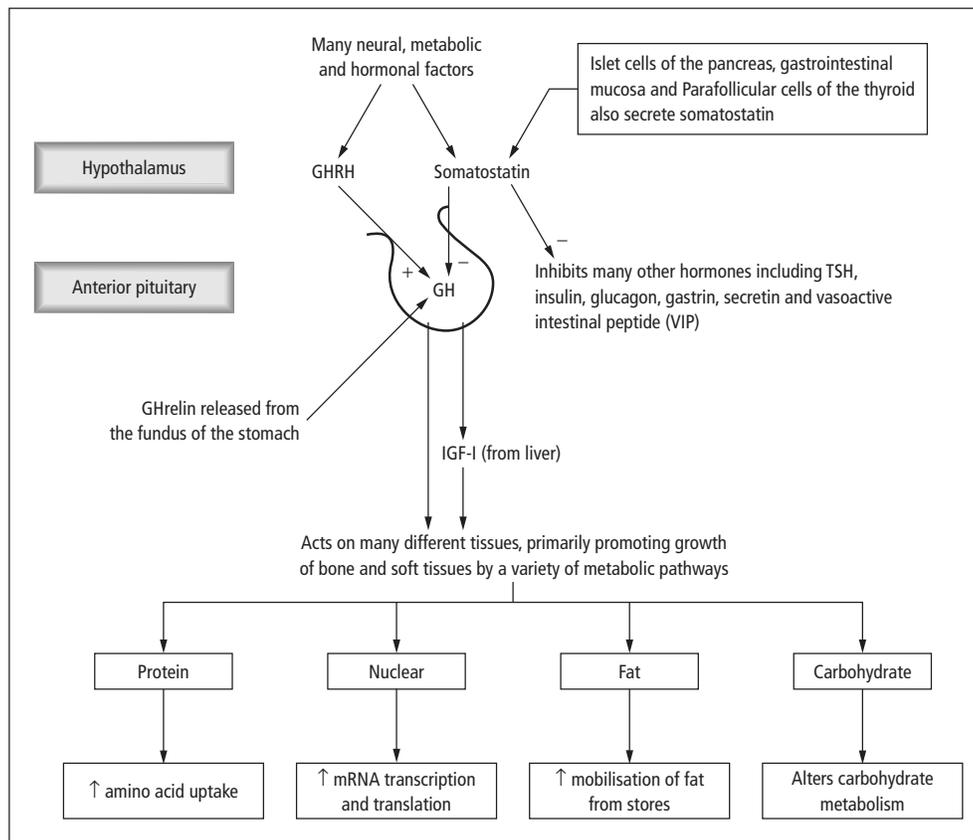
Figure 11.5 The growth axis.

Table 11.5 Causes of growth hormone excess and deficiency

Increase	Decrease
Sleep, exercise, stress	
Hypoglycaemia	Postprandial hyperglycaemia/ free fatty acids
	Glucocorticoids (hence short stature in children on long-term oral steroids)
Acromegaly (GH secreting tumour)	Hypopituitarism

The combination of high levels of GH and IGF-I leads to following:

- Overgrowth of bone and soft tissue, particularly the face and skull.
- These hormones are lipolytic, diabetogenic and cause sodium and water retention. Other endocrine and metabolic abnormalities may occur, due to the local mechanical effect of the adenoma on normal pituitary tissue.

Clinical features

The course of the disease is slowly progressive. Soft tissue overgrowth is the characteristic early feature, causing enlargement of hands and feet, coarse facial features.

- Face and skull: Thickened calvarium, prominent supraorbital ridges, enlarged nose, prognathic mandible, widely spaced teeth and puffiness of the face due to soft tissue overgrowth.
- Hands and feet are bulky, with blunt, spade-like fingers.
- Bones and joints: Arthralgia and degenerative arthritis of the spine, hips and knees due to bone and cartilage overgrowth. Carpal tunnel syndrome is common.

- Skin is thickened, oily and sweaty. Acne, sebaceous cysts and skin tags are common. Acanthosis nigricans of the axillae and neck may occur. Hypertrichosis in women.
- Cardiovascular: Hypertension in 25% of patients, and left ventricular hypertrophy and cardiomyopathy leading to cardiac failure in about 15%.
- Organomegaly: Thyroid and salivary gland enlargement, hepatomegaly.
- Diabetes in 40% of patients.

Macroscopy/microscopy

The tumour is solid and trabecular, often 1 cm in diameter by the time of diagnosis. Immunohistochemistry can be used to stain for GH.

Complications

- Renal calculi occur in 10% as a result of the hypercalciuria induced by GH excess.
- Local effects of a pituitary tumour include headache, and pressure effects such as bitemporal hemianopia. Panhypopituitarism may occur.
- Increased risk of uterine tumours and possibly of colonic polyps.

Investigations

- IGF-I and GH levels are raised, but GH levels are unreliable due to episodic secretion. An oral glucose suppression test is performed – a glucose load will fail to suppress growth hormone production.
- Imaging of the pituitary fossa by X-ray, CT or MRI.
- If there is no evidence of a pituitary adenoma GHRH may be assayed.

Management

- Wherever possible transphenoidal resection of the adenoma is the treatment of choice. Large tumours may be resected by transfrontal craniotomy. Prior to surgery hypopituitarism must be treated using cortisol and thyroxine.
- Octreotide or lanreotide, a long-acting somatostatin analogue, may be used prior to surgery, following incomplete resection or in elderly patients not fit for surgery. Dopamine agonists may be added in refractory cases.
- Irradiation may be used as an adjuvant to other therapies.

- Accompanying hypopituitarism is treated as appropriate with corticosteroids, thyroxine and gonadal steroids or gonadotrophins.

Prognosis

Follow-up is required for recurrence or loss of pituitary function. Acromegaly causes increased morbidity and mortality mainly due to diabetes and cardiovascular disease.

Thyroid axis

The thyroid axis

Thyrotrophin-releasing hormone (TRH) is released from the hypothalamus episodically and with a circadian rhythm. It stimulates the production of thyroid stimulating hormone (TSH) from the anterior pituitary gland. TSH is a glycoprotein, which binds to high-affinity receptors (TSH-R) in the thyroid gland. This in turn stimulates iodide uptake by the thyroid gland, and the synthesis and release of thyroxine (T_4) and triiodothyronine (T_3) through activation of adenylate cyclase (see Fig. 11.6).

Somatostatin and dopamine agonists decrease TSH secretion conversely dopamine antagonists increase TSH secretion. Other hormones affecting the thyroid axis include glucocorticoids, which in excess can impair the sensitivity of the pituitary to TRH and hence reduce TSH secretion. Oestrogens conversely increase the sensitivity of the pituitary to TRH.

Production and action of the thyroid hormones (T_3 and T_4)

The epithelial cells of the thyroid gland produce thyroglobulin, which can be seen in the centre of thyroid follicles and stains as pink 'colloid'. TSH stimulates the re-absorption of colloid by the cells and the production of T_3 and T_4. These hormones circulate in the blood bound to thyroxine binding globulin (TBG) and albumin. The majority of T_3 is converted from the less active T_4 by peripheral tissues. Disorders of the thyroid axis are shown in Table 11.6 and Fig. 11.7.

Goitre

A goitre is a visible or palpable enlarged thyroid. The enlargement may be generalised enlargement or diffuse

Table 11.6 Disorders of thyroid axis

|	Increased hormone	Decreased hormone
TSH	Hypothyroidism (thyroid failure and lack of feedback) TSH secreting pituitary adenoma (rare) Thyroid hormone resistance	Primary thyrotoxicosis, e.g. Graves' disease, toxic multinodular goitre (due to increased thyroid hormone negative feedback)
T_3 and T_4	Graves' disease Toxic multinodular goitre Early Hashimoto's disease	Hashimoto's disease Iatrogenic: following thyroidectomy or radioiodine treatment Iodine deficiency
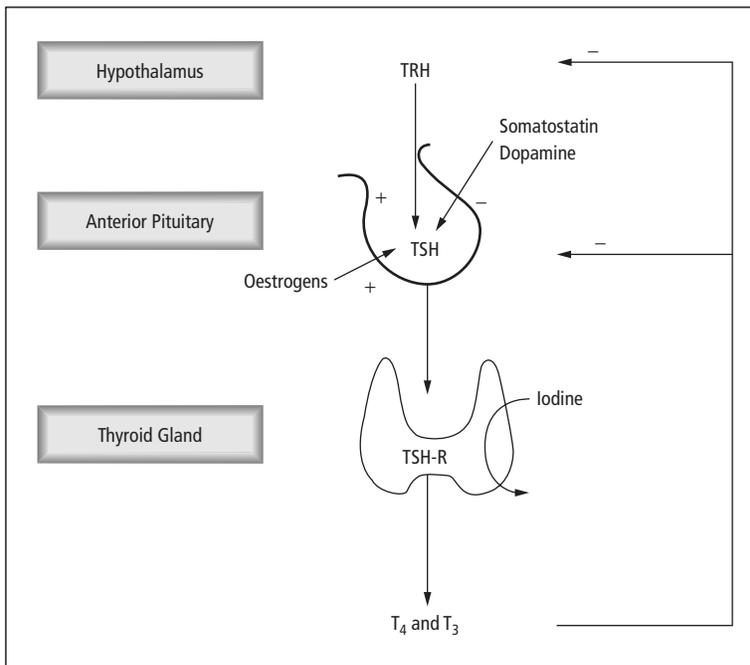
Figure 11.6 Production and action of the thyroid hormones.

goitre; or may consist of single or multiple nodules. Further classification is based on whether the patient is hyperthyroid, euthyroid or hypothyroid (see Table 11.7) and below.

Multinodular goitre

Definition
Irregular multinodular enlargement of the thyroid gland, which may be hyperthyroid (toxic) or is commonly euthyroid (nontoxic).

Incidence/prevalence
25% of cases of thyrotoxicosis are due to multinodular goitre.

Age
Increases with age.

Sex
F > M

Aetiology
Unknown. May be due to varying response of the thyroid tissue to TSH over many years.

Clinical features
Patients may present for cosmetic reasons, with thyrotoxic symptoms, or because of complications. Multinodular goitre can present with a particularly prominent thyroid nodule or a diffusely nodular gland. Most
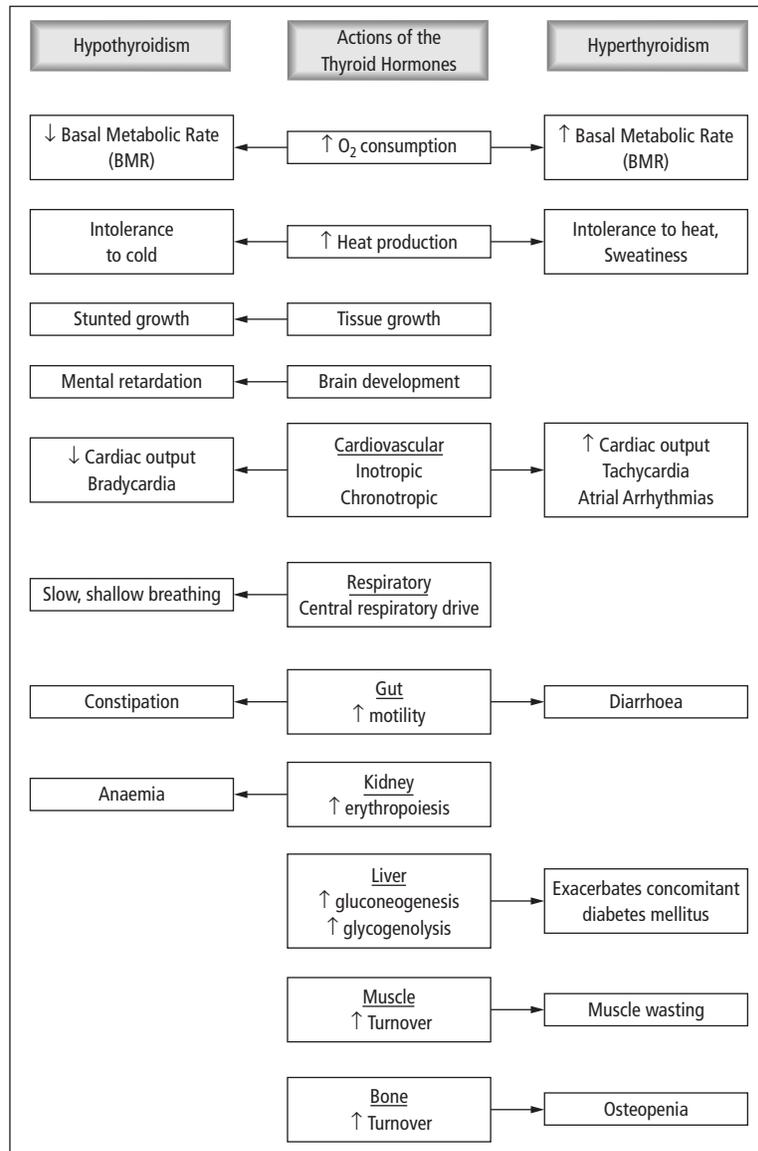
Figure 11.7 Actions of thyroid hormones in thyroid dysfunction.

Table 11.7 Causes of goitre

Hyperthyroid (toxic goitre)	Euthyroid (nontoxic goitre)	Hypothyroid
Graves' disease (thyrotoxicosis)	Pregnancy, puberty	De Quervain's thyroiditis
Toxic multinodular goitre	Endemic goitre (iodine deficiency)	Iodine deficiency
Solitary toxic nodule	Nontoxic multinodular goitre	Hashimoto's (autoimmune) thyroiditis
	Solitary thyroid nodule or cyst	

patients are euthyroid with a goitre, occasionally one or more nodules develop, which are TSH-independent and so cause thyrotoxicosis.

Macroscopy/microscopy

The thyroid is enlarged with irregular nodules of varying sizes. Nodules may be cystic, haemorrhagic and fibrosed. Microscopy reveals hyperplastic acini, with varying amounts of colloid.

Complications

Enlargement of the gland can cause tracheal compression leading to shortness of breath and choking. This is more common with retrosternal goitre, when the nodule(s) are in the isthmus. Toxic multinodular goitre has a particularly high incidence of cardiac arrhythmias and other cardiac complications.

Investigations

Thyroid function tests (TSH and thyroid hormone levels) are used to assess thyroid status. A chest X-ray can demonstrate any retrosternal mass or tracheal deviation. Ultrasound scanning of the thyroid may be useful to examine the structure of the thyroid and nature of lesions. Isotope scans are used to demonstrate areas of increased uptake in toxic multinodular goitres. Cysts and nodules may be aspirated by fine needle aspiration for cytology.

