

Pathology of the endocrine system

10



Objectives

In this chapter, you will learn to:

- Describe disorders of the pituitary gland leading to hyperpituitarism and hypopituitarism.
- Describe the causes and patterns of thyroid dysfunction.
- Describe the causes and patterns of parathyroid dysfunction.
- Understand Cushing's syndrome and other disorders of adrenal hyperfunction.
- Understand the importance of adrenal hypofunction and crisis.
- Recall the pathology and complications associated with diabetes mellitus.
- Briefly describe endocrine tumours including the important multiple endocrine neoplasia syndromes.

DISORDERS OF THE PITUITARY

The pituitary (hypophysis) is a small (500–1000 mg), bean-shaped gland lying in the sella turcica in the base of the skull. It is composed of two parts:

1. Anterior lobe (adenohypophysis)—synthesises and secretes a number of hormones (Fig. 10.1), most of which act on other endocrine glands.
2. Posterior lobe (neurohypophysis)—stores and secretes two hormones synthesised in the hypothalamus: antidiuretic hormone (ADH; vasopressin) and oxytocin. This lobe is in direct continuity with the hypothalamus, to which it is connected via the pituitary stalk.

Secretion of the pituitary hormones is regulated by neural and chemical stimuli from the hypothalamus, diseases of which cause secondary abnormalities in pituitary function.

This cooperation between the nervous system and endocrine apparatus is referred to as neuroendocrine signalling. Figure 10.2 shows the integration of signals between the hypothalamus, pituitary and thyroid gland in the release of thyroid hormones, with feedback loops acting at each level.

Neuroendocrine cells are defined as those that release a hormone in response to a neural stimulus. Important examples include:

- Neurons of the supra-optic nucleus (projecting into the posterior pituitary), which release ADH.
- Chromaffin cells of the adrenal medulla, which release epinephrine (adrenaline).

The anterior pituitary: hyperpituitarism

Hyperpituitarism is defined as excessive secretion of one or more of the pituitary hormones. Its most common causes are functioning (hormone-secreting) adenomas of the anterior lobe.

Anterior lobe adenomas

Anterior lobe adenomas comprise about 10% of all intracranial tumours (posterior lobe adenomas do not occur). These tumours do not usually metastasise, but they are often life threatening because of their position and ability to secrete excess hormone.

Effects of pituitary adenomas

Pituitary adenomas cause problems because of a combination of endocrine effects (excessive secretion of a particular hormone) and compressive effects, caused by an increase in local pressure of the following:

- Remainder of the pituitary → hypopituitarism.
- Optic chiasm → visual field defects, notably bitemporal haemianopia.

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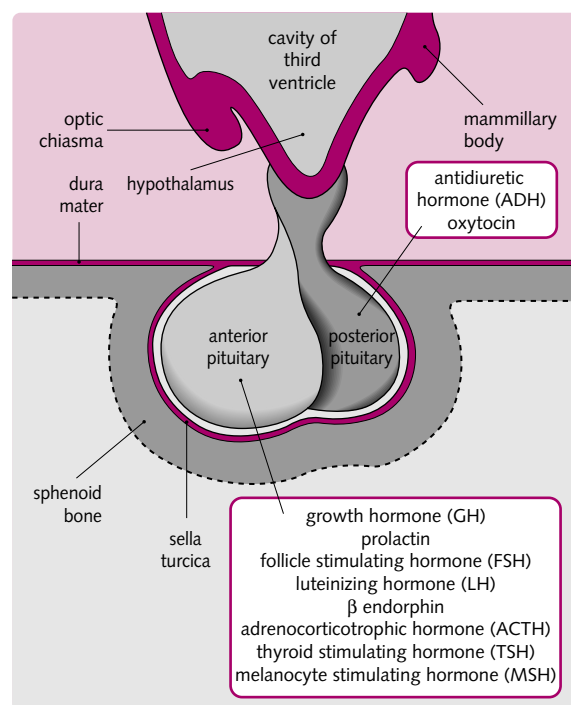


Fig. 10.1 Pituitary and hypothalamus, with the hormones released.

- Brain (large tumours) → distortion of the midbrain with raised intracranial pressure and hydrocephalus.
- Dura → headaches.
- Cavernous sinus → CN III, IV or VI nerve palsies.

The endocrine effects depend on which hormone is being excessively secreted (see below).

Investigations:

- Imaging—plain X-ray (can detect enlargement of sella turcica and erosion of the clinoid processes) and MRI (for visualisation and sizing of the tumour; this is superior to CT scanning).
- Hormone assays (e.g. growth hormone, prolactin).
- Functional testing of the pituitary–adrenal axis, e.g. ACTH stimulation test in which a dose of adrenocorticotrophic hormone (ACTH) is given and the plasma cortisol response measured.
- Visual field assessment.

Types of functioning adenomas

Functioning adenomas may produce any of the anterior lobe (adenophyseal) hormones but the majority produce prolactin (prolactinomas–lactotroph adenomas), growth hormone (somatotroph adenomas) or ACTH (corticotroph adenomas).

Prolactinomas

Abnormally raised serum prolactin levels are associated with menstrual irregularity and infertility in women, and with ejaculatory failure or impotence in men. Mild prolactin increases are seen with compression of the hypothalamus by any pituitary adenoma (the 'stalk effect').

Galactorrhoea is present in about 30% of affected women, but it is rare in men because oestrogen priming is required for lactation.

Somatotroph adenoma

This results in hypersecretion of growth hormone, the effects of which depend on the developmental stage of the affected individual:

- Pre-epiphyseal union (prepubertal) leads to gigantism (giantism), i.e. excessive growth in a regular and initially well-proportioned manner. Most giants also show some features of acromegaly with disproportionate enlargement, e.g. of the hands and jaw.

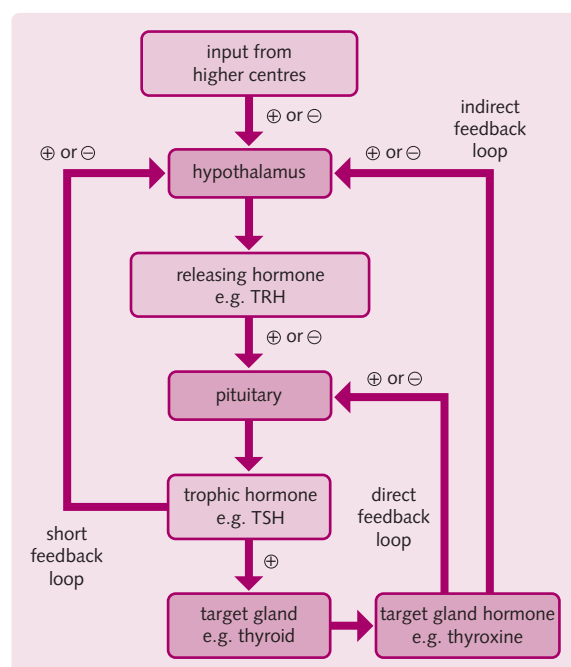


Fig. 10.2 Schematic representation of the integration between the higher centre, hypothalamus, pituitary and target organ signalling. The example is for thyroid function, highlighting the feedback loops that control hormone release at each level. (TRH, thyrotrophin releasing hormone, TSH, thyroid stimulating hormone). (Adapted with permission from *Essential Endocrinology*, 4th edn, by Brook and Marshall, Blackwell Publishing, 2001).

- Postepiphyseal union (adults) leads to acromegaly, which is characterised by enlargement of the hands, feet, and head. They may also present with secondary diabetes (growth hormone is an insulin antagonist) or cardiovascular effects (Fig. 10.3).

There are three types of treatment:

- Surgery—hypophysectomy (transfrontal or transphenoidal), especially where there are signs of compression of adjacent structures. This usually only debulks the tumour, with further (usually drug) therapy required.
- Radiotherapy—fewer complications than surgery but less successful.
- Drug therapy—bromocriptine (dopamine agonist) and octreotide (somatostatin analogue) can lower growth hormone levels in uncomplicated acromegaly.

Corticotrophin adenoma

Overproduction of ACTH by the pituitary gland (Cushing's disease) causes adrenal hyperplasia,

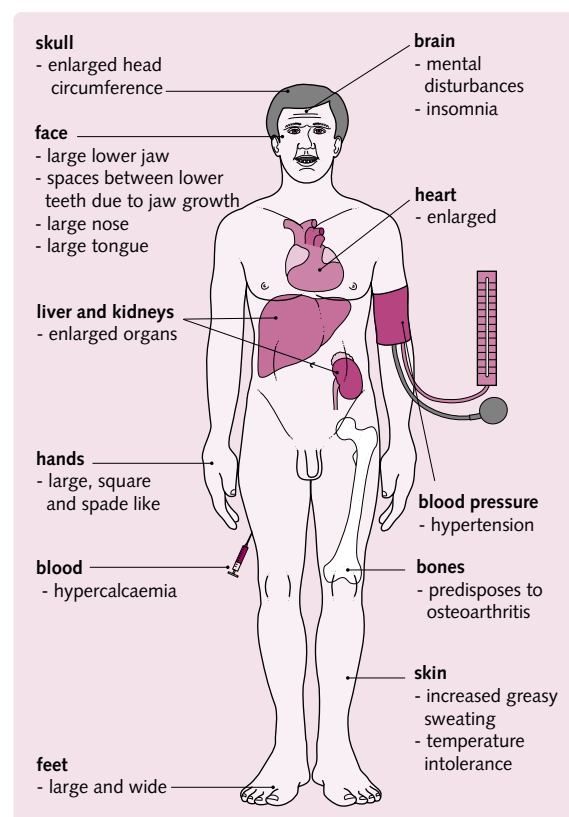


Fig. 10.3 Features of acromegaly.

resulting in the excessive secretion of glucocorticoids causing Cushing's syndrome, the effects of which are described later (see page 219).

Other functioning adenomas

Other endocrine secreting adenomas, e.g. of thyroid-stimulating hormone (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), are extremely rare.

The anterior pituitary: hypopituitarism

Hypopituitarism is defined as insufficient secretion of the pituitary hormones. The clinical features depend on the patient's age and on the type and severity of the hormone deficiencies (Fig. 10.4).

Hypopituitarism can be caused by either hypothalamic lesions or pituitary lesions.

Hypothalamic lesions are:

- Idiopathic deficiency of one or more of the releasing factors, e.g. gonadotrophin-releasing hormone (GnRH; Kallmann's syndrome), growth-hormone releasing factor (GHRH) or, more rarely, thyrotrophin-releasing hormone (TRH) or corticotrophin-releasing factor (CRF).
- Infarction.
- Inflammation, e.g. sarcoidosis, tuberculous meningitis.
- Suprasellar tumours, e.g. craniopharyngioma or, more rarely, pinealoma, teratoma or a secondary tumour from another site.

Pituitary lesions are:

- Idiopathic deficiency of one or more of the pituitary hormones.
- Non-functioning chromophobe pituitary adenomas—adenomas of the anterior pituitary (usually derived from non-hormone-secreting chromophobe cells), which may cause hypopituitarism by compression or obliteration of normal pituitary tissue.
- Sheehan's syndrome—iskaemic necrosis of the anterior pituitary due to hypotensive shock occurring as a result of obstetric haemorrhage.
- Empty sella syndrome—an enlarged, empty sella turcica that is not filled with pituitary tissue. This may be a primary anatomical variant or it may follow spontaneous infarction, surgery, or radiotherapy of a tumour.

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Fig. 10.4 Clinical features associated with specific forms of hypopituitarism.

Fig. 10.4 Clinical features associated with specific forms of hypopituitarism

Hormone deficiency	Clinical features	Tests to exclude hypofunction of anterior pituitary
Gonadotrophin deficiency	Prepubertal: <ul style="list-style-type: none"> • Failure to enter puberty • Undescended testes • Obesity • Eunuchoidism Postpubertal: <ul style="list-style-type: none"> • Infertility • Amenorrhoea • Oligospermia • Progressive loss of secondary sex characteristics (hypogonadism) • Osteoporotic collapse of spine → loss of stature 	LH reserves adequate if: <ul style="list-style-type: none"> • Males have a normal testosterone • Females are ovulating FSH reserves adequate if: <ul style="list-style-type: none"> • Males have a normal spermatogenesis • Females are ovulating
GH deficiency	Children: failure of longitudinal growth Adults: tendency to hypoglycaemia	GH reserves adequate if: random plasma level >20 mU/L stress or otherwise elevated GH peak >20 mU/L
TSH deficiency	Fetus or newborn: cretinism Adults: hypothyroidism	TSH reserves adequate if serum thyroxine within normal range
ACTH deficiency	Features of primary hypoadrenalism but with decreased pigmentation (rather than an increase)	ACTH reserves adequate if: random plasma cortisol >550 nmol/L stress-induced cortisol rise >550 nmol/L

Note: ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

- Trauma, including surgery and radiotherapy.
- Granulomatous lesions—sarcoidosis, tuberculosis, histiocytosis.

Management

Management is by substitution therapy according to the deficiencies demonstrated, e.g. cortisol replacement for ACTH deficiency, thyroid hormone replacement for TSH deficiency.

The posterior pituitary

Diseases of the posterior pituitary are much less common than those of the anterior pituitary and are usually the result of damage to the hypothalamus by tumour invasion or infarction. Posterior pituitary diseases typically cause disorders of abnormal ADH secretion. There are no known effects of abnormal oxytocin secretion.

Diabetes insipidus

Diabetes insipidus (DI) is a rare condition characterised by the persistent excretion of excessive

quantities of dilute urine (polyuria) and by constant thirst (polydipsia).

There are two types (Fig. 10.5):

1. Cranial DI—caused by the failure of ADH production.
2. Nephrogenic DI—distal tubules are refractory to the water reabsorptive action of ADH.

Clinical features—irrespective of aetiology, reabsorption of water from the glomerular filtrate in the renal collecting ducts does not occur, resulting in polyuria (up to 20 L per day is possible) and high risk of body water depletion. DI is potentially lethal without appropriate therapy.

Investigations—there is high clinical suspicion if a patient has a high plasma osmolality, with low or immeasurable plasma ADH, and a non-maximally concentrated urine. A water deprivation test is run for 8 hours or until 3% of the body weight is lost. Demonstration of continued polyuria and increased haemoconcentration indicates DI. This test serves to

Fig. 10.5 Causes of cranial and nephrogenic diabetes insipidus (DI)

	Cause	Features
Cranial DI	Hypothalamic or pituitary stalk damage	Surgical damage, usually in the course of tumour removal Head injury, usually transient Hypothalamic tumour (either primary or secondary) Hypothalamic inflammatory lesions, e.g. sarcoidosis, encephalitis, meningitis
	Genetic defect	Dominant Recessive: DIDMOAD syndrome—association of DI with diabetes mellitus (DM), optic atrophy (OA) and deafness (D)
	Idiopathic	About 30% of cases have no known cause
Nephrogenic DI	Hereditary	Abnormal ADH receptors
	Metabolic abnormalities	Hypokalaemia Hypercalcaemia
	Drug therapy	Lithium Demethylchlortetracycline
	Poisoning	Heavy metals

Note: ADH, antidiuretic hormone.

Fig. 10.5 Causes of cranial and nephrogenic diabetes insipidus (DI).

differentiate DI from psychogenic polydipsia. The test is then followed by ADH administration to differentiate between cranial DI (kidneys are responsive to ADH) or nephrogenic DI (kidneys are unresponsive to ADH).

Treatment of mild DI—the effects of dehydration can be counteracted by greatly increasing water intake (polydipsia).

Treatment of moderate to severe DI

- Cranial DI—treatment with desmopressin (ADH analogue but without vasoactive effects).
- Nephrogenic DI—treatment with thiazide diuretics, producing a decrease in urine volume by approximately 50%.

Syndrome of inappropriate antidiuretic hormone secretion

Increased secretion of ADH occurs as a complication of other diseases (primary hypersecretion of ADH is not recognised). The condition is characterised by water retention with haemodilution and by inappropriately concentrated urine. In severe cases, cerebral oedema supervenes with impaired consciousness, but body oedema is not usually seen as free water is evenly distributed to all body compartments.

The causes are:

- Idiopathic.
- Tumours—ectopic secretion of ADH, especially by small cell carcinomas of the lung and some other neuroendocrine tumours.
- Trauma—skull fracture, head injury or surgery may produce transiently increased secretion of ADH.
- Intracranial inflammation—meningitis, tuberculosis, syphilis.
- Non-neoplastic lung disease (e.g. pneumonia, pulmonary embolus) probably due to involvement of intrathoracic baroreceptors.

Diabetes insipidus and diabetes mellitus are two distinct conditions that both feature polyuria.



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Figure 10.6 shows a comparison table of features of DI with those of inappropriate ADH secretion.

Disorders of the pineal gland

The pineal gland is located above the third ventricle and it secretes the hormone melatonin. Melatonin is thought to function in circadian rhythm control and gonadal maturation.

Pinealomas (germinomas)

These tumours of young adults and children are often called germinomas. They are thought to originate from primitive germ cells and, histologically, they resemble testicular seminomas and/or teratomas:

- Pressure on the midbrain may produce Parinaud's syndrome (paralysis of the conjugate upward gaze without paralysis of convergence).
- Pressure on the hypothalamus can produce symptoms of DI, emaciation or precocious puberty.

remains connected to the tongue by a narrow canal, the thyroglossal duct, which later becomes solid and finally disappears.

Thyroglossal cysts

Cystic remnants of parts of the thyroglossal duct are known as thyroglossal cysts (Fig. 10.7). These cysts may form anywhere along the course of descent but are always located near or in the midline of the neck, most commonly just inferior to the hyoid bone. Cysts usually develop as painless, progressively enlarging and movable masses. Infection of cysts may result in the formation of sinuses that open through the skin.

Thyrotoxicosis (hyperthyroidism)

This syndrome is caused by the excessive secretion of thyroid hormones—typically both thyroxine (T_4) and tri-iodothyronine (T_3)—in the bloodstream. Symptoms include tachycardia, sweating, tremor, anxiety, increased appetite, loss of weight and intolerance of heat.

THYROID DISORDERS

Congenital disorders of the thyroid

Development of the thyroid

The thyroid gland develops from an endodermal thickening in the floor of the primitive pharynx at a point later indicated by the foramen caecum of the tongue (Fig. 10.7). As the embryo grows, the thyroid descends into the neck, passing anterior to the hyoid and laryngeal cartilages. During migration, the gland

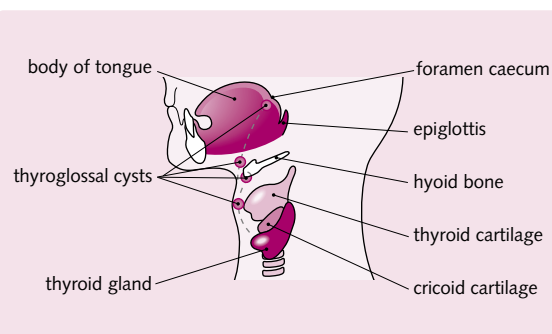


Fig. 10.7 Path of descent of thyroid gland (broken line) and localisation of thyroglossal cysts.

Fig. 10.6 Comparison of features of diabetes insipidus with those of inappropriate ADH secretion

Condition	Imbalance	Urinary and plasma osmolality	Symptoms
Diabetes insipidus	↓ ADH	Low urinary osmolality High plasma osmolality	Polyuria (5–20 L/day) Thirst Polydipsia (may lead to severe dehydration, exhaustion, coma)
Syndrome of inappropriate ADH secretion	↑ ADH	High urinary osmolality Low plasma osmolality (dilutional hyponatraemia)	Oliguria Water intoxication (may lead to confusion, neurological disturbances, coma)

Note: ADH, antidiuretic hormone.

Fig. 10.6 Comparison of features of diabetes insipidus with those of inappropriate antidiuretic hormone (ADH) secretion.