Management

Subtotal thyroidectomy may be required for cosmetic reasons or due to compression symptoms or thyrotoxicosis. Patients must be medically treated and euthyroid before surgery.

Solitary thyroid nodule

Definition

A solitary mass within the thyroid gland that may be solid or cystic.

Incidence

5% of population have a palpable solitary thyroid nodule. Up to 50% of population have a solitary nodule at postmortem.

Aetiology/pathophysiology

Solitary thyroid nodules are most commonly benign (over 90%). Causes include the following:

- Benign follicular adenoma: Single lesions with well-developed fibrous capsules. Adenomas are not under the control of TSH and continue to secrete thyroid hormones, which may result in hyperthyroidism. There are low levels of circulating TSH and hence suppression of the remainder of the thyroid gland.
- Colloid nodule that may be a dominant nodule in a multinodular goitre (see page 428).
- Malignant tumours of the thyroid follicle cells.
- Thyroid cyst (15–25%): These may be simple cysts or bleeding into a colloid nodule or adenoma. About 15% are necrotic papillary tumours.

Clinical features

Patients may present with a palpable lump or may be diagnosed on incidental imaging. Features suggestive of malignancy:

- Rapid painless growth.
- Family history of thyroid tumours or MEN 2 syndrome (see page 450).
- History of neck irradiation exposure.
- Hoarseness and vocal cord paralysis suggesting recurrent laryngeal nerve palsy.
- Malignancy is more common in children and patients over 60 years.

Investigations

- Thyroid function tests are used to determine thyroid status. Isotope scans may also be used to demonstrate either a cold nodule, a hyperactive gland (toxic multinodular goitre) or a 'cold' gland containing a 'hot' nodule (toxic adenoma). Cold nodules suggest malignancy.
- Ultrasound scan may be used to determine the anatomy of the lesion and distinguish solid from cystic nodules.
- Fine needle aspiration for cytology is used to differentiate benign cells, suspicious cells or malignant cells.

Management

Benign lesions only require treatment if they cause hyperthyroidism or for cosmetic reasons. Treatment options include surgical excision and radioactive iodine.

If suspicious cells are identified on cytology a thyroid lobectomy should be performed.

Graves' disease (primary thyrotoxicosis)

Definition
Graves' disease is an autoimmune thyroid disease.

Age
Any. Peak 20–40 years.

Sex
F > M

Aetiology
Graves' disease results from production of an autoantibody that binds to the TSH receptor and causes continuous gland stimulation.

- Fifteen per cent of patients have a close relative with Graves', and 50% of relatives have circulating thyroid autoantibodies.
- Associated with HLA-B8 and DR3 in Caucasians, and with HLA-B17 in Blacks.
- Environmental 'triggers' suggested: Pregnancy, iodide excess, infection.

Pathophysiology
Breakdown of self-tolerance results in the formation of stimulating autoantibody acting at the TSH receptor. This causes a generalised, uncontrolled stimulation of the thyroid gland initially causing hyperthyroidism. After many years the gland becomes non-functional and the patient becomes hypothyroid.

- The thyroid antigen shares epitopes with antigens on the orbital muscles, so that cytotoxic T-cells attack these tissues causing them to swell. Other complications of Graves' disease may also be due to similar epitopes being present in other tissues, e.g. skin and nail beds. These complications do not resolve on treatment to reduce the overactivity of the thyroid.
- Some symptoms of Graves' disease relate to apparent catecholamine (noradrenaline and adrenaline) excess, for example tachycardia, tremor and sweating. Thyroid hormones induce cardiac catecholamine receptors.

- The autoantibody can cross the placenta, causing neonatal hyperthyroidism.

Clinical features
Hyperthyroidism produces palpitations, nervousness, fatigue, diarrhoea, sweatiness, tremor and intolerance of heat. Weight loss with increased or normal appetite and hyperactivity are common. There is often muscle weakness, which can be severe.

The patient may have noticed the neck swelling, which is usually soft, diffusely and symmetrically enlarged. Proptosis (exophthalmos) with lid retraction, stare and lid lag are prominent features, and in its most severe form it may cause sight loss due to damage to the optic nerve. Involvement of the orbital muscles may also cause diplopia.

Less common symptoms and signs include atrial fibrillation and heart failure, depression (see also Fig. 11.7). Thyroid dermopathy (also called pretibial myxoedema) is a thickening or 'orange-peel appearance' of the skin, most often affecting the lower leg. Onycholysis (weakening, thinning and broken nails) may occur. Thyroid acropachy (osteopathy), which is a form of clubbing, is rare and may be complicated by hypercalcaemia.

Microscopy
The thyroid epithelial cells are increased in number and size with large nuclei. The colloid in the centre of the follicle shows scalloped edges, which although an artefact of processing does seem to indicate increased removal of colloid for production of thyroxine. Focal lymphocyte infiltration may also be seen.

Investigations
Thyroid function tests generally show high free triiodothyronine (T_3) and usually thyroxine (T_4), with a low thyroid-stimulating hormone (TSH). The diagnosis is made by a combination of clinical features and detection of thyroid autoantibodies.

Management
Antithyroid drugs (usually carbimazole) are given to suppress the gland. Graves' disease commonly enters remission after 12–18 months, so a trial of withdrawal is appropriate. Patients who are severely symptomatic with hyperthyroidism also benefit from β-blockers. Relapse is common (50%); treatment options include a

second course of antithyroid drugs, radioiodine therapy or surgery. Subtotal thyroidectomy results in normalisation of thyroid function in 70%. Recurrence can be treated by further surgery. The patient must be made euthyroid before surgery with antithyroid drugs and β-blockers (see page 436).

Prognosis
Thirty to fifty per cent of patients used to undergo spontaneous remission without treatment. Recurrence after treatment may be more likely in those with HLA association. Approximately 20% become hypothyroid with all types of treatment.

Thyrotoxic crisis (storm)

Definition
A rare syndrome of severe acute thyrotoxicosis, which may be life-threatening.

Aetiology
Surgery or radioactive iodine therapy in a patient with inadequately controlled thyrotoxicosis may precipitate a thyrotoxic storm. Other causes include severe illness or accident, uncontrolled diabetes, acute infection, severe drug reaction or myocardial infarction.

Pathophysiology
Levels of thyroid-binding protein in the serum fall and catecholamines are released. This results in increased free T3 and T4, coupled to increased sensitivity of the heart and nerves due to the presence of catecholamines.

Clinical features
The symptoms include life-threatening coma, heart failure and cardiogenic shock. There is a high fever (38–41°C), flushing and sweating, tachycardia, often with atrial fibrillation and heart failure. Central nervous symptoms include agitation, restlessness, delirium and coma. Nausea, vomiting, diarrhoea and jaundice occur.

Management
Concomitant use of propranolol, potassium iodide, antithyroid drugs and corticosteroids.

Table 11.8 Causes of hypothyroidism

Primary	Idiopathic/autoimmune thyroid atrophy
	Hashimoto's thyroiditis
	Iatrogenic: radioactive iodine, surgery, drugs
	Iodine deficiency (common in Nepal, Bangladesh)
	Inborn errors of hormone synthesis
Secondary	Panhypopituitarism due to pituitary adenoma
	Iatrogenic: pituitary ablative therapy/surgery
Tertiary	Hypothalamic dysfunction (rare)
	Peripheral resistance to thyroid hormone (rare)

Prognosis
Mortality of 10%.

Hypothyroidism (myxoedema)

Definition
Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones.

Aetiology
Hypothyroidism may be divided into primary thyroid failure, secondary hypothyroidism due to lack of pituitary TSH and tertiary hypothyroidism due to lack of hypothalamic thyrotrophin releasing hormone (TRH) (see Table 11.8).

Pathophysiology
Congenital hypothyroidism causes permanent developmental retardation. In children it causes reversible delayed growth and puberty, and developmental delay. Precocious puberty may occur in juveniles, due to pituitary hypertrophy. In adults it causes decreased removal of glycosaminoglycans and hence deposition in the extracellular space, especially skin, heart and skeletal muscle. There is also increased capillary permeability to albumin.

Clinical features
Usually insidious onset. Common symptoms are increasing lethargy, forgetfulness, intolerance to cold, weight gain, constipation and depression (see also Fig. 11.7).
- Cardiovascular system: The heart is less contractile causing bradycardia and reduced cardiac output. Hypercholesterolaemia increases the incidence of atherosclerosis.

- Respiratory system: Respiration may be slow and shallow. Respiratory failure occurs in myxoedema coma.
- Gastrointestinal system: Reduced peristalsis, leading to chronic constipation. Ileus may occur.
- Genitourinary system: Impaired ability to excrete water predisposes to water overload. Women may have menstrual irregularities, particularly heavy periods.
- Haematological: Anaemia (normally normochromic/normocytic).
- Other signs include a cool rough dry skin, hair loss, puffy face and hands, a hoarse husky voice and slowed reflexes. The skin may be yellowish (due to reduced conversion of carotene to vitamin A).

Complications
Pericardial and pleural effusions. Carpal tunnel syndrome. Deafness due to fluid in the middle ear.

Investigations
- Hypothyroidism is confirmed by a low T_3 and T_4 (except in end organ resistance) with a raised TSH in primary hypothyroidism. Thyroid autoantibodies are present in patients with autoimmune disease.
- Other investigations are aimed at diagnosing the underlying cause and are indicated according to the history and clinical suspicion.

Management
Thyroxine replacement starting with a low dose is required for life. Treatment of elderly patients should be undertaken with care, as any subclinical ischaemic heart disease may be unmasked. Thyroxine dosing is titrated according to thyroid function tests.

Hashimoto's disease (autoimmune thyroiditis)

Definition
Organ-specific autoimmune disease causing thyroiditis and later hypothyroidism.

Age
Peak in middle age.

Sex
F > M (10:1)

Aetiology
Patients have detectable anti-microsomal antibody and antithyroglobulin antibodies in most cases. Other autoantibodies include anti-thyroid cell cytosol and anti-microsomes associated with HLA-DR5 and other autoimmune diseases such as vitiligo and SLE.

Clinical features
The patient, typically a postmenopausal female, presents with a diffuse goitre. Although most patients are euthyroid, thyrotoxicosis can occur and if presentation is late, hypothyroidism may be present. On examination, the thyroid is firm and symmetrically enlarged with a bosselated surface.

Macroscopy/microscopy
The thyroid is diffusely enlarged and has a fleshy white cut surface due to lymphocytic infiltration, which is seen on microscopy around the destroyed follicles.

Investigations
High titres of circulating antithyroid antibodies, associated with a goitre on examination.

Management
Thyroxine may cause regression of small goitres. Large goitres require subtotal thyroidectomy if causing compression of local structures such as the oesophagus or trachea. Surgical complications include damage to the recurrent laryngeal nerves or parathyroids. Post-surgery or following significant thyroid destruction patients become hypothyroid requiring treatment with thyroxine for life.

Myxoedema coma

Definition
This is the end-stage of untreated hypothyroidism, leading to progressive weakness, hypothermia, respiratory failure, shock and death.

Incidence/prevalence
Rare

Age
Mainly in elderly.

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Sex

F > M

Aetiology

May occur in any patient with hypothyroidism (see page 432). Myxoedema coma may be precipitated by intercurrent illness or disorder, such as heart failure, perhaps following a myocardial infarction, stroke, pneumonia; iatrogenic causes include water overload and sedative or opiate drugs.

Pathophysiology

Thyroid hormones maintain many metabolic processes in the body. Severe and chronic lack of these hormones without adequate exogenous replacement leads to

- respiratory failure with CO_2 retention and hypoxia,
- water intoxication due to the syndrome of inappropriate antidiuretic hormone (SIADH) and hypothermia and
- adrenal insufficiency.

Clinical features

There may be a history of previous thyroid disease, followed by gradual onset of symptoms from lethargy through stupor to coma. The patient appears obese with hypothermia, yellowish dry skin, thinned hair, puffy eyes and has a slow pulse, respiration and reduced reflexes.

Investigations

Diagnosis may be made clinically, but is supported by a low free thyroxine (T_4) and a high TSH. Thyroid autoantibodies, blood gases, blood sugar, ECG, CXR are also required.

Management

Myxoedema coma requires admission to intensive care.

- Respiratory failure requires support and may necessitate ventilation.
- Thyroxine replacement is essential either orally or intravenously.
- Corticosteroids must be given if adrenal insufficiency is present.
- Patients also require gradual re-warming and dextrose support to prevent hypoglycaemia.

Prognosis

Myxoedema coma has a poor prognosis, particularly as it tends to occur in elderly patients who have little respiratory and cardiological functional reserve.

Malignant tumours of the thyroid

Papillary adenocarcinoma

Definition

A slow-growing, well-differentiated primary thyroid tumour arising from the thyroid epithelium.

Incidence/prevalence

50% of malignant tumours of the thyroid.

Age

Rare after the age of 40 years. Occurs in young adults.

Sex

F > M

Clinical features

Presents as a solitary or multifocal swelling of the thyroid. Lymph nodes are palpable in one-third of patients, and may be the only sign when there is a microscopic primary. Papillary tumours spread via lymphatics within the thyroid resulting in multifocal lesions and to neck nodes. Widespread metastases are rare.

Macroscopy/microscopy

Non-encapsulated mass in contrast to adenomas, which have a capsule. There is often infiltration into the surrounding tissue with associated fibrosis.

Investigations

Patients may be identified during investigation for a solitary thyroid nodule (see page 430). Definitive diagnosis is by histology, although cytology from fine needle aspiration may indicate malignancy.

Management

Total thyroidectomy with excision of involved neck lymph nodes and preservation of the parathyroid glands. Radical neck dissection is not necessary. Metastases may be treated by resection. Radioactive iodine therapy may

be used prophylactically or as treatment for metastases. Thyroxine replacement is necessary after surgery as replacement and to suppress TSH (in order to reduce the risk of recurrence).

Prognosis
Ten year survival rates of almost 90%. Cervical lymph nodes do not make the prognosis significantly worse, but if the tumour has spread from the thyroid into adjacent structures it has a poor prognosis.

Follicular adenocarcinoma

Definition
A primary malignancy of the thyroid gland arising from the thyroid epithelium.

Incidence/prevalence
Approximately 20% of cases of thyroid malignancies.

Age
Middle age

Sex
F > M

Clinical features
Typically presents as a solitary thyroid nodule in middle-aged patients.