Hyperthyroidism can be classified on the basis of aetiology into:

- Primary hyperthyroidism (\uparrow thyroid hormones, \downarrow TSH)—hypersecretion of thyroid hormones, which is not secondary to increased levels of TSH (the rise in thyroid hormones actually suppresses TSH).
- Secondary hyperthyroidism (\uparrow thyroid hormones, \uparrow TSH)—overstimulation of the thyroid gland caused by excess TSH produced by a tumour in the pituitary or elsewhere (rare).

Primary hyperthyroidism is caused by:

- Graves' disease (exophthalmic goitre)—the most common cause of thyrotoxicosis, characterised by a diffusely enlarged thyroid gland that is stimulated to produce excess hormone by an IgG autoantibody.
- Toxic multinodular goitre (Plummer's disease)—second most common cause of hyperthyroidism.
- Toxic adenoma—solitary thyroid nodule producing excess hormone with remainder of the thyroid gland being suppressed.
- Thyroiditis—inflammation of the thyroid causing hyperthyroidism (e.g. De Quervain's thyroiditis). Note that thyroiditis is more commonly associated with hypothyroidism (see below).
- Drugs—either direct ingestion of large doses of thyroid hormone (thyrotoxicosis factitia) or through iodide-inducing drugs (e.g. amiodarone).

Effects of thyrotoxicosis

Signs and symptoms of thyrotoxicosis are a consequence of an increase in the body's metabolism, which occurs as a direct result of increased concentrations of the thyroid hormones.

The most important symptoms diagnostically are:

- Heat intolerance and excessive sweating (hyperhidrosis).
- Nervousness and irritability.
- Weight loss with normal or increased appetite.
- Goitre (an enlargement of the thyroid gland).

Other symptoms are summarised in Fig. 10.8.

Investigations—hyperthyroidism is confirmed by raised serum thyroxine and/or lowered serum TSH.

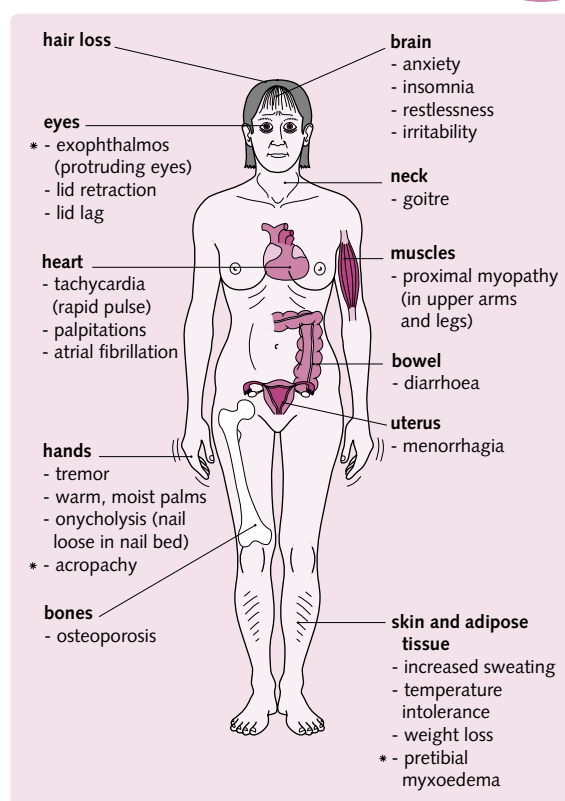


Fig. 10.8 Summary diagram illustrating features of thyrotoxicosis. (* = additional features seen only in Graves' disease.)

Management—options in thyrotoxicosis are:

- Surgery—reduces the amount of functioning thyroid tissue.
- Radioactive iodine—to destroy part of the gland.
- Drugs (such as carbimazole or propylthiouracil)—interfere with the production of thyroid hormones.

Graves' disease

Graves' disease is an organ-specific autoimmune disorder that results in thyrotoxicosis due to overstimulation of the thyroid gland by autoantibodies. It is the most common form of thyrotoxicosis, females being affected more than males by 8 : 1. It is usually associated with a diffuse enlargement of the thyroid.

Pathogenesis—IgG-type immunoglobulins bind to TSH membrane receptors and cause prolonged stimulation of the thyroid, lasting for as long as 12 hours (cf. 1 hour for TSH). The autoantibody binds at a site different to the hormone-binding locus and is termed the TSH-receptor autoantibody (TRAb); 95% of Graves' disease patients are positive for TRAbs.

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Histologically, the gland shows diffuse hypertrophy and hyperplasia of acinar epithelium, reduction of stored colloid and local accumulations of lymphocytes with lymphoid follicle formation.

The clinical features of Graves' disease are similar to those of general thyrotoxicosis but with some additional features (see Fig. 10.8), namely:

- Exophthalmos (protrusion of the eyeballs in their sockets)—due to the infiltration of orbital tissues by fat, mucopolysaccharides and lymphocytes. May cause compression of the optic nerve, hence blindness. However, only about 5% of Graves' patients show signs of exophthalmos.
- Thyroid acropachy—enlargement of fingernails.
- Pretibial myxoedema—accumulation of mucoproteins in the deep dermis of the skin.

Treatment is as for thyrotoxicosis.

Hypothyroidism

Decreased activity of the thyroid gland results in decreased production of thyroid hormones. There are two forms:

1. Hypothyroidism present at birth → cretinism or congenital hypothyroidism.
2. Hypothyroidism in adults → myxoedema.

Cretinism (congenital hypothyroidism)

This condition occurs as a result of extreme hypothyroidism during fetal life, infancy or childhood. It has the following types and aetiology:

- Endemic cretinism—occurs in iodine-deficient countries where goitre is common. The mother almost always has a goitre and the thyroid of the affected infant is usually enlarged and nodular.
- Sporadic cretinism—caused by congenital hypoplasia or absence of the thyroid gland and often associated with deaf mutism.
- Dyshormonogenesis—a congenital familial recessive enzyme defect causing an inability to complete the formation of thyroid hormones. TSH is increased, and the thyroid gland is enlarged and shows epithelial hyperplasia.

The clinical features of cretinism are:

- Mental retardation.
- Retarded growth—skeletal growth is inhibited more than soft tissue growth, resulting in an obese, stocky, short child.
- Coarse, dry skin.

- Lack of hair and teeth.
- Pot belly (often with umbilical hernia).
- Protruding tongue.

Management is by early detection and treatment with thyroxine, which can prevent an irreversible mental defect and cerebellar damage. Many countries now have screening programs to measure serum TSH and/or thyroxine levels on heel-prick blood samples taken on the fourth or fifth day of life.

Hypothyroidism in adults (myxoedema)

This common clinical condition is associated with decreased function of the thyroid gland and a decrease in the circulating level of thyroid hormones. It affects 1% of people in the UK, with females more than males by 6:1. It can present at any age but most commonly between 30 and 50 years of age.

Note that, strictly speaking, myxoedema describes a non-pitting, oedematous reaction characteristic of hypothyroidism caused by the deposition of a mucoid substance (*myxa*—is a Greek prefix denoting mucus) in the skin and elsewhere in the body. However, the terms 'myxoedema' and 'hypothyroidism of adults' are now frequently used interchangeably.

Hypothyroidism can be classified according to aetiology:

- Primary (↓ thyroid hormones, ↑ TSH)—failure of the thyroid gland itself. This is much more common than secondary hypothyroidism. Note that subclinical hypothyroidism describes an increase in TSH but with normal thyroid hormone levels, and is increasingly being treated with the aim of reducing progression to full disease.
- Secondary (↓ thyroid hormones, ↓ TSH)—failure of TSH production due to pituitary disease.

The causes of primary hypothyroidism are:

- Autoimmune thyroiditis—atrophic form, e.g. primary atrophic thyroiditis and goitrous form (such as Hashimoto's thyroiditis).
- Graves' disease—approximately 5% of patients with thyrotoxicosis develop hypothyroidism in later years, unrelated to treatment. Probably caused by a spectrum of antithyroid antibodies, some of which stimulate TSH receptor and some of which are destructive.
- Treatment of hyperthyroidism—surgical ablation, radioiodine or drug treatment.

- Severe iodine deficiency (rare in the UK)—iodine must be virtually absent from the diet before myxoedema develops.

The effects of hypothyroidism are shown in Fig. 10.9.

Signs and symptoms of hypothyroidism are both widespread (due to reduced body metabolism) and localised (myxoedema due to the accumulation of mucoproteins). The most important symptoms diagnostically are:

- Mental and physical slowness.
- Tiredness.
- Cold intolerance.
- Dryness of skin and hair.

Investigations are:

- Serum thyroxine concentration (decreased).
- Serum TSH concentration (reduced in secondary hypothyroidism but increased in primary hypothyroidism).

The treatment is oral thyroxine daily for life.

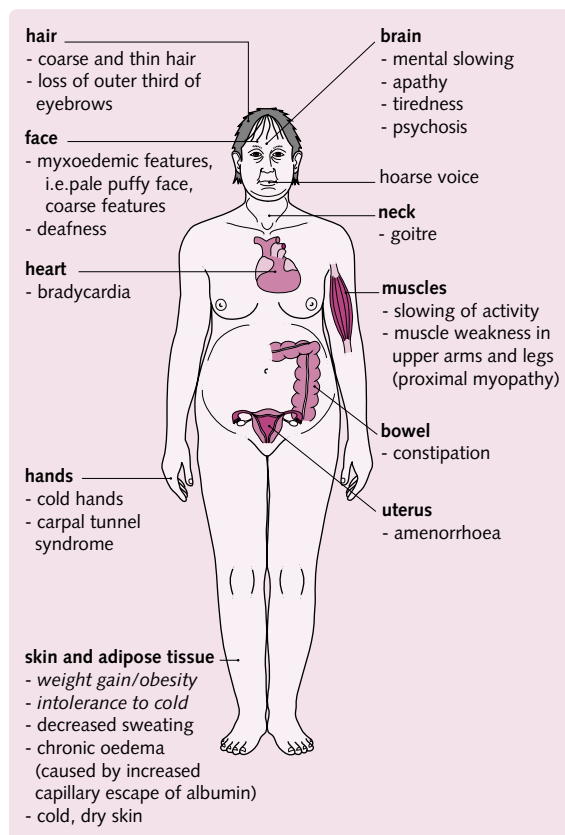


Fig. 10.9 Summary diagram illustrating features of hypothyroidism in the adult (myxoedema).

Thyroiditis

This inflammation of the thyroid gland can have a viral or autoimmune aetiology.

Hashimoto's thyroiditis (most common cause of hypothyroidism)

This organ-specific autoimmune disease results in destructive thyroiditis. It can occur at any age, but typically affects the middle-aged, and females more than males by 12 : 1.

Thyroid peroxidase antibodies are most commonly found in the serum of affected individuals (90% of cases). The disease is associated with the HLA-DR5 and HLA-B8 haplotypes, and patients with Hashimoto's disease (and Graves' disease) show a high incidence of other autoimmune diseases.

Macroscopically, the thyroid gland is usually:

- Diffusely enlarged (typically 2–5 times normal size).
- Firm in consistency.
- White or grey on a cut surface as a result of the disappearance of brown (iodine-rich) colloid (thyroglobulin), and its replacement by lymphocytes.

Microscopically, the thyroid gland shows:

- Small thyroid follicles infiltrated by lymphocytes and plasma cells.
- Lymphoid follicle formation and increased fibrous tissue stroma.
- Acini lined with abnormal, highly eosinophilic epithelial cells (proliferation of mitochondria) known as Askanazy or Hürthle cells.
- Reduced colloid content of disrupted acini.

The condition may present due to goitre formation or because of the symptoms of hypothyroidism. The hypothyroid state tends to develop slowly. However, damage to thyroid follicles may lead to the release of thyroglobulin into the circulation causing transient thyrotoxicosis. Some cases proceed to primary atrophic thyroiditis. Furthermore, there is an increased incidence of non-Hodgkin's lymphoma originating in the thyroid of patients with Hashimoto's thyroiditis.

Treatment is by oral thyroxine, which overcomes hypothyroidism and reduces the size of the goitre.

De Quervain's thyroiditis

A rare, viral thyroiditis seen in young and middle-aged women as a slightly diffuse tender swelling of the thyroid; this is also known as subacute, giant cell or

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granulomatous thyroiditis. The condition usually occurs in association with a transient febrile illness, often during various viral epidemics.

The most commonly associated viruses are Cocksackie, mumps and adenovirus.

Characteristic features are:

- Painful enlargement of the thyroid (about twice normal size; normal weight is 20–30 g).
- History of usually short duration.
- Preceding general malaise, pyrexia or upper respiratory infection.

Histological examination shows:

- Inflammation with a giant cell granulomatous reaction engulfing leaked colloid (hence the synonyms giant cell or granulomatous thyroiditis).
- Degeneration of follicles with inflammatory cell infiltration (neutrophils, plasma cells, lymphocytes and histiocytes).
- Fibrous scarring (late).

The illness is usually self-limiting and settles in a few weeks. Transient hyperthyroidism can result from the release of thyroglobulin and excessive amounts of thyroid hormone.

Severe thyroiditis may be fatal in the elderly and debilitated.

Subacute lymphocytic thyroiditis

This form of autoimmune thyroiditis is characterised by focal lymphocytic infiltration of the thyroid (also known as focal lymphocytic thyroiditis).

Histological changes are similar to those in Hashimoto's thyroiditis but they are focal rather than diffuse. The disease is less severe than

Hashimoto's thyroiditis, and it is often asymptomatic. It may also present with the symptoms of hyperthyroidism.

Note that some degree of progressive lymphocytic infiltration of the thyroid is seen in 5–10% of thyroid autopsies, and these are thought to be a normal ageing change. However, in subacute lymphocytic thyroiditis, lymphocytic infiltration is in excess of what would normally be expected for age-related change.

A comparison of the main types of thyroiditis is provided in Fig. 10.10.

Thyroid goitres

Definitions

A goitre is any enlargement of part or whole of the thyroid gland. There are two types:

1. Toxic goitre, i.e. goitre associated with thyrotoxicosis.
2. Non-toxic goitre, i.e. goitre associated with normal or reduced levels of thyroid hormones.

Toxic goitre

Graves' disease

This is the most common cause of toxic goitre (described above).

Toxic multinodular goitre

This results from the development of hyperthyroidism in a multinodular goitre (see below).

Non-toxic goitres

Diffuse non-toxic goitre (simple goitre)

This diffuse enlargement of the thyroid gland is classified into:

Fig. 10.10 Summary of features of thyroiditis.

Fig. 10.10 Summary of features of thyroiditis

	Hashimoto's thyroiditis	De Quervain's thyroiditis	Subacute lymphocytic thyroiditis
Aetiology	Autoimmune	Viral	Autoimmune
Histological features	Diffuse lymphocytic infiltration of thyroid	Giant cell granulomatous inflammatory reaction	Focal lymphocytic infiltration of thyroid
Hypothyroidism	Common	Rare	Rare

- Endemic goitre—due to iodine deficiency. Rare in the UK but may occur in certain geographical areas remote from the sea.
- Sporadic goitre—caused by goitrogenic agents (substances that induce goitre formation) or familial in origin. Examples of goitrogenic agents include certain cabbage species, because of their thiourea content, and specific drugs or chemicals, such as iodide, paraminosalicylic acid and drugs used in the treatment of thyrotoxicosis. Familial cases show inherited autosomal recessive traits, which interfere with hormone synthesis via various enzyme pathways (these are dyshormonogenic goitres).
- Physiological goitre—enlargement of the thyroid gland in females during puberty or pregnancy; the reason is unclear.

Multinodular goitre

This is the most common cause of thyroid enlargement and is seen particularly in the elderly (nearly all simple goitres eventually become multinodular). The exact aetiology is uncertain but it may represent an uneven responsiveness of various parts of the thyroid to fluctuating TSH levels over a period of many years. Morphological features are:

- Irregular hyperplastic enlargement of the entire thyroid gland due to the development of well-circumscribed nodules of varying size.
- Larger nodules filled with brown, gelatinous colloid; consequently, it is often termed multinodular colloid goitres.

Most patients have normal thyroid function and generally seek treatment for cosmetic reasons (an unsightly swelling in the neck) or compression symptoms, e.g. pressure on the trachea producing stridor or pressure on the recurrent laryngeal nerve producing hoarseness.

However, toxic changes occasionally occur in a multinodular goitre resulting in hyperthyroidism, when it is termed a toxic multinodular goitre.

Neoplasms of the thyroid

Tumours of the thyroid are generally benign. Carcinomas are rare and lymphomas are rarer still.

Benign tumours

Thyroid adenomas

These are solitary, or multiple, encapsulated solid nodules. Compression of the adjacent gland is a common

A reminder of the differences between primary and secondary hyperthyroidism and hypothyroidism:

- Primary hyperthyroidism—↑ thyroid hormones, ↓ TSH.
- Secondary hyperthyroidism—↑ thyroid hormones, ↑ TSH (excess TSH production due to pituitary tumour).
- Primary hypothyroidism—↓ thyroid hormones, ↑ TSH.
- Secondary hypothyroidism—↓ thyroid hormones, ↓ TSH (failure of TSH production due to pituitary disease).



feature, and the centre may show areas of haemorrhage and cystic changes. The most common type is follicular adenoma, which consists of colloid-containing microfollicles and columns of larger cells of alveolar arrangement.

Rarely, follicular adenomas may synthesise excess thyroid hormones ('toxic adenomas'), causing thyrotoxicosis.

Malignant tumours

These rare tumours account for less than 1% of total cancer deaths in the UK, with females affected more than males by 3 : 1. Although the aetiology of thyroid cancer is unknown in the majority, it is likely that childhood radiation exposure is involved in some cases (there is an increased incidence in those exposed to the Chernobyl fallout). Types of malignant thyroid tumours and their basic features are outlined in Fig. 10.11.

Papillary adenocarcinoma

This well-differentiated tumour is most commonly found in younger patients. It presents as a non-encapsulated infiltrative mass. It is a slow growing tumour with an excellent prognosis.

Histologically, it consists of epithelial papillary projections between which calcified spherules may be present. Epithelial cell nuclei are characteristically large with optically clear areas centrally (described as 'Orphan Annie nuclei').

Follicular adenocarcinoma

This well-differentiated, single, encapsulated lesion is histologically similar to follicular adenoma but can

Pathology of the endocrine system

Fig. 10.11 Types and features of malignant thyroid tumours

	Tumour type	Origin of tumour	Frequency (%)	Typical age range (years)	Spread	Prognosis (% for 10-year survival)
Differentiated carcinoma	Papillary	Follicular cells	70	20–40	Lymph nodes	95
	Follicular	Follicular cells	10	40–60	Bloodstream	60
Undifferentiated carcinoma	Anaplastic	Follicular cells	5	>60	Aggressive local invasion; bloodstream	1
Medullary carcinoma	—	Parafollicular C cells	5–10	>40	Local, lymphatic and blood	50 (but very variable)
Lymphoma	—	Lymphocytes	5–10	>60	Lymphatic	10

Fig. 10.11 Types and features of malignant thyroid tumours.

be differentiated by its invasion of the capsule and/or blood vessels. Spread is usually to bones, lungs and brain via the bloodstream.

Many of these tumours retain the ability to take up radioactive iodine (^{131}I), which may be used as a highly effective targeted form of radiotherapy, usually after surgical thyroidectomy. The prognosis, therefore, is good.

Anaplastic carcinoma

This highly malignant, poorly differentiated adenocarcinoma usually presents in the elderly as a diffusely infiltrative mass. In about half of cases there is a history of multinodular goitre.

Histologically, the dominant features are those of a spindle cell tumour with or without giant cell areas, or a small cell pattern.

The prognosis is very poor due to the rapid local invasion of structures such as the trachea, producing respiratory obstruction.

Medullary carcinoma

This rare neuroendocrine tumour arises from parafollicular C cells, which commonly synthesise and secrete calcitonin but which may also secrete 5-hydroxytryptamine (serotonin), various peptides of the tachykinin family, ACTH and prostaglandins.

High levels of serum calcitonin are useful diagnostically but produce no clinical effects.