Investigations
Patients are investigated as for a solitary thyroid nodule (see page 430). Isotope scanning of the nodule reveals it to be non-functioning or 'cold'. Definitive diagnosis requires tissue from fine needle aspiration.

Complications
Predominantly haematogenous spread. Twenty per cent of patients have metastases in the lungs, bone or liver.

Macroscopy/microscopy
Resembles a benign solitary thyroid nodule, a round encapsulated mass, but less colloid and more solid in appearance. Histology reveals invasion of the capsule, blood vessels and surrounding gland.

Management
Total thyroidectomy with preservation of the parathyroids is required. All palpable lymph nodes are removed. If these contain tumour, a modified radical neck dissection is required. A postoperative radioisotope scan of the skeleton and neck detects metastases as 'hot spots', and further treatment is with radioiodine. Thyroxine is given to suppress TSH secretion, as well as for replacement.

Prognosis
Follicular carcinoma is more aggressive than papillary carcinoma. Ten year survival is 50%. Plasma thyroglobulin levels can be monitored for recurrence.

Medullary carcinoma

Definition
Tumour of the thyroid that arises from the parafollicular C-cells, which secrete calcitonin.

Aetiology
Approximately one-third are seen in children and young adults as part of MEN (multiple endocrine neoplasia) type II syndrome (see page 450). The other two-thirds are sporadic cases.

Pathophysiology
The parafollicular cells originate from neural crest tissue during embryonic life, but merge with the embryonic thyroid and are dispersed amongst the follicular cells. Parafollicular cells normally secrete calcitonin, a polypeptide, in response to small increases in calcium. The tumour cells secrete calcitonin and carcinoembryonic antigen (CEA) and are also capable of secreting prostaglandins and serotonin.

Clinical features
One or both thyroid lobes are enlarged and firm. Cervical lymph nodes are palpable in about half of cases, but the tumour is generally slow growing and tends only to metastasise to local lymph nodes. Those associated with MEN syndrome tend to be more aggressive.

Microscopy
The tumour is composed of sheets of small cells containing neuroendocrine granules with a hyaline

stroma between them. Spread is mainly to local lymph nodes.

Investigations

Calcitonin levels are raised, although serum calcium levels are normal. Calcitonin is also used for follow-up and for screening of relatives.

Management

Total thyroidectomy and dissection of lymph nodes in the central neck compartment.

Anaplastic carcinoma

Definition

This is a highly malignant tumour of the thyroid.

Incidence/prevalence

10–15% of cases of malignant tumours of the thyroid.

Pathophysiology

There is evidence that these are poorly differentiated adenocarcinomas derived from thyroid epithelium. They often arise in elderly patients with a long history of goitre in whom the gland suddenly enlarges.

Clinical features

These tumours are rapidly growing and invade local structures early, most patients present with a rapidly enlarging neck swelling and complications such as hoarseness, dyspnoea and stridor, dysphagia and Horner's syndrome (miosis, partial ptosis and anhydrosis).

Macroscopy/microscopy

Diffusely infiltrative mass, often invading neighbouring tissues. Composed of various undifferentiated cells.

Management

Resection is rarely possible, but may be carried out for palliative relief of tracheal compression. Radioactive iodine and radiotherapy are ineffective.

Prognosis

Poor: 1-year survival is ∼30%.

Thyroidectomy

Hyperthyroid patients must be made euthyroid before thyroid surgery using antithyroid drugs and β-blockers to reduce complications such as cardiac arrhythmias, excessive sympathetic activity and bleeding.

The thyroid is exposed via a transverse skin-crease incision above the sternal notch. The lobes of the thyroid are supplied by the superior and inferior artery, and drained by the middle and inferior veins. These are dissected out, ligated and divided removing the desired amount of thyroid tissue. Surrounding structures that require identification and protection include the parathyroid glands and the recurrent laryngeal nerves.

- Complications include haemorrhage, leading to tracheal compression; damage to the superior or recurrent laryngeal nerve; damage or excision of parathyroid glands; and scarring. Neuropraxia (temporary damage) of the recurrent laryngeal nerve occurs in 5% of operations. The ipsilateral vocal cord becomes paralysed and fixed midway between closed and open. Bilateral nerve injury is rare but causes stridor and may subsequently require laryngoplasty or permanent tracheostomy.
- Postoperative calcium levels should be monitored to look for hypocalcaemia, which is usually transient, due to damage to the parathyroid glands. Subsequent hypothyroidism is treated with lifelong thyroxine supplements.

Adrenal axis

Corticotrophin releasing hormone (CRH) is secreted from the hypothalamus in a diurnal pattern. Adrenocorticotrophic hormone (ACTH) is secreted by the pituitary in response to CRH that in turn activates the enzyme desmolase in the adrenal glands converting cholesterol to pregnenolone. This is the rate-limiting step for the production of all the adrenocortical hormones. Cortisol is mainly controlled in this way, aldosterone is mainly controlled by the renin-angiotensin system, and androgens

Table 11.9 Abnormalities of the adrenal axis

	Increased hormone	Decreased hormone
CRH	Cushing's disease	
	CRH-secreting tumour (very rare)	
ACTH	Cushing's disease	Hypopituitarism
	(ACTH-secreting pituitary tumour)	
	Addison's disease	
	Nelson's syndrome	
Mineralocortic oids	Primary hyperaldosteronism (adenoma or hyperplasia)	Adrenocortical insufficiency
	Secondary hyperaldosteronism	
Glucocorticoids	Cushing's syndrome	Adrenocortical insufficiency
	Causes include nodular hyperplasia, adrenal cortex tumour	
Androgens	Congenital adrenal hyperplasia	Adrenocortical insufficiency
	Also hyperplasia and tumours	
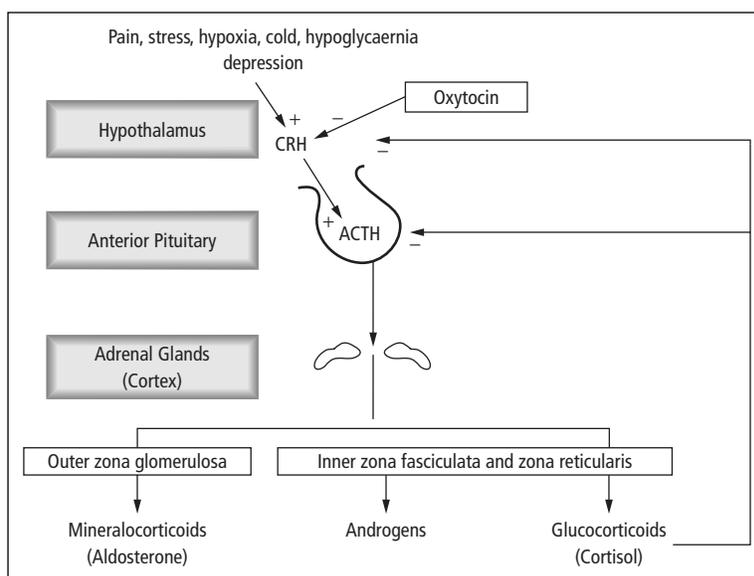
Figure 11.8 The adrenal axis.

are also secreted by the gonads (see Fig. 11.8 and Table 11.9).

Aldosterone

Aldosterone is the corticosteroid with the most mineralocorticoid activity, so-called because it controls sodium, potassium and water balance. Its production is stimulated mainly by the renin–angiotensin system. Renin is secreted from the juxtaglomerular apparatus in the kidney in response to reduced renal blood flow, for example due to hypotension. In response aldosterone acts on the kidney and vasculature (see Fig. 11.9).

When aldosterone levels are high this may be due to high renin levels (secondary hyperaldosteronism) or it may be independent of renin production (primary hyperaldosteronism).

Cortisol

Cortisol is the major glucocorticoid, although aldosterone and corticosterone also have some effect. The glucocorticoids control glucose metabolism, for example gluconeogenesis, and mobilisation of fat stores (lipolysis) amongst other actions. Cortisol exerts a negative feedback on ACTH and CRH secretion. Glucocorticoids
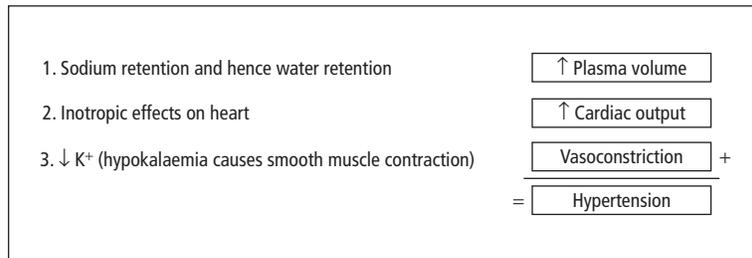
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1. Sodium retention and hence water retention	↑ Plasma volume
2. Inotropic effects on heart	↑ Cardiac output
3. ↓ K⁺ (hypokalaemia causes smooth muscle contraction)	Vasoconstriction +
	= Hypertension

Figure 11.9 Effects of aldosterone.

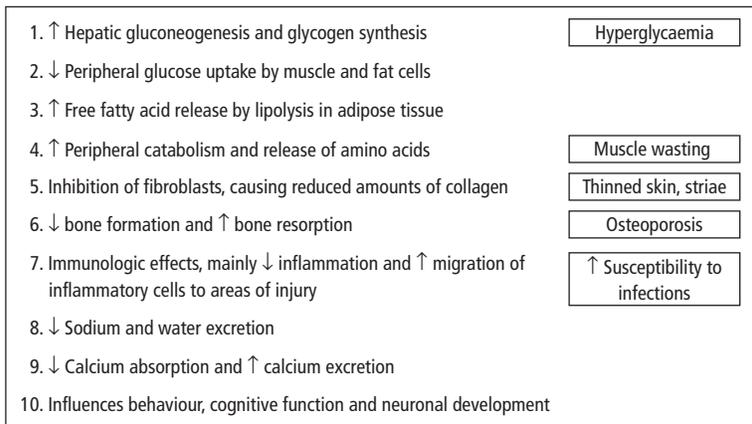| 1. ↑ Hepatic gluconeogenesis and glycogen synthesis | Hyperglycaemia |
2. ↓ Peripheral glucose uptake by muscle and fat cells	
3. ↑ Free fatty acid release by lipolysis in adipose tissue	
4. ↑ Peripheral catabolism and release of amino acids	Muscle wasting
5. Inhibition of fibroblasts, causing reduced amounts of collagen	Thinned skin, striae
6. ↓ bone formation and ↑ bone resorption	Osteoporosis
7. Immunologic effects, mainly ↓ inflammation and ↑ migration of inflammatory cells to areas of injury	↑ Susceptibility to infections
8. ↓ Sodium and water excretion	
9. ↓ Calcium absorption and ↑ calcium excretion	
10. Influences behaviour, cognitive function and neuronal development	

Figure 11.10 Effects of cortisol.

are most important during fasting, illness or surgery (see Fig. 11.10).

Androgens

Androstenedione is produced by the adrenal cortex and is converted to testosterone and dihydrotesterone. In males, 95% of active testosterone is derived from the testis, so adrenal androgen excess or deficiency is relatively insignificant. In females 50% of the peripheral production of testosterone is from adrenal androgens. Female neonates with congenital adrenal hyperplasia have ambiguous genitalia (clitoromegaly). Adults with Cushing's syndrome and adrenal tumours with hypersecretion of adrenal androgens have acne, hirsutism and virilisation.

Cushing's syndrome

Definition

Cushing's syndrome is the clinical syndrome resulting from excess circulating glucocorticoids.

Aetiology

The excess of glucocorticoid may be endogenous or exogenous. Endogenous glucocorticoids may result from high ACTH causing excessive adrenal stimulation or may result from a primary adrenal disease in which case ACTH levels will be low (see Table 11.10).

Pathophysiology

Cortisol opposes insulin, with a catabolic effect. Adrenal mineralocorticoid secretion is mildly raised, but the glucocorticoids also have some mineralocorticoid effect. Excess androgens can cause mild hirsutism, menstrual irregularities in women, and can inhibit LH and testosterone secretion in men, reducing libido.

Clinical features

Common features include centripetal obesity (moon face, buffalo hump), plethora, osteoporosis, proximal myopathy, easy bruising, striae, acne, hirsutism, poor wound healing and glucose intolerance. Gonadal dysfunction leads to oligo- or amenorrhoea or impotence.

Table 11.10 Causes of Cushing's syndrome

ACTH-dependent (83%)	
Pituitary-dependent (∼80%)	Pituitary hyperplasia
	Pituitary adenoma (Cushing's disease)
	Pituitary carcinoma
Ectopic ACTH secretion (<20%)	Neuroendocrine tumours: oat cell carcinoma, bronchial carcinoid tumour, medullary thyroid carcinoma, pancreatic carcinoma, phaeochromocytoma
Non-ACTH dependent (16%)	
Primary adrenal disorder	Adrenal adenoma (58%)
	Adrenal carcinoma (42%)
Unknown/mixed aetiology (1%)	Multinodular hyperplasia of the adrenals
Cushingoid appearance	
Iatrogenic	Glucocorticoid therapy
	ACTH therapy (rare)
Pseudo-Cushing's syndrome	Alcoholics
	Severe depression

Hypertension, hypokalaemia and metabolic alkalosis may be present. Euphoria, mania and depression may also be features.

Patients with ectopic ACTH syndrome may have profound hypokalaemia, weight loss (therefore lack of obesity) and anaemia. Hyperpigmentation in an Addisonian distribution (skin creases, pressure points, in the mouth) suggests ACTH excess, and thus an ACTH-dependent cause.

Investigations
Initial diagnosis is confirmed by demonstrating high cortisol levels. As there is a diurnal rhythm and variable cortisol secretion a 24-hour urine collection or low-dose dexamethasone suppression test is used (see Fig. 11.11).

Management
Adrenal adenomas and carcinomas should be resected if possible. Pituitary tumours may also be resected. If surgery is not possible, drugs that block cortisol synthesis such as metyrapone, which inhibits 11-hydroxylase, are used, but these cause a rise in ACTH, which overcomes the inhibition. Radiotherapy is used in treatment of unresectable pituitary adenomas.

Prognosis
Patients require lifelong steroid replacement therapy after bilateral adrenalectomy, but may only need it for 1–2 years after unilateral removal.

Cushing's disease

Definition
In 1932, Harvey Cushing described pituitary adenomas as a cause of adrenocortical excess.

Incidence/prevalence
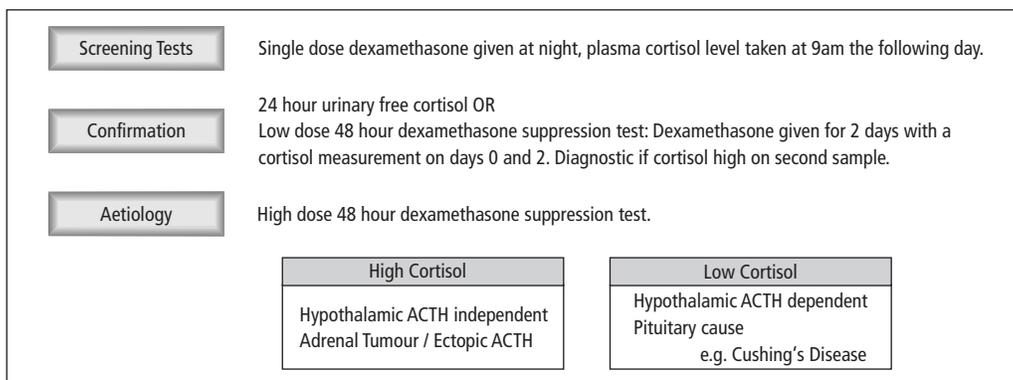80% of Cushing's syndrome are due to a pituitary cause.

Figure 11.11 Tests used in the screening for and diagnosis of Cushing's syndrome.

Age
Any age, peak 20–40 years.

Sex
8F : 1M

Aetiology
In virtually all patients, an ACTH-secreting pituitary adenoma is found, occasionally the cause is hypothalamic oversecretion of corticotrophin releasing hormone (CRH).

Pathophysiology/clinical features
As for Cushing's syndrome. Unlike patients with ectopic ACTH syndrome, patients with pituitary adenomas rarely have hypokalaemia, weight loss, anaemia or hyperpigmentation.

Macroscopy
Bilateral adrenocortical hyperplasia twice the size of normal, with thickening of zona reticularis and the zona fasciculata. The zona glomerulosa appears normal, because mineralocorticoid production is controlled primarily by the renin–angiotensin system.

Microscopy
The pituitary tumour is normally a microadenoma. The cells contain ACTH and its related peptides.

Investigations
As for Cushing's syndrome (see page 438).

Management
The treatment of choice is transsphenoidal hypophysectomy. Irradiation is used post-surgery, for patients where complete resection was not possible. Drugs which inhibit adrenal cortisol synthesis are often used as adjunctive therapy, e.g. ketoconazole, metyrapone and aminoglutethimide. Their disadvantage is that they increase ACTH secretion so this enzyme inhibition is overcome and the clinical effect is short-lived.

Bilateral adrenalectomy is still used if the adrenals have become semi-autonomous, however it must be followed by pituitary treatment (e.g. irradiation) as otherwise the pituitary adenoma can progress to cause hyperpigmentation, local pressure effects and Nelson's syndrome (an ACTH-secreting tumour of the pituitary which enlarges post-bilateral adrenalectomy).

Addison's disease

Definition
First described by Thomas Addison in 1857, Addison's disease is primary adrenal insufficiency.

Aetiology
In Western countries autoimmune disease is the commonest cause (80%). It is familial, and associated with other organ specific autoimmune diseases, especially thyroid failure (Schmidt syndrome), autoimmune gastritis, pernicious anaemia and vitiligo. Presence of HLA-B8 association carries a x12 risk of developing disease. Worldwide, tuberculosis is still a very important cause (see Table 11.11).

Pathophysiology
- The mineralocorticoids (90% activity by aldosterone, some by cortisol) act on the kidneys to conserve sodium by increasing Na^+/ K^+ exchange in the distal tubules and collecting ducts. In Addison's disease, gradual loss of these hormones causes increased sodium and water loss with a consequent decrease in

Table 11.11 Causes of adrenal insufficiency

Primary
Congenital/familial
Adrenal enzyme defects
Congenital adrenal hypoplasia
Acquired
Infectious – TB, histoplasmosis, HIV associated cytomegalovirus
Autoimmune
Vascular – haemorrhage (associated with meningococcal septicaemia – Waterhouse-Friderichsen syndrome), thrombosis
Neoplastic – secondary carcinoma (e.g. lung)
Degenerative – amyloid
Secondary
Hypopituitarism
Isolated ACTH deficiency
Following glucocorticoid therapy
Drug-induced glucocorticoid metabolism
Rifampicin, carbamazepine

extracellular fluid volume. Failure to exchange Na$^+$ for H$^+$ ions can lead to a mild acidosis.

- The glucocorticoids (cortisol) allow gluconeogenesis to maintain glucose concentrations between meals, and mediate protein and fat mobilisation from the tissues. Reduced cortisol may lead to symptomatic hypoglycaemia.
- Lack of cortisol feedback leads to increased ACTH (adrenocorticotrophin) secretion from the anterior pituitary. When ACTH is secreted by the anterior pituitary, other hormones are also secreted such as β-endorphin and melanocyte-stimulating hormone (MSH) causing skin pigmentation.
- Once mineralocorticoid secretion ceases completely, the patient will die within 2 weeks if not treated, from progressive weakness and eventual shock.

Clinical features

Patients present with gradual onset of weakness, tiredness and fatigue. There are often gastrointestinal complaints such as anorexia, nausea, vomiting, abdominal pain, constipation or diarrhoea. The patient may report salt craving.

Examination reveals weight loss, hyperpigmentation especially in mouth, skin creases and pressure areas. Chronic dehydration leads to general and especially postural hypotension.

Complications

Renal failure due to decreased perfusion. Sudden cardiac arrest or arrhythmias due to electrolyte imbalance.

Investigations

- Hyponatremia, hyperkalemia and a hyperchloraemic acidosis due to mineralocorticoid deficiency. Glucose should be measured to detect hypoglycaemia.
- Screening can be performed by measurement of early morning cortisol and 24 hour urinary cortisol.
- Primary adrenal insufficiency is confirmed by use of the short Synacthen (ACTH analogue) test. Cortisol levels are measured before and 30 mins after administration of synacthen and show a low base line and a lack of rise in Addison's Disease. Adrenal insufficiency that results from ACTH deficiency (secondary and tertiary adrenal insufficiency) will result in an appropriate rise in cortisol following Synacthen. A long Synacthen test using a depot injection and repeated cortisol

samples over a 24-hour period is used to distinguish between Addison's disease (primary adrenal failure) and adrenal suppression.

Management

Chronic adrenal insufficiency is treated with glucocorticoids and mineralocorticoids. Patients require significant education about the illness and how to manage co-existing illness or stress, such as at the time of operations when increased steroids may be required. Parenteral steroids are needed if vomiting occurs. All patients requiring replacement steroids should carry a steroid (blue) card.

Addisonian crisis

Definition

Acute presentation of complete adrenal failure.

Aetiology

Patients may already be diagnosed with Addison's Disease or may present in crisis for the first time. Precipitating factors include trauma, illness or surgery. It may also be caused acutely by bilateral adrenal haemorrhage, due to meningococcal septicaemia (Waterhouse-Friderichsen syndrome) or anti-coagulant therapy. An Addisonian crisis may also occur on cessation of glucocorticoid treatment including inhaled glucocorticoids in children.

Pathophysiology

In adrenal failure, there is no glucocorticoid response to stress. If exogenous high-dose steroids are not provided the condition is fatal.

Clinical features

The patient is ill with anorexia, vomiting and abdominal pain. This may suggest an acute abdomen. Signs include pyrexia and dehydration with tachycardia, hypotension (postural drop) decreased skin turgor and sunken eyes. Increased pigmentation may be noticed, especially in mouth, skin creases and pressure areas.

Investigations

- Urgent cortisol and ACTH if possible.
- U&Es (hyponatraemia, hyperkalaemia and hyperchloraemia).

- Blood sugar monitoring to detect hypoglycaemia.
- Definitive investigations should not delay treatment, steroids will not interfere with test results in the short-term.

Management
Immediate fluid resuscitation with 0.9% saline (and 5% dextrose if hypoglycaemia is present). Intravenous hydrocortisone and broad-spectrum antibiotics are given. Any underlying causes need to be identified and appropriately managed.

Prognosis
Has a high mortality.

Conn's syndrome

Definition
Conn's syndrome is a condition of primary hyperaldosteronism.

Incidence/prevalence
Rare. Accounts for 1% patients with hypertension.

Aetiology
Eighty per cent of cases are due to an adrenal adenoma. In the remainder, there is diffuse hyperplasia of the zona glomerulosa. Very rarely it is caused by an adrenal carcinoma. Raised aldosterone is much more commonly a physiological response to reduced renal perfusion as in renal artery stenosis or congestive cardiac failure.

Pathophysiology
Aldosterone is the most important mineralocorticoid produced by the zona glomerulosa. It acts on the Na^+/K^+ pump in renal tubular epithelial cells in the collecting tubules, distal tubule and collecting duct increasing the absorption of sodium and hence water with increased loss of potassium. The rise in blood volume increases renal perfusion and arterial blood pressure. However there is a significant loss of K^+ leading to hypokalaemia and resistance to antidiuretic hormone. This causes increased urinary volumes and hence increased thirst.

Clinical features
Hypertension and symptoms resulting from the hypokalaemia such as cardiac arrhythmias, muscle weakness, cramps, latent tetany and paraesthesiae. The muscle weakness may present with paralysis. Polydipsia and polyuria may be a feature.

Macroscopy/microscopy
Adrenal cortical adenomas are well-circumscribed, yellow lipid laden tumours within the adrenal cortex. Adrenal cortical carcinomas are larger, with local invasion and metastatic spread. In hyperplasia, the glands are enlarged, with increased number, size and secretory activity of the cells within the zona glomerulosa.

Investigations
- Urea and electrolytes demonstrate the hypokalaemia and may show a mild rise in sodium. Hypokalaemia may lead to a mild metabolic alkalosis (H^+/K^+ exchange in the kidney). However, the use of diuretics to treat hypertension may mimic or mask these features. A high urinary K^+ (>30 mmol/24 h) suggests primary aldosteronism.
- The definitive test is to measure aldosterone and renin baselines after a night's rest (low in $1°$ aldosteronism, high in $2°$ aldosteronism) and after being upright (stimulates renin in normal individuals, but aldosteronism suppresses renin).
- CT scan of the adrenal glands. If negative, selective blood sampling may be required to find the source of aldosterone.

Management
Bilateral adrenal hyperplasia is usually treated with spironalactone (inhibits the Na^+/K^+ pump, i.e. antagonises aldosterone) to control the blood pressure. Adenomas and carcinomas should be removed surgically. Spironalactone may be used prior to surgery.

Prognosis
30% have persistent hypertension after treatment, thought to be due to irreversible renal damage.

Phaeochromocytoma

Definition
An APUD (amine precursor uptake and decarboxylation) tumour of the adrenal medulla which produces adrenaline and noradrenaline.

Incidence
Uncommon. The cause of 0.2–0.5% of cases of adult hypertension.

Age
Peak age 40–60 years.

Sex
M = F

Aetiology
Associated with the Multiple Endocrine Neoplasia (MEN) type II (see page 450). Also may be associated with von Hippel-Lindau syndrome, neurofibromatosis, tuberose sclerosis and the Sturge-Weber syndrome.

Pathophysiology
10% of cases are malignant, 10% are extra-adrenal and 10% are bilateral. The adrenal medulla is functionally related to the sympathetic nervous system, secreting adrenaline and noradrenaline in response to sympathetic stimulation. High levels of sympathetic stimulation result in increased heart rate, blood pressure, and sweating. There is decreased blood supply to the gut, increased sphincter activity and metabolic effects, such as diabetes and thyrotoxicosis.

Clinical features
Patients normally present with episodic headache, sweating, and palpitations. They are found to be hypertensive which may be paroxysmal or continuous. Other signs include pallor, dilated pupils and tachycardia. There may be a postural hypotension secondary to volume depletion. Phaeochromocytoma may present in pregnancy, or with sudden death following trauma or surgery.

Macroscopy
Usually up to 5 cm spherical tumour with a pale cut surface that oxidises to brown when exposed to air. Extramedullary tumours are usually found in the sympathetic chain, alongside the abdominal aorta.

Complications
Cardiovascular disease or cerebral haemorrhage. Persistent hypertension causes hypertensive retinopathy.

Investigations
Diagnosis is by measuring plasma levels of noradrenaline, and urinary adrenaline and noradrenaline or their metabolites vanillylmandelic acid (VMA) and homovanilyic acid (HVA). The paroxysmal secretion of the hormones may mean repeated measurements are needed. Adrenal CT scan is used to locate the tumour, scanning with a radiolabelled catecholamine precursor (MIBG) can identify extra-adrenal tumours.

Management
- Surgical excision where possible is the treatment of choice. Surgery has a high peri-operative risk and requires expert anaesthetic supervision. The blood pressure must be carefully monitored and any rise countered with i.v. phentolamine (α-receptor antagonist) or nitroprusside. Intensive care postoperatively is preferred.
- Adrenergic blockade is necessary to oppose the catecholamine effects before surgery. Phenoxybenzamine (an α-receptor antagonist) is used initially, followed by β-blockade with propanolol.
- In cases where surgery is not possible combined long term α- and β-blockers are used.

Prognosis
10% of phaechromocytomas are malignant these have a 5 year survival of less than 50%. Overall recurrence rate of 10–15%.

Adrenalectomy

Surgical removal of the adrenal glands may be necessary for a number of conditions (see Table 11.12). Large tumours, which may be malignant, are removed via a

Table 11.12 Indications for adrenalectomy

Unilateral adrenal adenomas	Cushing's syndrome
	Conn's syndrome
	Phaeochromocytoma
	Secondary metastases, e.g. renal cell carcinoma
Bilateral adrenalectomy	Bilateral tumours
	Nodular hyperplasia (causing Cushing's or Conn's syndrome)
	Cushing's syndrome if pituitary treatment fails

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flank incision following removal of a rib. The diaphragm, pleura and peritoneum are left intact wherever possible. A posterior approach through the bed of the 11th or 12 rib is more difficult, but has a lower morbidity. Lifelong corticosteroid (both glucocorticoid and mineralocorticoid with hydrocortisone and fludocortisone) replacement therapy is needed following bilateral adrenalectomy. Laparoscopic adrenalectomy is increasingly being used.

Replacement is monitored by blood pressure measurement, serum electrolytes and patient well-being. Stress, infection and surgery may all increase corticosteroid requirements, and may precipitate an Addisonian crisis (see page 441). Patients need to be advised of the signs and symptoms and management of such events.