Although medullary carcinoma is most common in the elderly, it also occurs in younger individuals, where it is commonly associated with other endocrine tumours, such as pheochromocytoma as part of the

multiple endocrine neoplasia (MEN) syndromes IIa and IIb (see pages 227–228).

Lymphomas

Most thyroid lymphomas are regarded as tumours of mucosa-associated lymphoma tissue. Interestingly, non-Hodgkin's B cell lymphomas occasionally arise in long-standing, autoimmune thyroiditis, especially Hashimoto's disease.

PARATHYROID DISORDERS

Parathyroid hormone

Parathyroid hormone (PTH) is a polypeptide (84 amino acid residues) secreted by the chief cells of the parathyroid glands (four glands: two in each of the superior and inferior lobes of the thyroid; total weight 120 mg).

The main action of PTH is to increase serum calcium and decrease serum phosphate. Its actions are mediated by the bones and kidneys as described below.

In bone, PTH stimulates osteoclastic bone resorption and inhibits osteoblastic bone deposition. The net effect is the release of calcium from bone.

In the kidney, PTH has the following effects:

- Increases calcium reabsorption.
- Decreases phosphate reabsorption.
- Increases 1-hydroxylation of 25-hydroxyvitamin D (i.e. activates vitamin D).

PTH also increases gastrointestinal calcium absorption.

Hyperparathyroidism

Hyperparathyroidism is defined as an elevated secretion of PTH, of which there are three main types:

1. Primary—hypersecretion of PTH by adenoma or hyperplasia of the gland.
2. Secondary—physiological increase in PTH secretions in response to hypocalcaemia of any cause.
3. Tertiary—supervention of an autonomous hypersecreting adenoma in long-standing secondary hyperparathyroidism.



Understanding the physiological functions of PTH is essential to an understanding of the clinical effects produced by its hypo- or hypersecretion.

Primary hyperparathyroidism

This is the most common of the parathyroid disorders, with a prevalence of about 1 per 800 in the UK. It is an important cause of hypercalcaemia. More than 90% of patients are over 50 years of age and the condition affects females more than males by nearly 3 : 1. The aetiology of primary hyperparathyroidism is outlined in Fig. 10.12.

Fig. 10.12 Aetiology of primary hyperparathyroidism

Type	Frequency	Features
Adenoma	75%	Orange-brown, well-encapsulated tumour of various size but seldom > 1 cm diameter Tumours are usually solitary, affecting only one of the parathyroids, the others often showing atrophy; they are deep seated and rarely palpable
Primary hyperplasia	20%	Diffuse enlargement of all the parathyroid glands
Parathyroid carcinoma	5%	Usually resembles adenoma but is poorly encapsulated and invasive locally

Fig. 10.12 Aetiology of primary hyperparathyroidism.

Effects of hyperparathyroidism

The clinical effects are the result of hypercalcaemia and bone resorption.

Effects of hypercalcaemia:

- Renal stones due to hypercalcuria.
- Excessive calcification of blood vessels.
- Corneal calcification.
- General muscle weakness and tiredness.
- Exacerbation of hypertension and potential shortening of the QT interval.
- Thirst and polyuria (may be dehydrated due to impaired concentrating ability of kidney).
- Anorexia and constipation.

Effects of bone resorption:

- Osteitis fibrosa—increased bone resorption with fibrous replacement in the lacunae.
- ‘Brown tumours’—haemorrhagic and cystic tumour-like areas in the bone, containing large masses of giant osteoclastic cells.
- Osteitis fibrosa cystica (von Recklinghausen disease of bone)—multiple brown tumours combined with osteitis fibrosa.
- Changes may present clinically as bone pain, fracture or deformity.

However, about 50% of patients with biochemical evidence of primary hyperparathyroidism are asymptomatic.

Investigations are:

- Biochemical—increased PTH and Ca^{2+} , and decreased PO_4^{3-} .
- Radiological—90% normal; 10% show evidence of bone resorption, particularly phalangeal erosions.

Management is by rehydration, medical reduction in plasma calcium using bisphosphonates and eventual surgical removal of abnormal parathyroid glands.

Secondary hyperparathyroidism

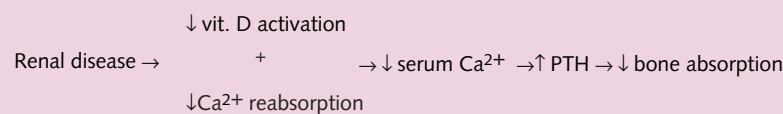
This is compensatory hyperplasia of the parathyroid glands, occurring in response to diseases of chronic low serum calcium or increased serum phosphate.

Its causes are:

- Chronic renal failure and some renal tubular disorders (most common cause).
- Steatorrhoea and other malabsorption syndromes.
- Osteomalacia and rickets.
- Pregnancy and lactation.

Pathology of the endocrine system

Fig. 10.13 Pathogenesis of renal osteodystrophy.



Morphological changes of the parathyroid glands are:

- Hyperplastic enlargement of all parathyroid glands, but to a lesser degree than in primary hyperplasia.
- Increase in 'water clear' cells and chief cells of the parathyroid glands, with loss of stromal fat cells.

Clinical manifestations—symptoms of bone resorption are dominant.

Renal osteodystrophy

Skeletal abnormalities, arising as a result of raised PTH secondary to chronic renal disease, are known as renal osteodystrophy.

The pathogenesis of renal osteodystrophy is shown in Fig. 10.13.

Abnormalities vary widely according to the nature of the renal lesion, its duration and the age of the patient, but include:

- Osteitis fibrosa (see above).
- Rickets or osteomalacia due to reduced activation of vitamin D.
- Osteosclerosis—increased radiodensity of certain bones, particularly the parts of vertebrae adjacent to the intervertebral discs.

Note that the symptoms of hypercalcaemia are not a feature of secondary hyperparathyroidism; calcium

levels are likely to be decreased as this is driving the compensatory PTH secretion.

The investigations are both biochemical (raised PTH and normal or lowered Ca^{2+}) and radiological (bone changes).

Management is by treatment of the underlying disease and oral calcium supplements to correct hypocalcaemia.

Tertiary hyperparathyroidism

This condition, resulting from chronic overstimulation of the parathyroid glands in renal failure, causes one or more of the glands to become an autonomous hypersecreting adenoma with resultant hypercalcaemia.

Figure 10.14 gives a comparison of primary, secondary and tertiary hyperparathyroidism.

Hypoparathyroidism

Hypoparathyroidism is a condition of reduced or absent PTH secretion, resulting in hypocalcaemia and hyperphosphataemia. It is far less common than hyperparathyroidism.

The causes of hypoparathyroidism are:

- Removal or damage of the parathyroid glands during thyroidectomy—most common cause of

Fig. 10.14 Comparison of primary, secondary and tertiary hyperparathyroidism.

Fig. 10.14 Comparison of primary, secondary and tertiary hyperparathyroidism

	Primary	Secondary	Tertiary
Serum PTH and Ca^{2+}	↑PTH; ↑ Ca^{2+}	↑PTH; normal or ↑ Ca^{2+}	↑PTH; ↑ Ca^{2+}
Aetiology	Adenoma Hyperplasia Carcinoma	Chronic renal failure Malabsorption Osteomalacia and rickets Pregnancy and lactation	Adenoma resulting from overstimulation of glands in secondary hyperparathyroidism
Predominant effects	Hypercalcaemia	Increased bone absorption	Hypercalcaemia and increased bone resorption

Note: PTH, parathyroid hormone.

hypoparathyroidism resulting from inadvertent damage or removal.

- Autoimmune parathyroid disease—usually occurs in patients who have another autoimmune endocrine disease, e.g. Addison's disease (autoimmune endocrine syndrome type 1).
- Congenital deficiency (DiGeorge syndrome)—rare, congenital disorder caused by arrested development of the third and fourth branchial arches, resulting in an almost complete absence of the thymus (see Chapter 13) and parathyroid gland.

The effects of hypoparathyroidism are:

- ↓ release of Ca^{2+} from bones.
- ↓ Ca^{2+} reabsorption but ↑ PO_4^{3-} reabsorption by kidney.
- ↓ 1-hydroxylation of 25-hydroxyvitamin D by kidney.

Most symptoms of hypoparathyroidism are those of hypocalcaemia:

- Tetany—muscular spasm provoked by lowered plasma Ca^{2+} .
- Convulsions.
- Paraesthesiae.
- Psychiatric disturbances, e.g. depression, confusional state and even psychosis.
- Rarely—cataracts, parkinsonian-like movement disorders, alopecia, brittle nails.

Management is by treatment with large doses of oral vitamin D; the acute phase requires intravenous calcium and calcitriol (1,25-dihydroxycholecalciferol, i.e. activated vitamin D).

DISORDERS OF THE ADRENAL GLAND

Hormones of the adrenal gland

The adrenal gland has two structurally and functionally distinct endocrine components derived from different embryonic tissue: the cortex and the medulla.

Cortex

This is the outer part of the gland, which is derived from the mesoderm. It synthesises, stores, and secretes various cholesterol-derived hormones, namely:

- Glucocorticoid hormones, e.g. cortisol—primarily from the zona fasciculata.
- Mineralocorticoid hormones, e.g. aldosterone—from the zona glomerulosa.
- Sex steroids, i.e. oestrogens and androgens—from the zona reticularis.

Medulla

This is the inner part of the gland, which is derived from the neuroectoderm, forming part of the sympathetic nervous system. Chromaffin cells synthesise and secrete the vasoactive amines epinephrine (adrenaline) and norepinephrine (noradrenaline).

Hyperfunction of the adrenal cortex

Cushing's syndrome

The symptoms and signs of Cushing's syndrome are associated with prolonged inappropriate elevation of free corticosteroid levels (Fig. 10.15).

Clinical features—the main effects of sustained elevation of glucocorticoid secretion are:

- Central obesity and moon face.
- Plethora and acne.
- Menstrual irregularity.
- Hirsutism and hair thinning.
- Hypertension.
- Diabetes.
- Osteoporosis—may cause collapse of vertebrae, rib fractures.
- Muscle wasting and weakness.
- Atrophy of skin and dermis—paper thin skin with bruising tendency, purple striae.