Thirst axis

Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)

Definition
SIADH is characterised by the persistence of ADH secretion despite decreased plasma osmolality and normal or increased extracellular fluid volume.
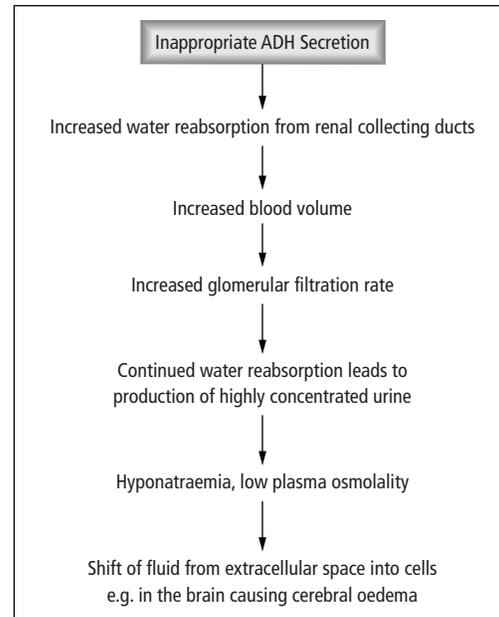
Aetiology
See Table 11.13.

Figure 11.12 Pathophysiology of SIADH.

Pathophysiology
ADH is a peptide hormone similar to oxytocin which is normally secreted from the posterior pituitary, in response to an increase in plasma osmolality. It acts on the collecting tubules in the kidney to make them more permeable to water molecules. Hence its secretion causes water retention (see Fig. 11.12).

Table 11.13 Causes of syndrome of inappropriate anti-diuretic hormone secretion (SIADH)

Ectopic secretion	Small-cell bronchial carcinoma
	Rarely carcinoma of the thymus, prostate, pancreas, duodenum, adrenal, ureter or nasopharynx
	Lymphoma, leukaemia
Inappropriate secretion (hypothalamus)	
Lung disease	Pneumonia, tuberculosis, aspergillosis
	Positive pressure mechanical ventilation (stretch receptors)
Neurological	Trauma (including neurosurgery or major surgery)
	Encephalitis, post-meningitis
	Ischaemia (stroke, vasculitis)
	Tumours
Drugs	Carbamazepine, chlorpropamide, tricyclics, phenothiazines, syntocinon, narcotics and cytotoxic drugs (vinca alkaloids – cyclophosphamide, vincristine)
Other	Pain, intermittent acute porphyria, Guillain–Barré syndrome, hypothyroidism, symptomatic HIV infection or AIDS

Clinical features

Patients present with headache, confusion, behavioural changes, convulsions and coma. On examination there is no peripheral oedema. There may be muscle twitching with an extensor plantar reflex.

Investigations

Electrolyte analysis will reveal hyponatraemia with reduced plasma osmolality, and high urinary osmolality and sodium. Plasma osmolality can be estimated from the sodium, urea and glucose concentrations ($\sim$2x [Na] + [Urea] + [glucose]).

Management

Fluid restriction is the mainstay of treatment, although this is unpleasant for the patient and often difficult to enforce. It is also a useful diagnostic test. Demeclocycline, an ADH antagonist at the renal collecting ducts can be used, but is nephrotoxic, especially in the elderly. If water intoxication is severe, diuretics with hypertonic saline infusion is used. Any underlying cause should be identified and treated.

Prognosis

In many cases the syndrome is temporary.

Diabetes insipidus

Definition

Polyuria, thirst & polydipsia resulting from deficiency of or resistance to antidiuretic hormone (vasopressin).

Aetiology

Diabetes insipidus results from either a deficiency in anti diuretic hormone (central or cranial diabetes insipidus, see Table 11.14) or from renal resistance to ADH (nephrogenic diabetes insipidus, see Table 11.15).

Pathophysiology

Normally ADH acts on the renal collecting ducts to increase water reabsorption preventing plasma osmolality from rising. Lack of vasopressin, or renal resistance to vasopressin leads to loss of water (water depletion), leading to polyuria. Unless the thirst centre is also impaired, rising osmolality stimulates thirst and the person drinks water in increased quantities. The urine is dilute.

Table 11.14 Causes of cranial diabetes insipidus

Cranial causes (more common)	Examples
Infective	Meningitis, encephalitis
Inflammatory	Granulomatous (TB, sarcoidosis, etc)
Vascular	Ischaemia (CVA)
Trauma	Head injury
Neoplastic	Craniopharyngioma, secondary tumours, pituitary tumours with suprasellar extension
Iatrogenic	Intracranial surgery (often transient)
Idiopathic	DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and nerve deafness)

Table 11.15 Causes of nephrogenic diabetes insipidous

Nephrogenic causes	
Congenital	X-linked recessive genetic
Metabolic	Hypokalaemia, hypercalcaemia
Drugs	Lithium, demeclocycline
Kidney disease	Post-obstructive uropathy
Chronic kidney diseases	Pyelonephritis, polycystic kidneys, amyloid
	Sickle cell disease

Clinical features

Polyuria, polydipsia. Daily urine output may be $>$10 L a day.

Complications

Hypernatraemia if patient is denied access to water or is unconscious. If left untreated there is progression to severe irreversible brain damage and cerebral vessels may tear causing intracranial haemorrhage (see page 3). Rapid rehydration can cause a similar problem.

Investigations

Plasma osmolality is normal to high ($>$295 mmol/kg) with associated hypernatraemia, The urine osmolality is low. In the water deprivation test the patient is weighed, plasma and urine osmolality measured, then they are deprived of fluid for 8 hours under constant supervision.
- Diabetes insipidus is diagnosed if body weight falls by $>$3%, if plasma osmolality exceeds 300 mmol/kg, or if the urine:plasma osmolality ratio remains $<$1.9 (provided plasma osmolality exceeds 285 mmol/kg).

After 8 hours, the patient is allowed to drink freely and desmopressin (DDAVP – desamino-D-arginine vasopressin, a long-acting vasopressin analogue) is given intranasally or i.v. Urine output is monitored.
• If the kidneys are then able to produce concentrated urine the diabetes insipidus is due to ADH deficiency, i.e. central diabetes insipidus. If the urine remains dilute the kidneys are insensitive to ADH, i.e. nephrogenic diabetes insipidus.

Management
Any underlying cause should be sought and treated if possible. DDAVP intranasally is used in cranial diabetes insipidus. There is no specific treatment for nephrogenic diabetes insipidus.

Disorders of the parathyroids

Hyperparathyroidism

Definition
Increased secretion of parathyroid hormone (PTH) from the parathyroid glands located on the posterior surface of the thyroid gland.

Aetiology
Hyperparathyroidism may be primary, secondary or tertiary (see Table 11.16). Secretion of PTH like peptide is seen in squamous cell bronchial carcinoma (see page 134).

Pathophysiology
PTH is an 84 amino acid polypeptide, which controls normal calcium homeostasis (see Fig. 11.13).

Primary hyperparathyroidism

Definition
Primary oversecretion of parathyroid hormone (PTH) by the parathyroid glands.

Incidence/prevalence
Common amongst middle-aged and elderly. In patients over the age of 40, incidence may be as high as 1 in 1000 to 1 in 2000.

Age
Increases with age.

Sex
2–4F : 1M

Aetiology
Neoplasia of the parathyroid gland(s). There are thought to be genetic and environmental predisposing factors including a family history of Multiple Endocrine Neoplasia (see page 450) and neck irradiation.
• Single benign adenoma 75%
• Multiple adenomata or hyperplasia 24%
• Parathyroid carcinoma 1%

Pathophysiology
Autonomous hypersecretion from one or more glands result in hyperparathyroidism, with hypercalcaemia, hypophosphataemia and osteoporosis.

Clinical features
Presentation ranges from asymptomatic (diagnosed incidentally on a calcium measurement) to severe and life-threatening hypercalcaemia. Patients commonly remain asymptomatic for many years, then develop insidious

Table 11.16 Causes of hyperparathyroidisim

Type	Causes
Primary hyperparathyroidism	Primary tumour or hyperplasia of the parathyroid gland(s)
Secondary hyperparathyroidism	Appropriate increased PTH in response to prolonged hypocalcaemia or vitamin D deficiency especially in chronic renal failure
Tertiary hyperparathyroidism	Prolonged secondary hyperparathyroidism, causing autonomous secretion of PTH and hypercalcaemia
Pseudohypoparathyroidism	End-organ resistance to PTH leads to hypocalcaemia and therefore increased PTH occurs

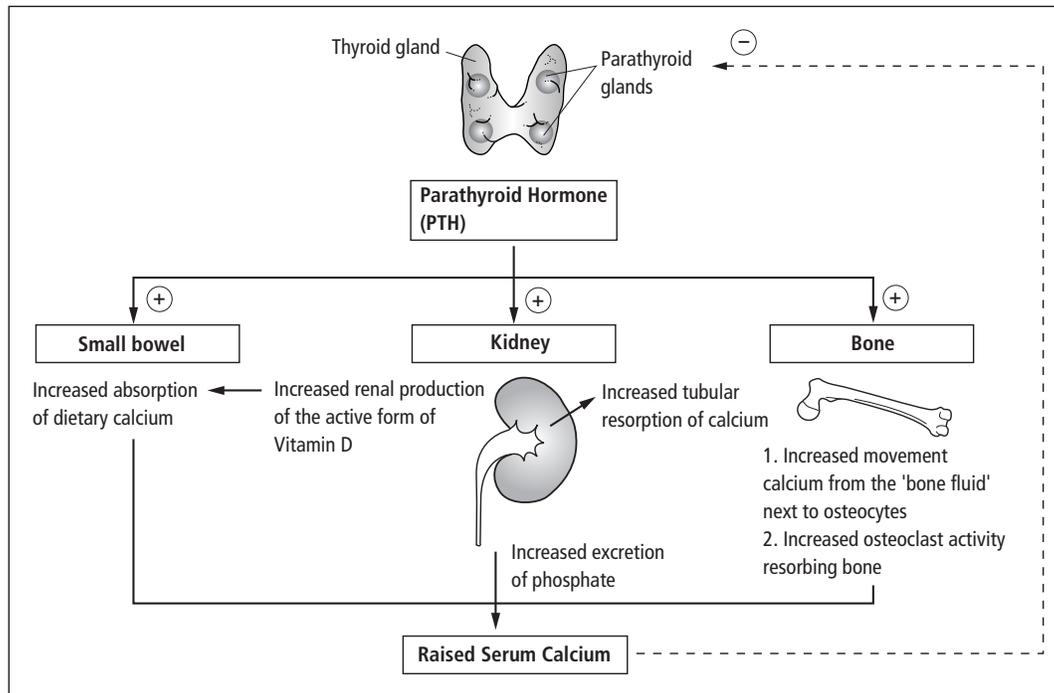**Figure 11.13** Effects of parathyroid hormone.

weakness, fatigue, anorexia, thirst, constipation and confusion.
- Bones: Increased calcium resorption, classically causes bone cysts (osteitis fibrosa cystica) which may present with diffuse pain or rarely fractures.
- Stones: Urinary stones and nephrocalcinosis (calcification of the kidney), due to hypercalciuria. Hypertension is common, possibly due to renal damage.
- Groans: Abdominal symptoms such as nausea, vomiting, pain and constipation.
- Moans: Psychosis, confusion and drowsiness.

Complications
Fractures, complications of urinary stones, seizures, coma, sudden death due to cardiac arrest. Dehydration occurs secondary to hypercalcaemia, which can cause a nephrogenic diabetes insipidus.

Investigations
- Serum calcium, PTH and albumin levels (for corrected calcium) should be measured. If hypercalcaemia is found, and PTH is detectable the likely diagnosis is primary or tertiary hyperparathyroidism. In other causes of hypercalcaemia, PTH is suppressed to below detectable values.
- Ultrasound of the neck may be able to differentiate between parathyroid adenoma or hyperplasia. The tumour(s) may be located by technetium-thallium subtraction scanning or selective venous catheterisation to assay PTH and find the source.

Management
- Surgery is the only curative option. The parathyroids are exposed by a transverse neck incision. Each lobe of the thyroid is mobilised and the parathyroids identified. Abnormal glands are removed and frozen sections examined. If all four glands are enlarged, all but a portion of one gland is removed.
- If symptomatic, treatment should be directed at correcting the hypercalcaemia with fluids. If Ca >3.5 mmol/L, the patient is vomiting, pyrexial or there

are severe symptoms or signs such as confusion, intravenous saline together with iv furosemide are used. Potassium and magnesium often fall and need supplements. Bisphosphonates may also be used, although they can take some time to act.

- If surgery is not possible, oral phosphates or bisphosphonates reduce bone resorption and osteoclast activity.

Secondary hyperparathyroidism

Definition
This is a syndrome of appropriately raised parathyroid hormone (PTH) in response to hypocalcaemia.

Incidence/prevalence
Increasing because of survival of renal patients on dialysis.

Aetiology
Common causes of chronic hypocalcaemia are chronic renal failure and vitamin D deficiency.

Pathophysiology
1 Chronic renal failure leads to reduced hydroxylation of inactive vitamin D (25-hydroxycholecalciferol $25(OH)D_3$) to the active vitamin D (calcitriol or $1,25(OH)_2D_3$) in the kidney, and hence a functional vitamin D deficiency.
2 Chronic hypocalcaemia caused by vitamin D deficiency stimulates chronically increased parathyroid hormone secretion, which may cause some restoration of serum calcium. The failing kidney also retains phosphate which binds calcium, reducing serum levels further.
3 The pathological effects are due to raised PTH levels which cause loss of calcium from the skeleton.

Clinical features
This condition is usually asymptomatic and chronic, although hyperparathyroidism may cause vague bone pains. Hypocalcaemia is rarely severe.

Complications
Tertiary hyperparathyroidism (hypercalcaemia due to autonomous parathyroids).

Investigations
Low or normal serum calcium, with a raised PTH. Phosphate is high. Skeletal X-ray classically shows subperiosteal erosions, 'brown tumours' which are areas of radiolucency which mimic lytic bone lesions and a ground-glass appearance of the skull.

Management
Dietary calcium and Vitamin D supplements. For renal patients alfacalcidol and calcitriol are suitable forms of vitamin D, as they do not require hydroxylation by the kidney to become active.

Tertiary hyperparathyroidism

Definition
Development of parathyroid hyperplasia or adenomas and autonomous parathyroid hormone (PTH) secretion following chronically low calcium levels.

Aetiology
Any cause of chronic secondary hyperparathyroidism, in particular chronic renal failure. Often becomes apparent post-renal transplantation.

Pathophysiology
During secondary hyperparathyroidism, the glands may become autonomous, either developing an adenoma or hyperplasia which secretes excessive PTH resulting in hypercalcaemia. In a patient with renal failure and secondary hyperparathyroidism who undergoes renal transplantation, PTH secretion may fall as the glands recover normal activity.

Clinical features
History of previous secondary hyperparathyroidism. Clinical features are those of hypercalcaemia (bones, stones, groans and moans).

Complications
Acute severe hypercalcaemia may cause seizures, abdominal pain, nausea and vomiting, confusion and pyschosis.

Investigations
Hypercalcaemia with markedly raised PTH.

Management

Total parathyroidectomy possibly with autotransplantation of parathyroid tissue equivalent to a normal gland into the arm, where it can be readily accessed for further treatment. Calcium replacement, phosphate binders and alfacalcidol (1-alpha hydroxyvitamin D_3) to increase calcium absorption and serum levels may be effective by negative feedback on the parathyroids.

Hypoparathyroidism

Definition

A deficiency of parathyroid hormone (PTH) characterised by hypocalcaemia and hyperphosphataemia, with normal renal function.

Aetiology

Most commonly occurs following surgery with removal of abnormal parathyroid glands or removal of neck malignancies. Gland failure may be caused by direct damage to the glands or their blood supply.

Idiopathic hypoparathyroidism:
- Genetic abnormalities are usually autosomal recessive and manifest at an early age. Associated with autoantibodies specific for parathyroid and adrenal tissue.
- Associated autoimmune syndromes include pernicious anaemia, ovarian failure, autoimmune thyroiditis, and diabetes mellitus.
- Late onset idiopathic hypoparathyroidism occurs without circulating autoantibodies.

Functional hypoparathyroidism occurs in patients with chronic hypomagnesaemia which results in a failure of PTH release.

Pathophysiology

PTH is normally released in response to hypocalcaemia, to restore calcium levels. The consequences of reduced PTH are decreased calcium levels, increased phosphate levels, decreased $1,25(OH)_2D_3$ and alkalosis (due to decreased bicarbonate excretion).
- In chronic cases of hypoparathyroidism, calcification of the basal ganglia causing extrapyramidal signs and calcification of cornea may occur.
- Cardiovascular problems with prolongation of the QT interval in ECGs associated with hypocalcaemia, hypotension and refractory congestive heart failure.

Clinical features

Hypocalcaemia and alkalosis cause increased neuromuscular excitability: paraesthesias of the fingertips and toes, tetany (spasms of muscles of extremities and face)
- Trousseau's sign: Inflating a blood pressure cuff to above systolic BP for at least 2 minutes causes carpal spasm, which does not relax for a few seconds after deflation.
- Chvostek's sign: Tapping the facial nerve anterior to the ear lobe causes twitching of the facial muscles.
- Convulsions occur more commonly in young people.

Investigations

Low calcium with normal or high phosphate with no detectable PTH on immunoassay. Alkaline phosphatase is normal. U&Es should be normal, or a renal cause is suspected.

Management

Replacement therapy with $1,25(OH)_2D_3$ (calcitriol, vitamin D_2) or $1(OH)D_3$. Serum and urinary calcium must be measured, as hypercalcaemia and hypercalciuria can occur. Vitamin D intoxication causes irreversible renal damage. Thiazide diuretics which increase renal tubular reabsorption of calcium may be useful in treating hypercalciuria.

Prognosis

Lifelong treatment and follow-up.

Pseudohypoparathyroidism

Definition

This is a rare condition in which there is impaired response to circulating parathyroid hormone, and hence hypocalcaemia and hyperphosphataemia.

Aetiology

Failure of the target cell response to parathyroid hormone, thought to be due to a PTH receptor defect or its coupling to the second messenger system, adenylate cyclase.

Clinical features

Round face, short stature with short fourth and fifth metacarpals and metatarsals. Other features are the same

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as those of hypoparathyroidism. Some patients have the somatic manifestations, but without the biochemical abnormalities and clinical signs of hypocalcaemia and hyperphosphataemia. This is called 'pseudopseudoparathyroidism'.

Investigations
Low calcium with normal or high phosphate, unlike primary hypoparathyroidism normal or high PTH and alkaline phosphatase.

Management
Lifelong replacement therapy with $1,25(OH)_2D_3$ or $1(OH)D_3$.

Multiple endocrine neoplasia syndrome

Multiple endocrine neoplasia (MEN)

Definition
Multiple endocrine neoplasia is a group of inherited syndromes characterised by multiple tumours of endocrine glands.

Multiple endocrine neoplasia type I
- Inherited in an autosomal dominant pattern. The function of the gene products are unknown but it is suggested that susceptible individuals inherit a gene defect from one parent, tumour growth occurs when the remaining copy of the gene is inactivated by somatic mutation.
- Tumours occur within the parathyroids in 90% (resulting in primary hyperparathyroidism), anterior pituitary (pituitary adenomas see page 421) and pancreatic islet cells (see page 222). MEN I is defined as the presence of at least two of the three main tumour types.

Multiple endocrine neoplasia type II
- Inherited in an autosomal dominant pattern with high penetrance. Mutations occur in the RET proto-oncogene.
- Tumours include medullary carcinoma of the thyroid, phaeochromocytomas (may be bilateral or multiple) and parathyroid tumours.

- Type IIb MEN may also have numerous mucosal neuromas, intestinal ganglioneuromas and a Marfanoid appearance.

Management
Tumours are surgically removed wherever possible, however recurrence is common. When an index case has been identified family members require screening either using genetic probes (when the mutation is known) or with endocrine testing for glandular dysfunction.

Diabetes mellitus

Diabetes mellitus type 1

Definition
Type 1 diabetes mellitus is a chronic disorder of carbohydrate, fat and protein metabolism with hyperglycaemia resulting in most cases from autoimmune destruction of pancreatic β cells.

Incidence/prevalence
Rare in infancy but rises to 2 per 1000 at age 16. Approximately 10% of all diabetic patients in the UK have Type 1 diabetes.

Age
Any age. Most present aged less than 20 years (peaks at 3–4 years and around puberty).

Geography
Wide variation between countries. High in Northern Europe, low in Japan.

Aetiology
Environmentally triggered autoimmune destruction of the pancreatic islet β-cells in a genetically susceptible individual. There is a concordance of 20–40% in monozygotic twins.
- Patients have autoantibodies directed against pancreatic islet constituents which may precede the clinical diagnosis by many years.
- Polygenic inheritance with Class II MHC associated genes. The IDDM1 major susceptibility gene is involved in familial clustering.

- There are specific high risk MHC II haplotypes including HLA-DR3 and -DR4. Having both HLA-DR3 and -DR4 gives an even greater risk than having one or the other. The MHC class II encoded for by these high risk haplotypes is able to present the auto-antigen causing lymphocyte activation and hence autoimmune destruction of islet β-cells. The target autoantigens include glutamate decarboxylase, and insulin. β-cells may be induced to express MHC Class II by viral infection, which makes the β-cell present one of its components as an auto-antigen on the cell surface.
- Non-MHC related genes are also of importance.
- The autoimmune destruction of islet β-cells is probably triggered by an environmental agent. Type 1 diabetes presents most commonly in autumn and winter, with suggestion of a role for both coxsackie and enteroviruses. Type 1 diabetes is the culmination of an occult process of β-cell destruction. The autoimmune activity begins up to 10 years before the presentation, which occurs when >95% of the β-cells have died.

Pathophysiology

The actions of insulin are anabolic (see Fig. 11.14).

In type 1 diabetes, there is hyperglycaemia due to failure of glucose uptake and uncontrolled gluconeogenesis, glycogenolysis, lipolysis and proteolysis:

- Osmotic diuresis – there is a renal threshold for glucose reabsorption, once the levels in the blood rise above 10 mmol/L the kidney is no longer able to completely reabsorb it from the proximal tubule resulting in glycosuria and an osmotic diuresis.

- Polydipsia is secondary to the hyperosmolarity and water depletion.
- Increased appetite occurs.

Clinical features

Patients may present with a history of polyuria, polydipsia and weight loss often despite increased appetite. Young patient often present acutely in diabetic ketoacidosis (see page 460).

Complications

Acute complications include insulin-induced hypoglycaemia and diabetic ketoacidosis.

Chronic complications can be considered as microvascular or macrovascular.

- Microvascular (microangiopathic) disease includes diabetic retinopathy, diabetic nephropathy and the neuropathies seen in diabetes.
- Macrovascular (large vessel) disease due to atherosclerosis which leads to complications such as myocardial infarction, strokes, gangrene of the legs and mesenteric artery occlusion.

Investigations

Diagnosis is made on finding symptoms of diabetes (i.e. polyuria, polydipsia and unexplained weight loss) plus one of:

- A random venous plasma glucose concentration $\geq$11.1 mmol/L or
- A fasting plasma glucose concentration $\geq$ 7.0 mmol/L or
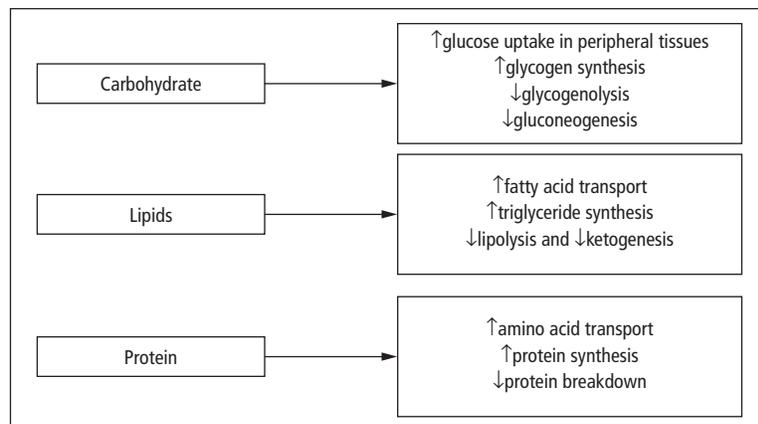

Figure 11.14 The anabolic actions of insulin.

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- A plasma glucose concentration $\geq$11.1 mmol/L 2 hours after 75 g anhydrous glucose in an oral glucose tolerance test (OGTT).

If there are no symptoms diagnosis should not be based on a single glucose determination. Impaired Fasting Glucose (IFG) is defined as a fasting plasma glucose above the normal range but below those diagnostic of diabetes ($\geq$ 6.1 mmol/L but <7.0 mmol/L). These patients require an oral glucose tolerance test to exclude diabetes. This is also a risk factor for the future development of diabetes.

Impaired Glucose Tolerance (IGT) is a state of impaired glucose regulation defined as a fasting plasma glucose < 7.0 mmol/L and OGTT two hour value $\geq$ 7.8 mmol/L but <11.1 mmol/L). This is a risk factor for the development of diabetes and cardiovascular disease.

Other investigations that may be of value include C-peptide measurement (the cleavage product when pro-insulin is converted to insulin) and detection of autoantibodies. These tests are useful in distinguishing patients with type 1 from type 2 diabetes.

Management

Diabetes requires a combination of education, dietary advice, insulin regimens and careful monitoring and follow-up.

Diet: Good nutrition based on a normal proportion of carbohydrate particularly high fibre evenly divided between three main meals. In addition, snacks between meals and at bedtime may be required.

Insulin: It is difficult for subcutaneous insulin therapy to mimic the normal pancreatic secretion into the portal system. Normally the liver immediately takes up 50% of insulin output of the pancreas. Most patients are managed on a twice-daily regimen or basal bolus regimen (see page 454).

Good control of blood glucose reduces small vessel disease. The Diabetes Control and Complications Trial has shown that only 12% of intensively monitored and treated patients developed retinopathy after 9 years, compared to >50% of the conventionally treated patients.

Monitoring:
- Regular capillary blood glucose measurement often pre-meals, two hours post meals and during the night when changing doses, or at times of instability. Once a patient is stabilised on a particular regimen monitoring may be less frequent.

- Glycosylated Hb (HbA1c) is used to assess long-term glycaemic control. It gives an estimate of the average blood glucose over the previous 1–2 months.
- Patients should be regularly assessed for the development of long-term complications such as nephropathy, neuropathy and retinopathy.

Research is continuing into pancreatic and islet-cell transplantation. Immunosuppression itself may prevent autoimmune destruction of islet β-cells and can prevent the development of diabetes in animal models. However there are severe side effects to this treatment.

Diabetes mellitus type 2

Definition

Type 2 diabetes mellitus is a chronic disorder of carbohydrate, fat and protein metabolism with hyperglycaemia as its principal feature. It is characterised by impaired insulin secretion and insulin resistance.
- Type 2 diabetes used to be called non-insulin dependent diabetes (NIDDM) but this term is confusing, as many patients require insulin for good diabetic control.

Incidence/prevalence

Approximately 2% prevalence in UK; 75% of UK diabetic patients.

Age

Increases with age.

Sex

M = F

Geography

Wide geographic variation. More common in Asian immigrants to UK than indigenous population.

Aetiology

A combination of genetic and environmental factors both in the development of insulin resistance and impaired insulin secretion. The overall concordance in monozygotic twins is up to 90%. Environmental factors include diet both in relation to obesity, lack of exercise and the epidemiological evidence that once 'westernised' ethnic migrants have significantly increased prevalence.

Maturity onset diabetes of the young (MODY) occurs in a small subgroup of patients who present under the age of 25. MODY results from specific mono-genetic disorders which are inherited in an autosomal dominant fashion.

Pathophysiology
- Insulin resistance in the liver, skeletal muscle and adipose tissue (by about 40%) secondary to a decrease in the number of insulin receptors, decreased receptor tyrosine kinase activity and post-receptor defects causing impaired glucose transport.
- Defective insulin secretion due to islet cell dysfunction with increased secretion of proinsulin and cleavage products. Amylin, an amyloid protein, is found in increased amounts in the islets cells. It may disrupt the normal insulin secretion.
- Reduced effective insulin causes increased gluconeogenesis by the liver and reduced peripheral uptake, leading to hyperglycaemia. However, there is sufficient insulin to suppress lipolysis and ketogenesis, so that ketosis and ketoacidosis do not occur.

Clinical features
Type 2 diabetes may be diagnosed on routine blood testing (this may follow detection of glycosuria). Symptomatic patients have an insidious onset of polyuria, polydipsia and are usually obese. Diabetes causes an increased predisposition to infections, such as abscesses, pyelonephritis and candidiasis.