Aetiopathogenesis—patients with Cushing's syndrome can be classified into two groups on the basis of whether the aetiology of the condition is ACTH-dependent or independent (Fig. 10.16).

ACTH-dependent aetiology:

- Pituitary hypersecretion of ACTH (Cushing's disease)—bilateral adrenal hyperplasia secondary to excessive secretion of ACTH by a corticotroph adenoma of the pituitary gland (see page 207).
- Production of ectopic ACTH or corticotrophin-releasing hormone (CRH) by non-endocrine neoplasm, e.g. small cell lung cancer and some carcinoid tumours. In cases of malignant bronchial tumour, the patient rarely survives long enough to develop any physical features of Cushing's syndrome.

Pathology of the endocrine system

Fig. 10.15 Systemic effects of Cushing's syndrome.

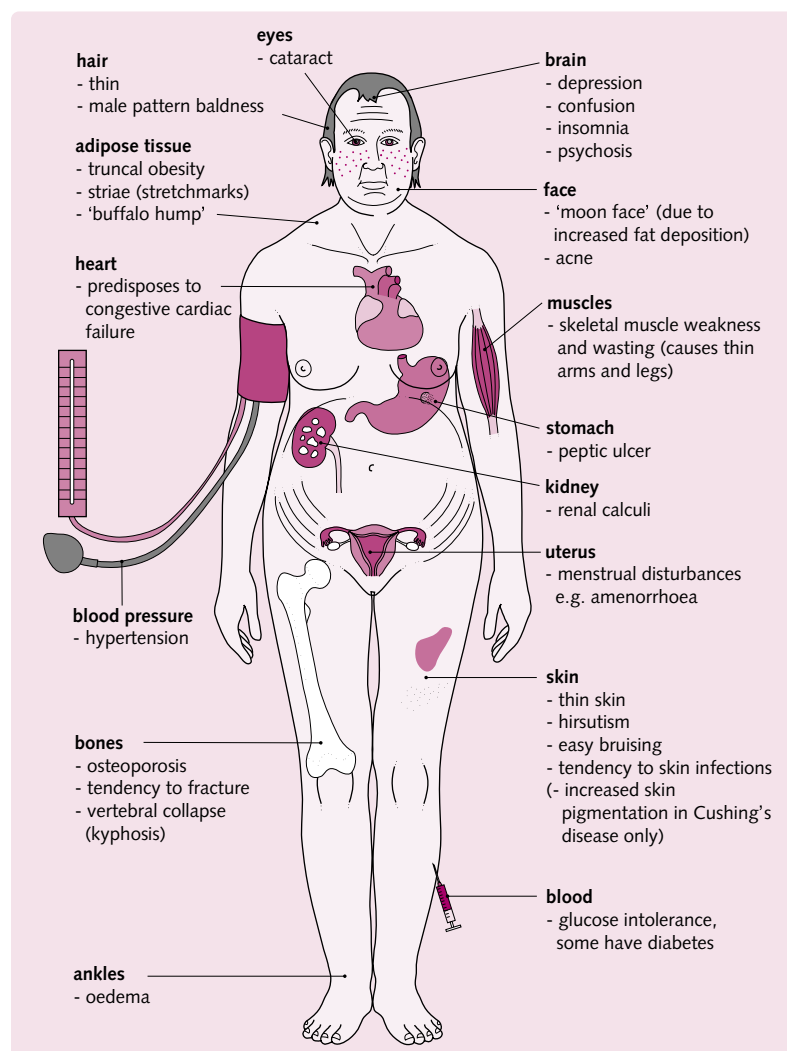


Fig. 10.16 Classification of Cushing's syndrome

Type	Cause
ACTH dependent	iatrogenic (ACTH therapy) Pituitary hypersecretion of ACTH Ectopic ACTH syndrome (benign or malignant non-endocrine tumour)
Non-ACTH dependent	iatrogenic, e.g. prednisolone Adrenal cortical adenoma Adrenal cortical carcinoma

Fig. 10.16 Classification of Cushing's syndrome.

Non-ACTH-dependent aetiology:

- Iatrogenic steroid therapy—most common cause of Cushing's syndrome.
- Adrenal cortical adenoma—well-circumscribed yellow tumour usually 2–5 cm in diameter. Extremely common as an incidental finding in up to 30% of all post-mortem examinations. The yellow colour is due to stored lipid (mainly cholesterol) from which the hormones are synthesised. The vast majority have no clinical effects (i.e. they are non-functioning adenomas), with only a small percentage producing Cushing's syndrome.

- Adrenal cortical carcinoma—rare and almost always associated with the overproduction of hormones, usually glucocorticoids and sex steroids. Patients usually have features of Cushing's syndrome mixed with androgenic effects which are particularly noticeable in women. Tumours are usually large and yellowish-white in colour. Local invasion and metastatic spread are common.

The therapeutic administration of glucocorticosteroids (e.g. prednisolone) is a common cause of the features of Cushing's syndrome. Avoid confusing the disease and the syndrome. *Remember:* Cushing's disease is used specifically to describe Cushing's syndrome secondary to excessive pituitary ACTH secretion.



Irrespective of the aetiology, the diagnosis is based on clinical features and the demonstration of a raised plasma cortisol level.

The aetiology of the disorder is elucidated through:

- Raised urinary cortisol in the first instance, but further testing is required.
- Low-dose dexamethasone suppression test (suppression of cortisol levels in Cushing's disease due to suppression of pituitary ACTH secretion, but a lack of suppression suggests ACTH-independent Cushing's syndrome).
- MRI and CT scan visualisation of pituitary and adrenal glands.
- Analysis of blood ACTH (high = pituitary adenoma or ectopic ACTH source; low = primary adrenal tumour due to feedback suppression).

Treatment of the underlying cause is essential as untreated Cushing's syndrome has a 50% 5-year mortality rate.

Hyperaldosteronism

Excessive production of aldosterone by the zona glomerulosa of the adrenal cortex results in increased Na^+ retention and increased K^+ loss.

The aetiology is as follows:

- Primary hyperaldosteronism—autonomous hypersecretion of aldosterone, which is almost

invariably caused by adrenal cortical adenoma (Conn's syndrome).

- Secondary hyperaldosteronism—hypersecretion of aldosterone secondary to an increased production of angiotensin II following activation of the renin–angiotensin system. May be precipitated by congestive cardiac failure, cirrhosis, pregnancy, nephrotic syndrome or decreased renal perfusion. This is more common than the primary form of the disorder.

The effects of hyperaldosteronism are shown in Fig. 10.17.

Clinical features are:

- Hypertension—often the only presenting feature. Commonly occurs in the younger age group.
- Hypokalaemia—usually accompanies hypertension and may give rise to polyuria, nocturia, polydipsia, paraesthesia, cardiac arrhythmias, muscle weakness or paralysis.

Secondary hyperaldosteronism also has additional features of underlying disease.

Biochemical diagnosis:

- $\uparrow \text{Na}^+$, $\downarrow \text{K}^+$.
- \uparrow Aldosterone.
- Plasma renin— \downarrow in Conn's syndrome but \uparrow in secondary hyperaldosteronism.

Radiological diagnosis is by visualisation of adrenal cortical adenoma by CT scan or MRI.

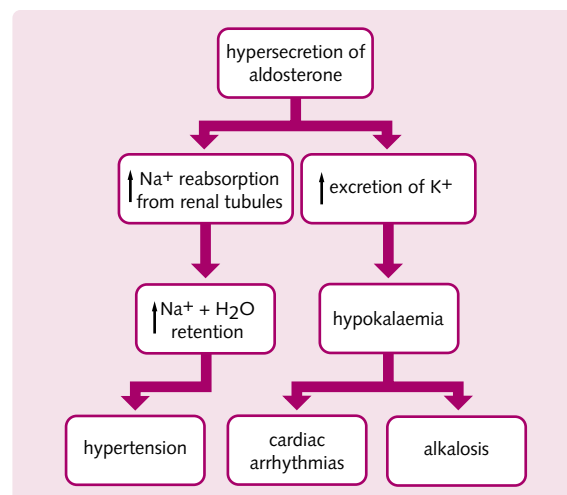


Fig. 10.17 Effects of hyperaldosteronism.

Pathology of the endocrine system

Management:

- Primary hyperaldosteronism—medical aldosterone antagonism (e.g. spironolactone) or surgical removal of the affected adrenal.
- Secondary hyperaldosteronism—treatment of the underlying cause.

Congenital adrenal hyperplasia

This rare, autosomal recessive disorder is usually caused by a deficiency of the enzyme 21-hydroxylase, required for the synthesis of both cortisol and aldosterone. 21-hydroxylase acts on 17OH-progesterone, and consequently raised levels of 17OH-progesterone are measured in the blood of affected individuals; this is routinely tested in the first week of life. Failure of cortisol production produces an increase in ACTH secretion by the pituitary and hyperplasia of the adrenal cortex.

Production of androgens by the adrenal cortex does not require 21-hydroxylase. Consequently, adrenal hyperplasia causes excessive secretion of androgens resulting in masculinisation of females and precocious puberty in males. Also, aldosterone deficiency is serious, causing a life-threatening salt loss ('salt wasting syndrome') unless replacement therapy is given.

Hypofunction of the adrenal cortex

Addison's disease

This rare condition of chronic adrenal insufficiency is due to a lack of glucocorticoids and mineralocorticoids. Its estimated prevalence in the developed world is 0.8 cases per 100 000 population.

The clinical features outlined in Fig. 10.18 are a result of glucocorticoid and mineralocorticoid

insufficiency, loss of adrenal androgen production and increased ACTH secretion.

Aetiology—autoimmune destruction of the cortex of both adrenals is the most common cause of Addison's disease. It is often associated with autoimmune thyroid disease, autoimmune gastritis and other endocrine organ autoimmune diseases. Addison's disease is also a well-recognised complication of patients with acquired immune deficiency syndrome (AIDS), bilateral adrenal tuberculosis (caseous necrosis) and, more rarely, metastatic cancers, haemochromatosis and amyloidosis.