Complications
- Acute complications: Hyperglycaemic coma which is usually hyperosmolar non-ketotic coma and complications of therapy such as hypoglycaemia due to insulin or sulphonylureas, metformin-induced lactic acidosis.
- Chronic complications include:
  Microvascular (microangiopathic) disease: Includes diabetic maculopathy and retinopathy, nephropathy and neuropathy.
Macrovascular (large vessel) disease: Atherosclerosis which leads to complications such as myocardial infarction, strokes, gangrene of the legs and mesenteric artery occlusion.

Investigations
The diagnostic criteria are as for type 1 diabetes.

Management
Involves changing the diet, lifestyle (exercise, losing weight) and using oral hypoglycaemic drugs if the former are not effective. Some patients require insulin for adequate glycaemic control.

Loss of weight by an obese patient can lead to normalisation of blood glucose levels and resolution of symptoms. It also reduces insulin resistance. Dietary recommendations include:
- Increase complex carbohydrates (CHO) i.e. bread, cereal, pasta.
- Decrease refined sugars i.e. cakes and sweets.
- Decrease fats, particularly saturated fat.
- Decrease alcohol if excessive, and dry wine is better than beer (less CHO).

Oral hypoglycaemic drugs:
- Biguanides (metformin) reduce insulin resistance, but may cause lactic acidosis with a mortality rate of up to 50%. It may be prevented by avoiding the use of biguanides in patients with moderate renal or hepatic failure.
- Sulphonylureas (glicazide and glibenclamide) increase insulin secretion by the β-cells. These increase levels of plasma insulin and may result in more weight gain, insulin resistance and a higher risk of complications, they are often avoided in the early treatment, unless symptoms are severe.
- Thiazolidinediones (glitazones) increase peripheral insulin sensitivity. They take 3–4 months to achieve maximal effect. They can be used as monotherapy or combined with other drugs.
- $\alpha-$glucosidase inhibitors (acarbose) which reduce the activity of the enzyme responsible for digesting carbohydrates in the intestine, thus delaying and reducing postprandial blood glucose peaks.

Management also requires careful monitoring for and treatment of complications.

Prognosis
75% of patients die from vascular and related disease.

Secondary diabetes mellitus

Definition
Chronic hyperglycaemia and other metabolic abnormalities seen in diabetes mellitus due to another identifiable cause.

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Pancreatic disease: At least two thirds of the pancreas must be lost to cause a type 1 diabetes like syndrome. Causes include chronic pancreatitis, post-pancreatectomy, pancreatic cancer, cystic fibrosis or haemochromatosis.

Insulin counter-regulatory hormones inhibit insulin secretion or cause insulin resistance. This includes drugs and results in a type 2 diabetes like syndrome.

- Growth hormone (acromegaly)
- Glucocorticoids (Cushing's syndrome or disease, iatrogenic)
- Glucagon (glucagonoma)
- Catecholamines (phaeochromocytoma)
- Somatostatin (pancreatic somatostatinoma)
- Oral contraceptives and pregnancy probably due to the oestrogens (and also increased cortisol seen in pregnancy).

Drugs may inhibit insulin secretion or cause damage to the pancreatic islets.

- Thiazides and phenytoin inhibit insulin secretion.
- Pentamidine damages the β-cells.

Insulin receptor defects. These are rare disorders and include:

- DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness)

- Insulin-resistant diabetes with acanthosis nigricans
  i. Young women who have polycystic ovaries and reduced numbers of insulin receptors due to mutations in the allele for the receptor gene.
  ii. Older patients with antibodies to insulin receptors reducing their affinity for insulin.

Insulin therapy

Synthetic insulin is administered subcutaneously in a variety of regimens. Various insulins have been 'designed' with different pharmacokinetic effects (see Table 11.17).

Two common regimens are used (see Fig. 11.15):

- A twice daily adminstration of biphasic insulin, with two thirds of the total daily dose given before breakfast and one third given before the evening meal.
- A bolus of short or immediate acting insulin given three times a day at meal times and a medium or long-acting insulin given at night. The advantage of this regimen is that meal times and quantities can be varied. If immediate acting insulin is used it is taken at or immediately after the meal, if short acting is used then this is administered 30 minutes before the meal.

Table 11.17 Insulin regimens

| Type of Insulin (length of action)	No. of injections per day (usual)	Description	Name
Immediate Onset Immediate Duration 4 h	2 or 3 (plus once daily medium or long acting)		Lispro Novorapid
Short Onset 0.5 h Peak 2–4 h Duration 4–6 h	2–4 (plus once daily medium or long acting)	Soluble	Actrapid Velosulin Humulin S
Medium Onset 3 h Peak 6–10 h Duration 12–24 h	2	Isophane (insulin zinc and protamine (a protein) suspension) Insulin detemir (soluble insulin analogue)	Insulatard Protaphane Humulin I Levemir
Long Onset 3–4 h Peak 12–18 h Duration ~24 h	1	Insulin zinc suspension (protein and zinc crystals) Insulin glargine (forms slowly absorbed subcutaneous crystals)	Human ultratard Lantus
Biphasic Onset 0.5 h Peak 2–10 h Duration 12–18 h	1–2	Mixture of soluble and isophane	Human mixtard Humulin M5
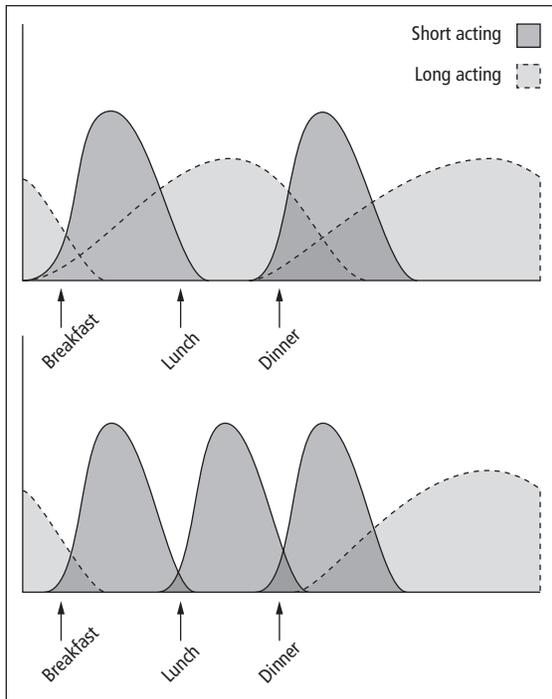
Figure 11.15 Twice daily and basal bolus administration of insulin.

A continuous subcutaneous insulin infusion or continuous intravenous infusion via a tunelled line may also be used. An infusion pump controls the rate and preprandial boosts can be given simply and easily. They are expensive and if they fail, they can cause diabetic ketoacidosis, as there is no longer-acting reserve.

The site of injection also affects the absorption rate:
- The abdominal wall is quickest (use before mealtimes).
- The arms are intermediate.
- The legs are the slowest (night-time).

Temperature and exercise affect absorption. Exercise also increases the use of glucose and hence reduces the amount of insulin needed. Patients must be educated about the problems with insulin therapy. For example, common sites of injection may develop fat hypertrophy or fat atrophy. These sites then release insulin poorly. Rotating the sites prevents these problems. Hypoglycaemia may result from having too much insulin and not eating enough, or exercising. If a patient is not eating, e.g. with vomiting due to gastroenteritis, then insulin

treatment should not be omitted, as the body still requires insulin to utilise glucose. Instead, lower amounts should be used with careful monitoring, or the patient will need to be admitted for intravenous glucose and insulin to avoid either diabetic ketoacidosis or hyperosmolar non-ketotic coma.

Complications of diabetes

Diabetic microvascular disease

Definition
Microvascular diabetic complications includes diabetic retinopathy, nephropathy and the neuropathies.

Aetiology
It is thought that microvascular complications are secondary to the metabolic derangements of diabetes, in particular hyperglycaemia. Good glycaemic control of diabetes and control of hypertension can reduce the incidence of complications.

Pathophysiology
- Hyperglycaemia leads to glycosylation of proteins including haemoglobin, collagen and proteins of blood vessels by non-enzymatic means. This may impair the function of the proteins.
- Intracellular hyperglycaemia in nerves, kidney, blood vessels and the lens which do not require insulin for glucose uptake. The excess intracellular glucose is metabolised to sorbitol and fructose increasing the osmolarity so that water is drawn into cells, causing cell injury.
- Increased blood flow in the capillaries of the retina, kidney and other microcirculations could cause increased damage to the capillary wall. Other factors include smoking (at least as common in diabetics as non-diabetics) and hypertension.
- An inherited factor has been postulated as some patients do not develop microvascular disease.

Diabetic retinopathy

Definition
Diabetes can affect almost all the structures of the eye but the retina and the lens are most commonly affected.

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Incidence
Leading cause of blindness under the age of 65 in the developed world. After 20 years of diabetes almost all patients have some retinopathy. Around 40% of type 1 and 20% of type 2 diabetics have proliferative retinopathy.

Aetiology
Control of blood sugars and concomitant hypertension has been shown to reduce risk of retinopathy and other microvascular complications.

Pathophysiology
There is a thickening of the capillary basement membrane and hyaline arteriosclerosis. Microaneurysms (dot haemorrhages) occur in some vessels while others become occluded. The weakening of the vessel walls leads to blot haemorrhages, and transudates of fluid and lipid (hard exudates). The obliteration of capillaries causes retinal ischaemia (cotton wool spots) which in turn stimulates the formation of new vessels at the surface of the retina and iris.

Clinical features
All patients with diabetes should be screened regularly for diabetic retinopathy.
- Background diabetic retinopathy is the earliest sign of diabetic retinopathy. Initially there are microaneurysms later accompanied by blot haemorrhages and scattered hard exudates. Vision is generally unaffected.
- Diabetic maculopathy causes gradual loss of vision due to:
    i. Capillary leakage causing macular oedema
    ii. Lipid deposition
    iii. Extensive obliteration of macular capillaries
- Pre-proliferative retinopathy is seen most commonly in young patients on insulin for about 10 years. Retinal ischaemia is seen as 'soft exudates' or cotton wool spots. Fifty per cent of patients with pre-proliferative changes develop proliferative retinopathy within a year.
- Proliferative retinopathy: New vessels develop most commonly at the optic disc on the venous side adjacent to the temporal vessels. They grow into the vitreous and round to the front of the eye when they are visible on the iris. These vessels may bleed either as vitreous (blue-grey opacity) or pre-retinal haemorrhages (usually flat upper surface), which may cause obscuring of

vision for months or years. Scar formation leads to a traction retinal detachment. New vessels forming at the iris are accompanied by obstruction at the drainage angle causing a neovascular or thrombotic glaucoma (a type of secondary closed angle glaucoma).

Complications
Proliferative retinopathy may cause sudden loss of vision from extensive haemorrhage or retinal detachment. Thrombotic glaucoma may also occur.

Investigations
Screening is by fundoscopic or retinal camera examination. Patients require dilation of the pupils. Fluorescein angiography can be used to show very early disease. Acuity testing should be performed to detect early macular disease.

Management
- No specific treatment is required for background retinopathy except to maximise diabetic control and manage any coexisting hypertension.
- Maculopathy is treated by laser to the centre of a hard exudate.
- Proliferative retinopathy is treated by panretinal photocoagulation (PRP), widespread pinpoint laser treatment to the periphery of the retina, destroying the ischaemic retina. There is then reduction in the growth factors which promote neovascularisation and hence regression of new vessels. Laser treatment also helps prevent neovascular glaucoma.
- Surgery may be required to remove vitreous haemorrhage and fibrous tissue or to repair a detached or torn retina.

Prognosis
Prevention is the best management, by regular screening and good control of blood sugar.

Diabetic nephropathy

Definition
Diabetic nephropathy is a microvascular disease of type 1 and 2 diabetes.

Incidence
Patient individual risk is falling however due to increasing rates of diabetes the overall prevalence of diabetic nephropathy is rising.

Age
Increases with age.

Aetiology
Associated with hypertension, smoking and poor glycaemic control.

Pathophysiology
In addition to the other microvascular mechanisms hypertension can accelerate nephropathy by causing further thickening of the capillary walls and reduced glomerular filtration rate. This further increases hypertension.

Glomerular basement membrane (GBM) thickening and glomerulosclerosis due to an increase in the mesangial matrix. It leads to diffuse sclerosis of the glomerulus, which later condenses into nodular lesions, called Kimmelstiel-Wilson lesions. The thickening of the basement membrane increases its permeability to albumin. As the disease progresses, the amount of protein lost increases.

The glomerular filtration rate is initially normal, but falls with progressive renal damage and chronic renal failure occurs around 5–7 years after macroalbuminuria occurs.

Clinical features
The condition is asymptomatic until chronic renal failure or nephrotic syndrome develops. Patients should be screened annually for all diabetic complications and hypertension.

Microscopy
The GBM is thickened (can be seen on electron microscopy). There are exudative lesions on the surface of the glomerulus, which are masses of red-staining fibrin protein. The mesangial matrix is expanded and there are round hyaline areas in the glomeruli (Kimmelstiel-Wilson nodules).

Investigations
Annual screening of urine for microalbuminuria. Amount of albumin lost per 24 hours:

30–300 mg/24 hours	Microalbuminuria
>300 mg/24 hours	Proteinuria
>3.6 g/24 hours	Hypoalbuminaemia and Nephrotic syndrome

Diabetic patients may have other causes for proteinuria and renal failure, so particularly if there are atypical features such as haematuria, rapid onset or absent retinopathy further investigation must be carried out to look for another cause.

Management
- Microalbuminuria and proteinuria require aggressive treatment of hypertension (<130/75), better glycaemic control and cessation of smoking. ACE inhibitors and angiotensin II blockers appear to be most effective in reducing protein loss and delaying progression.
- End-stage renal failure is treated as for non-diabetics. Haemodialysis may be more complicated because of increased cardiovascular disease and autonomic neuropathy which exacerbates postural hypotension. Hypoglycaemia may occur because insulin and sulphonylureas accumulate in renal failure.
- Renal transplantation is the preferred option in younger patients, and pancreatic-renal transplants may be of value in reducing diabetic complications.

Diabetic neuropathy

Definition
Nerve damage is one of the microvascular complications of diabetes mellitus.

Incidence/prevalence
Diabetes is the most common metabolic disorder causing neuropathy: 10% of diabetics have significant symptoms and 30% have evidence on testing.