Biochemical features:

- Measurement of plasma ACTH and cortisol— \uparrow ACTH, \downarrow cortisol.
- ACTH stimulation test—ACTH is administered and plasma cortisol levels are monitored. Failure of cortisol levels to rise indicates Addison's disease.
- Plasma electrolytes— \downarrow Na⁺, normal or \uparrow K⁺, \uparrow urea.
- Blood glucose—usually low.
- \uparrow Plasma renin activity and normal or \downarrow aldosterone.

Management is by glucocorticoid replacement therapy, and usually mineralocorticoid therapy.

Primary acute adrenocortical insufficiency (adrenal crisis)

This may occur as a result of:

- Iatrogenic—abrupt cessation of prolonged high-dose therapeutic corticosteroids (prolonged corticosteroid therapy produces lowered endogenous steroid production, leading to atrophy of the adrenal cortex).

Fig. 10.18 Clinical features of Addison's disease.

Fig. 10.18 Clinical features of Addison's disease

Hormonal abnormality	Clinical features
Glucocorticoid insufficiency	Vomiting and loss of appetite Weight loss Lethargy and weakness Postural hypotension Hypoglycaemia
Mineralocorticoid insufficiency	\downarrow serum Na ⁺ , \uparrow serum K ⁺ Chronic dehydration Hypotension
Increased ACTH secretion	Brownish pigmentation of skin and buccal mucosa
Loss of adrenal androgen	Decreased body hair, especially in females

Note: ACTH, adrenocorticotrophic hormone

- Bilateral massive adrenal haemorrhage—caused by Gram-negative (usually meningococcal) septicaemia (Waterhouse–Friderichsen syndrome) producing haemorrhage and disseminated intravascular coagulation. Adrenal haemorrhage is also seen in neonates following traumatic birth.
- Complication of chronic adrenal failure—Addisonian crisis is precipitated by sudden stress requiring increased output from chronically failing adrenal glands.

Clinical features of an adrenal crisis are:

- Profound hypotension and cardiovascular collapse (shock).
- Vomiting.
- Diarrhoea.
- Abdominal pain.
- Pyrexia.

An adrenal crisis is a medical emergency and requires intravenous hydrocortisone and fluid replacement. The precipitating cause should be sought and if possible treated.

Secondary adrenocortical insufficiency

This adrenocortical insufficiency is caused by adrenal atrophy secondary to:

- Hypothalamic or pituitary disease (tumours, infection, infarction, surgical destruction), which produces lowered ACTH, hence lowered endogenous glucocorticoids and aldosterone.
- Glucocorticoid therapy, which produces lowered ACTH (suppression), hence lowered endogenous glucocorticoids and aldosterone.

The adrenal medulla

Phaeochromocytoma

This is a rare tumour of the chromaffin cells—the cells that secrete epinephrine (adrenaline) and norepinephrine (noradrenaline) in the adrenal medulla (see page 62).

Tumours of extra-adrenal paraganglia

Neuroblastomas

These rare tumours are derived from neuroblasts. Affected sites are the adrenal medulla, the mediastinum (usually in association with the sympathetic chain) and the coeliac plexus.

Neuroblastomas are almost exclusively tumours of children, occurring very rarely over the age of 5 years. They are highly malignant and usually inoperable.

Ganglioneuroma

A benign tumour derived from sympathetic nerves. Most commonly found in the posterior mediastinum, although 10% of cases arise in the adrenal medulla.

DISORDERS OF THE ENDOCRINE PANCREAS

Diabetes mellitus

Diabetes mellitus (DM) is a multisystem disease of an abnormal metabolic state characterised by hyperglycaemia due to inadequate insulin action/production. It can be classified into primary and secondary.

Primary DM is a disorder of insulin production/action. It accounts for 95% of diabetic cases.

In 5% of cases, diabetes may be secondary to:

- Pancreatic diseases, e.g. chronic pancreatitis.
- Hypersecretion of hormones that antagonise the effects of insulin, e.g. glucocorticoids in Cushing's syndrome, growth hormone in acromegaly, epinephrine (adrenaline) in pheochromocytomas.

Primary DM is by far the most important cause of diabetes and it is further classified into:

- Type I, also known as insulin-dependent DM (IDDM) or juvenile-onset diabetes.
- Type II, also known as non-insulin-dependent DM (NIDDM) or mature-onset diabetes.

The basic features of these two types of diabetes are described in Fig. 10.19.

Type I diabetes mellitus

Aetiology and pathogenesis—type I diabetes mellitus is an organ-specific, autoimmune-induced disorder characterised by antibody-mediated destruction of the β -cell population of the islet of Langerhans.

Two main factors are thought to predispose to autoimmunity:

1. Genetic predisposition—90–95% of patients with type I diabetes are HLA-DR3 or HLA-DR4 positive, a feature that is also seen in other organ-specific autoimmune diseases. However, identical twins show a 40% concordance in the

Pathology of the endocrine system

Fig. 10.19 Table comparing type I and type II diabetes mellitus (DM).

Fig. 10.19 Table comparing type I and type II diabetes mellitus (DM)

Type I	Type II
Childhood/adolescent onset	Middle-aged/elderly onset
1/3 of primary diabetes	2/3 of primary diabetes
Females = males	Females = males
Acute/subacute onset	Gradual onset
Thin	Obese
Ketoacidosis common	Ketoacidosis rare
Plasma insulin absent or low	Plasma insulin normal or raised
Insulin sensitive	Insulin insensitive (end-organ resistance)
Autoimmune mechanism (islet cell antibodies present)	Non-autoimmune mechanism (no islet cell antibodies)
Genetic predisposition associated with HLA-DR genotype	Polygenic inheritance

development of the disease, indicating the additional importance of environmental factors.

2. Viral infection—viral infection may trigger the autoimmune reaction; viruses implicated include mumps, measles and Coxsackie B.

One postulated mechanism is that viruses induce mild structural damage to the islet cells, thereby releasing previously shielded β -cell antigens and leading to the recruitment and activation of lymphocytes in the pancreatic tissue.

Histologically, the pancreas shows lymphocytic infiltration and destruction of insulin-secreting cells of islets of Langerhans (β -cells). This results in insulin deficiency with hyperglycaemia and other secondary metabolic complications.

Type II diabetes mellitus

Aetiology and pathogenesis—the precise aetiopathogenesis of type II diabetes is unclear but the following factors are thought to be involved:

- Genetic factors—familial tendency with up to 90% concordance rate amongst identical twins. However, there are no HLA associations and inheritance is considered to be polygenic.
- Insulin resistance—tissues are unable to respond to insulin because of an impairment in the function of insulin receptors on the surface of

target cells. This is associated with obesity, sedentary lifestyle and poor diet; it is increasingly being seen in younger (even adolescent) individuals.

- Relative insulin deficiency—reduced secretion compared with the amounts required, possibly related to islet cell ageing.

Diagnosis of diabetes mellitus

Irrespective of aetiology, the diagnosis of DM depends on the finding of hyperglycaemia. However, the distribution curve of blood glucose concentration for whole populations is unimodal, with no clear division between normal and abnormal values.

Diagnostic criteria (Fig. 10.20) are, therefore, arbitrary and, in general, diabetes mellitus is indicated by either:

- Fasting venous plasma glucose level of > 7.0 mmol/L.
- Random venous plasma glucose level of > 11.1 mmol/L.

A distinction is made between diabetes mellitus and impaired glucose tolerance in cases where fasting or random blood sugar level is borderline; in this case, the response to an oral load of glucose can be assessed via a glucose tolerance test.

Fig. 10.20 Diagnostic criteria for diabetes mellitus using an oral glucose tolerance test

Diagnosis	Venous plasma blood glucose	
	Fasting sample	2 hours after 75g glucose load
Normal	<5.6 mmol/L	<7.8 mmol/L
Impaired glucose tolerance	5.6–6.9 mmol/L	7.8–11.0 mmol/L
Diabetes mellitus	≥7.0 mmol/L	≥11.1 mmol/L

Fig. 10.20 Diagnostic criteria for diabetes mellitus using an oral glucose tolerance test.

Complications of diabetes mellitus

Acute complications

Individuals with diabetes are particularly prone to several types of coma. These result from (in decreasing order of frequency):

- Hypoglycaemia—complication of overtreatment with insulin.
- Diabetic ketoacidosis (DKA)—common in type I diabetes due to ↑ breakdown of triglycerides → ↑ production of ketone bodies → ketoacidosis → impaired consciousness.
- Hyperosmolar non-ketotic (HONK) state—↑ plasma glucose concentration → ↑ plasma osmolarity → cerebral dehydration → coma. More common in type II diabetes.
- Lactic acidosis—increased concentrations of lactic acid (produced as an end product of glycolysis instead of pyruvate) may cause coma.

The complications of DM are important; 80% of adults with diabetes die from cardiovascular disease and patients frequently develop serious renal and retinal disease.



Chronic complications

In recent years, with the advent of insulin therapy and various oral hypoglycaemic agents, morbidity and mortality associated with DM are more commonly

the result of the chronic rather than the acute complications of the disorder (Fig. 10.21).

The complications of diabetes are macrovascular (affecting large and medium-sized muscular arteries) and microvascular (small vessel microangiopathy).

Macrovascular changes involve accelerated atherosclerosis. In diabetic microangiopathy, small arterioles and capillaries show a characteristic pattern of wall thickening, which is due to a marked expansion of the basement membrane (termed hyaline arteriolosclerosis).

Therefore, the most important chronic complications of diabetes are:

- Macrovascular accelerated atherosclerosis increasing stroke and myocardial infarction risk.
- Renal disease—diabetic nephropathy (mainly microvascular).
- Eye disease—diabetic retinopathy (microvascular).
- Peripheral nerve damage—diabetic neuropathy (microvascular).
- Predisposition to infections.

Macrovascular disease

Compared with non-affected people of the same age and sex, individuals with diabetes suffer from an increased severity of atherosclerosis, probably due to the increased plasma levels of cholesterol and triglycerides.

The main clinical sequelae of this are seen in:

- Heart → ischaemic heart disease.
- Brain → cerebral ischaemia.
- Legs and feet → gangrene—ischæmia of toes and areas on the heel is a characteristic feature of diabetic gangrene.
- Kidney → chronic nephron ischaemia, an important component of the multiple renal lesions in diabetes.

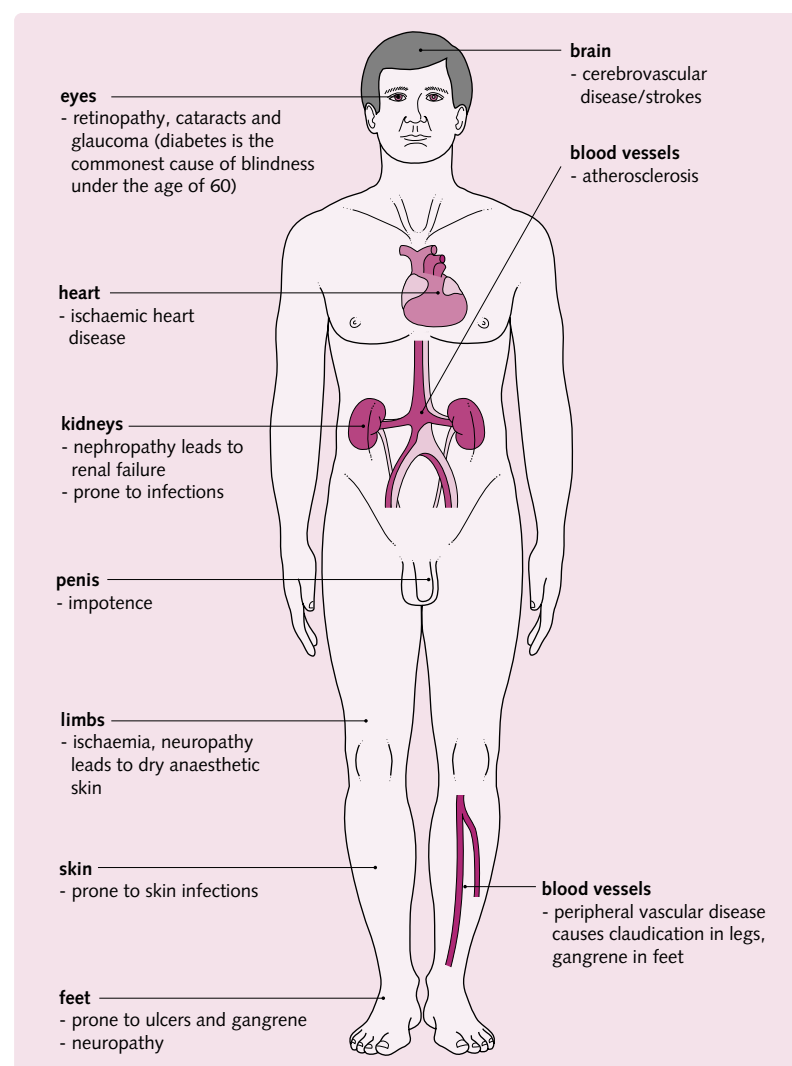
Diabetic nephropathy

Diabetes is now one of the most common causes of end-stage renal failure. Associated renal disease can be divided into three forms:

- Complications of diabetic vascular disease—macrovascular atherosclerosis affecting aorta and renal arteries → ischaemia; microvascular glomerular capillary basement membrane thickening (hyaline arteriolosclerosis) → ischaemic glomerular damage. Microalbuminuria is a reliable marker of the progression of diabetic nephropathy.

Pathology of the endocrine system

Fig. 10.21 Chronic complications of diabetes mellitus.



- Diabetic glomerulosclerosis (diffuse and nodular types)— \uparrow leakage of plasma proteins through capillary wall into glomerular filtrate \rightarrow proteinuria and progressive glomerular hyalinisation with eventual chronic renal failure.
 - Increased susceptibility to infections \rightarrow papillary necrosis. Acute pyelonephritis is a common complication of diabetes mellitus and occurs as a result of the relative immunosuppression of diabetes together with reduced neutrophil function.
- Eye disease**
- Diabetes is the most common cause of acquired blindness in the Western world. It can affect the eyes in five main ways:
1. Background retinopathy—small vessel abnormalities in the retina leading to hard exudates, haemorrhages and microaneurysms. Does not usually affect acuity.
 2. Proliferative retinopathy—extensive proliferation of new capillaries in the retina. Sudden deterioration in vision may result from vitreous haemorrhage as a consequence of proliferating new vessels or from the development of retinal detachment.
 3. Maculopathy—caused by oedema, hard exudates or retinal ischaemia and results in a marked reduction of acuity.
 4. Cataract formation—greatly increased incidence in individuals with diabetes.

5. Glaucoma—increased incidence in those with diabetes due to neovascularisation of the iris (rubeosis iridis).

Predisposition to infections

Patients with diabetes have an increased tendency to develop infections, usually of a bacterial or fungal nature. The main target organs are:

- Skin—folliculitis, erysipelas, cellulitis and superficial fungal infections.
- Oral and genital mucosae—especially with *Candida*.
- Urinary tract—increased predisposition to acute pyelonephritis, often associated with recurrent lower urinary tract infections.

Persistent glycosuria in individuals with poorly controlled diabetes predisposes to urinary and genital infection.

Diabetic neuropathy

Clinically, most cases of diabetic neuropathy affect the peripheral nervous system, although central nervous system pathology does occur. The main effects are:

- Microvascular thickening of basement membrane and microthrombi formation in small vessels supplying peripheral nerves.
- Axonal degeneration with patchy, segmental demyelination.
- Thickening of Schwann cell basal lamina.

The presentation may be of polyneuropathy (classically 'glove and stocking' sensory impairment), mononeuropathy (e.g. carpal tunnel syndrome) or autonomic neuropathy (symptoms include postural hypotension, nausea, vomiting, impotence and gustatory sweating).

Blood glucose control in diabetes lowers the incidence and progression of vascular complications. This can be achieved by:

- Diet alone—in type II patients.
- Diet and oral hypoglycaemic drugs (e.g. sulphonylureas, biguanides, thiazolidinediones)—in type II patients who fail on diet alone.
- Diet and insulin—all type I patients and some type II.

Pancreatic transplantation is curative in type I diabetes but is limited by organ availability. Islet cell transplants are a potential future therapy.

Islet cell tumours

These tumours are rare compared with those of the exocrine pancreas. They occur most commonly in individuals aged 30–50 years.

Insulinomas

The most common tumour of the islet cells. Insulinomas are derived from pancreatic β -cells:

- Produce hypoglycaemia through hypersecretion of insulin.
- May produce attacks of confusion, stupor and loss of consciousness.
- Majority are solitary, non-metastasising lesions (10% are multiple and 10% are malignant).

Zollinger–Ellison syndrome

This syndrome of gastric hypersecretion, multiple peptic ulcers and diarrhoea is caused by the gastrin-secreting tumour (gastrinoma) of the pancreatic G cells. Tumours are multiple in 50% of cases and are often malignant, with 10–20% occurring in other sites, e.g. the duodenum.

It may also be part of the MEN I syndrome, with adenomas also present in other endocrine glands (see below).

Other islet cell tumours

For a summary of islet cell tumours see Fig. 10.22.

VIPomas

These produce vasoactive intestinal polypeptide (VIP), resulting in a syndrome of watery diarrhoea, hypokalaemia and achlorhydria (WDHA).

Glucagonomas

These glucagon-secreting tumours are derived from pancreatic α -cells and cause secondary diabetes mellitus (usually mild), necrolytic migratory erythema (skin rash) and uraemia.

Somatostatinomas

These somatostatin-producing tumours derived from pancreatic δ -cells are associated with diabetes mellitus, cholelithiasis and steatorrhoea.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

These are syndromes in which patients develop tumours in a number of different endocrine organs.

Pathology of the endocrine system

Fig. 10.22 Summary of islet cell tumours.

Fig. 10.22 Summary of islet cell tumours		
Islet cell tumour	Occurrence	Clinical features
Insulinoma	70–75%	Hypoglycaemia
Gastrinoma	20–25%	Zollinger–Ellison syndrome: gastric hypersecretion, multiple peptic ulcers and diarrhoea
VIPoma	Rare	Water diarrhoea, hypokalaemia and achlorhydria
Glucagonoma	Rare	Secondary diabetes mellitus, necrolytic migratory erythema and uraemia
Somatostatinoma	Rare	Diabetes mellitus, cholelithiasis and steatorrhoea

Patients are younger than those who develop single sporadic tumours and usually have a strong family history of multiple endocrine tumours with autosomal dominant inheritance.

There are three main types of MEN syndrome:

1. MEN I (Werner's) syndrome.
2. MEN IIa (Sipple's) syndrome.
3. MEN IIb (sometimes called MEN III) syndrome.

MEN I (Werner's) syndrome

Patients usually show a combination of hyperparathyroidism (chief cell hyperplasia and adenomas), pituitary adenomas (usually prolactinomas) and pancreatic tumours (gastrin and insulin producing). Rarely, there may also be thyroid tumours and adrenal cortical adenomas. MEN I syndrome is caused by a germ-line mutation in the MEN-1 tumour suppressor gene.

MEN IIa (Sipple's) syndrome

Patients have a combination of pheochromocytoma (50% bilateral) and medullary carcinoma of the

thyroid (often bilateral and multinodular). Rarely, there may also be hyperparathyroidism due to parathyroid hyperplasia. MEN IIa and IIb syndromes have been linked to mutations in the *RET* oncogene, with near 100% disease penetrance

MEN IIb (MEN III) syndrome

Patients have all of the features of MEN IIa with additional features of:

- Neuromas and ganglioneuromas in the dermis and submucosal regions throughout the body.
- Marfanoid body habitus with poor muscle development.
- Skeletal abnormalities, e.g. kyphosis, pes cavus and high arch palate.

The facial appearance is characteristic with thick, bumpy lips, broad-based nose, everted eyelids and grossly abnormal dental enamel.

Genetic screening of at-risk family members in MEN II families now allows prophylactic thyroidectomy in those with *RET* mutations to avoid the near certainty of medullary carcinoma.