Aetiology
It is thought to be secondary to hyperglycaemia and microvascular disease.
There are three main types of diabetic neuropathy:
- Symmetrical peripheral neuropathy: Affecting sensory and motor function diffusely, particularly in the lower limbs. This can be a painful neuropathy.
- Focal and multifocal neuropathy: Affecting one or more cranial or peripheral nerves.
- Autonomic neuropathy: Affecting the sympathetic and parasympathetic nerves.

Pathophysiology
- Hyperglycaemia may damage nerves through non-enzymatic glycosylation of proteins or through the

accumulation of sorbitol in nerve cells, which can take up glucose without the aid of insulin.
- Microvascular damage (which itself is thought to be secondary to hyperglycaemia and other factors) to the capillaries which supply nerves probably cause ischaemic nerve damage. Focal nerve palsies may be due to sudden occlusion of a larger vessel causing infarction.

Symmetrical peripheral neuropathy

A diffuse symmetrical pattern of damage to the nerves, most commonly the sensory nerves, which has a glove and stocking distribution. There is Schwann cell injury, myelin degeneration and axonal damage.

Clinical features
Sensory neuropathy:
- Sensory symptoms in the feet and legs are most common and may be insidious or sudden in onset. In the case of the latter it may follow an episode of severe hyperglycaemia. Paraesthesia (pins and needles, burning, shooting pains) which may be precipitated by normal sensations such as contact with bedclothes, this is called allodynia. The pain is worse at night and keeps the patient awake.
- Chronic loss of sensation, most importantly of pain. The patient completely loses the sense of pain, so that severe damage such as burns, cuts, ulcers, infection and gangrene can occur without being noticed by the patient (the neuropathic foot).
- On examination, there is reduced sensation, often in a glove and stocking distribution, and tendon reflexes may be reduced or absent. Vibration sense is often lost early in the course of peripheral neuropathy. Motor nerve damage causes muscle wasting. The feet and ankles in particular may be damaged.

Motor neuropathy:
- This may be asymptomatic, accompanying the sensory neuropathy.
- Painful neuropathy: It may also cause intense pain in a glove and stocking distribution.

Investigations
A careful neurological examination should be carried out, including joint position sense, vibration, pinprick and light touch, tendon reflexes and muscle power. Most cases do not require further investigation as the cause is clear, however, occasionally it is appropriate to exclude other causes of the neuropathy e.g. by checking vitamin B_{12} level.

Management
Improving glycaemic control may be of benefit. Pain can be treated by a step-wise approach using aspirin and codeine, tricyclic antidepressants, carbamazepine or gabapentin. Feet should be inspected and examined at each review including sensation to a 10 g monofilament or vibration and palpation of foot pulses. Examination may need to be repeated 1–3 monthly in high-risk patients. New ulceration, swelling, discolouration is a foot care emergency and requires multidisciplinary assessment within 24 hours.

Prognosis
The acute form may resolve with time and better glycaemic control. The chronic form is persistent and irreversible. Symptoms may be intractable in some patients.

Focal and multifocal neuropathy

Pathophysiology
A focal nerve lesion, either of a cranial or peripheral nerve, which is thought to be due to occlusion of a larger vessel supplying the nerve, or pressure damage, when it may be seen in the context of impaired sensation of pain. Several nerves may be affected.
- The cranial nerves most affected are III, IV and VI.
- The peripheral nerves most affected are the median, ulnar and lateral popliteal nerves.
- If a large nerve trunk or root is affected, such as the femoral nerve, radiculopathy results, causing proximal pain and wasting, for example in the thigh, with weakness and wasting of quadriceps (diabetic amyotrophy).

Clinical features
Any nerve(s) can be involved.
- Third nerve palsy typically presents with pain, diplopia and ptosis. It may resolve spontaneously.
- Peripheral nerve palsies recover only slowly and often incompletely.

- Diabetic amyotrophy present with sudden onset of pain and weakness with an absent tendon jerk (usually the knee). The important differential diagnosis is a spinal or cauda equina cause of the radiculopathy.

Investigations
In most cases, this is not necessary, as the cause is clear. Occasionally, it may be useful to exclude other causes, particularly in cranial nerve palsies when a space-occupying lesion may be excluded with CT or MRI.

Management
Management is as for diffuse symmetrical neuropathies.

Autonomic neuropathy

Incidence
About 40% of diabetic patients have autonomic neuropathy on screening. It increases with the duration of the disease.

Pathophysiology
This probably has similar pathogenesis to the diffuse, symmetrical neuropathy. The autonomic nervous system is involved, causing disturbance of functions such as postural vasoconstriction, gastrointestinal motility, bladder emptying, sexual function (erection and ejaculation). Life-threatening disturbances include reduced awareness of hypoglycaemia and cardiorespiratory arrest. Sudden unexplained death is more common.

Clinical features
- Postural hypotension, causing dizziness, faints and falls.
- Nausea, vomiting and diarrhoea or constipation due to abnormal gastrointestinal motility.
- Bladder problems include incomplete emptying, chronic urinary retention and this predisposes to more severe urinary tract infections, such as pyelonephritis.
- Failure of erection is due to reduced parasympathetic activity (may also result from depression or atheroma in the pudendal arteries). Failure of ejaculation due to impaired sympathetic activity.
- Increased sweating.

Examination shows a >20 mmHg fall in systolic BP on standing, loss of normal sinus arrhythmia on breathing and lack of reflex bradycardia on the Valsalva maneouvre. The bladder may be palpable.

Complications
Pyelonephritis, overgrowth of bowel bacteria causing diarrhoea.

Management
Treatment depends on the symptoms and complications. Postural hypotension is treatable with fludrocortisone (a mineralocorticoid), but this may cause hypertension to be worse. Impotence is treatable with sildenafil.

Prognosis
Symptomatic autonomic neuropathy is associated with a reduced life expectancy.

Diabetic ketoacidosis (DKA)

Definition
The hyperglycaemic and metabolic acidotic state which occurs in Type I diabetes due to excess ketone production as a result of insulin deficiency.

Aetiology
Precipitating factors include infection, trauma, surgery, burns and myocardial infarction. It is associated with poor diabetic control.

Pathophysiology
- Patients may omit or reduce their insulin when ill, because they are eating less and therefore believe they require less insulin. In fact, stresses such as an intercurrent infection increase the secretion of glucagon and other counter-regulatory hormones which oppose insulin, so that insulin requirements increase during illness.
- The result of this is a severe catabolic state: there is uncontrolled glycolysis, lipolysis and protelolysis. This causes hyperglycaemia and a rise in free fatty acids which are the substrates for ketone body formation (ketogenesis) within the liver. Normally insulin opposes ketogenesis, but in conditions of insulin deficiency, glucagon and catecholamines increase ketogenesis. The ketone bodies produced are acetoacetic acid, acetone and hydroxybutyrate which result in a metabolic acidosis.

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- As the production rate exceeds the body's capacity to utilise ketone bodies, both ketone body and glucose concentrations rise, causing hyperosmolarity of the extracellular fluid. The renal threshold for glucose reabsorption ($\sim$10 mmol/L) is exceeded, and an osmotic diuresis occurs so that water and electrolytes, especially sodium and potassium, are rapidly lost. This causes a severe dehydration, hypovolaemia and this compounds the problem by reducing renal perfusion, thereby reducing glucose clearance.
- Dehydration is exacerbated by vomiting, which is due to central effects of ketosis.
- Death is usually due to cardiac arrest.

Clinical features
Nausea, vomiting, abdominal pain, hyperventilation, shock, coma, signs of dehydration and ketotic smelling breath. Normally this occurs in a known diabetic, but it may occur as the presenting feature, particularly in young patients.

Complications
Shock and acute renal failure, cerebral oedema may occur during rehydration, adult respiratory distress syndrome, acute gastric dilatation, aspiration, hypothermia, and coma.

Investigations
The diagnosis requires the demonstration of diabetes, ketosis and a metabolic acidosis. Blood glucose should be checked on capillary bedside testing and confirmed with a laboratory sample. Ketones may be detected in the urine on urinalysis. Some bedside blood glucose monitors can also detect ketones. An arterial blood gas sample is also required to demonstrate and assess the severity of metabolic acidosis.

- U&Es and osmolality should be sent urgently.
- Full blood count, amylase, blood cultures, urine culture, CXR and ECG are checked to identify underlying causes and complications. Consider cardiac enzymes in older patients. Serum amylase greater than threefold normal is suggestive of acute pancreatitis, which may be the cause of DKA in up to 10% of cases.

Management
DKA is a medical emergency. The initial management is rehydration and correction of electrolyte imbalances.

Insulin replacement is also needed to correct the hyperglycaemia and prevent further osmotic diuresis. Any underlying illness must be treated as appropriate. Patients require a nasogastric tube for gastric decompression and emptying as there is a high risk of aspiration. Fluid and electrolytes: Patients can be as much as 10 L fluid depleted, with a K^+ and Na^+ deficit. Monitor fluid balance (urine output etc.) during treatment. A central venous catheter may be placed to measure central venous pressure to guide fluid management. Care must be taken not to change the osmolality too rapidly, as this can lead to cerebral oedema. The osmolality will drop as glucose levels fall, and so sodium and potassium need to be given to counter this. For this reason, normal saline is always used initially:

- 1st hour   1.5 L
- 2nd hour   1.0 L
- 3rd to 4th hour   1.0 L over 2 hours
- > 5th hour   2.0 L every 8 hours
- Change to 5% or 10% dextrose, 1 L every 8 hours once the patient is rehydrated and blood glucose is back down to 12 mmol/L. Replacement should be faster if patients are shocked and slower if there are signs of cardiac failure, fluid overload or cerebral oedema.

There is always a depletion of total body potassium, but serum K^+ may be normal, high or low. Supplementation is always needed, because potassium follows glucose into the cells. However, there is a danger of hyperkalaemia, causing cardiac arrhythmias, so if K^+ levels are >5 mmol/l withhold K^+ and recheck after 30 minutes.

Normal K^+	20 mmol per litre of fluid
<3.5 (hypo)	40 mmol per litre

Insulin: Soluble insulin is administered intravenously by an infusion pump – start with 10 units per hour and then titrate to response. Therapy should aim to produce a gradual reduction to a glucose level of 10–15 mmol/L over a period of several hours. Hourly blood sugar and 1–2 hourly U&E's, plasma osmolality monitoring are required. If intravenous access is not possible then subcutaneous or intramuscular insulin can reverse the ketoacidosis.

Bicarbonate: The use of bicarbonate is contentious. It is unlikely to improve the acidosis and has the potential of doing harm including making cerebral oedema more likely. It therefore should not normally be used in the treatment of diabetic ketoacidosis.

Prognosis

Overall mortality is ∼10% and as high as 50% in older patients with severe intercurrent illness. It is the most common cause of death in diabetic patients under 20 years old.

Hyperosmolar, non-ketotic coma (HONK)

Definition

This occurs in people who have type 2 diabetes mellitus and is characterised by hyperglycaemia without severe hyperketonaemia or metabolic acidosis.

Age

More common in the elderly.

Sex

M = F

Aetiology

Precipitating factors include infection, myocardial infarction and stroke, or diabetogenic drugs such as glucocorticoids and thiazide diuretics.

Pathophysiology

The pathophysiology is essentially the same as for diabetic ketoacidosis (DKA), except that because the person has enough insulin to suppress lipolysis and ketogenesis, uncontrolled ketogenesis does not occur. There is insufficient insulin to prevent increased glucose production and reduced glucose uptake by cells and so hyperglycaemia occurs. The hyperglycaemia is often much more extreme than in DKA and causes severe hyperosmolarity with an osmotic diuresis which unless compensated for by water intake leads to progressive severe dehydration. This compounds the hyperosmolarity caused by the hyperglycaemia, which increases blood viscosity, predisposing to thromboembolic disorders. If untreated, it leads to confusion and eventually coma.

Clinical features

Often occurs in elderly undiagnosed patients, who present with polyuria, intense thirst, weight loss and blurred vision. The symptoms and signs of ketoacidosis are absent (hyperventilation, ketotic breath) but confusion, drowsiness and coma are more common.

Complications

Thromboembolic disease, such as stroke, mesenteric artery thrombosis, deep vein thrombosis and pulmonary embolism.

Investigations

- Blood and urinary ketones are absent or only slightly raised.
- Blood glucose is raised and can be as high as 100 mmol/L.
- U&Es: Markedly raised sodium (often over 155 mmol /L) and urea due to dehydration.
- Very high plasma osmolality (>350 mosmol/kg) but anion gap is normal, as is pH on arterial blood gas.
- Full blood count, blood cultures, urine culture, CXR and ECG are checked to identify underlying causes and complications. Consider cardiac enzymes in older patients.

Management

Patients require emergency fluid resuscitation with normal saline and potassium replacement (as for diabetic ketoacidosis). Low-dose intravenous insulin is used to reduce the hyperglycaemia but patients are often very sensitive and rapid reductions in glucose should be avoided. Prophylactic low-dose heparin to prevent thromboembolic complications. Any underlying cause should be identified and treated.

Prognosis

Mortality is higher overall (∼30%) than DKA, because these patients are more elderly.

Hypoglycaemia

Definition

Low serum glucose caused by insufficient hepatic glucose production for peripheral requirements.

Aetiology

Insulin overdose (accidental or deliberate self harm), sulphonylurea overdose, malnutrition, fasting, exercise or severe liver disease. Alcohol impairs gluconeogenesis

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and can cause hypoglycaemia in diabetic patients. Rare causes include insulinomas (see page 222) and Addison's disease (see page 440).

Clinical features

Patients become irritable, pale, weak and sweaty. In patients who have regular hypoglycaemic episodes and in autonomic neuropathy the awareness of symptoms is reduced. Untreated the condition progresses to confusion, seizures and coma. Prolonged or severe hypoglycaemia risks permanent neurological damage and death.

Investigations

The diagnosis can be confirmed on bedside blood sugar testing, a formal laboratory glucose sample should be sent but treatment should not be delayed. Other tests may be required to identify the underlying cause.

Management

This is a medical emergency and requires immediate treatment.

- In conscious patients the blood sugar can be raised by oral administration of a sugary drink. This should be followed by a more complex carbohydrate to prevent a further rebound hypoglycaemia.
- In unconscious patients or those unable to tolerate oral fluids blood sugar can be raised by administration of glucose gel to the gums (e.g. Hypostop), intravenous dextrose or intramuscular glucagon.
- Further management depends on severity and the underlying cause.