The thyroid is a small gland that weighs less than 30g and is located at the front of the neck, just below the larynx. It has two lobes, which lie along the trachea and are joined by the isthmus, a band of thyroid tissue. Thyroid cells are the only cells in the body that absorb iodine. The function of the thyroid gland is to convert dietary iodine into thyroid hormones. When released into the bloodstream, thyroid hormones regulate the metabolism of carbohydrates, fats and proteins (this is mediated through other hormones such as insulin).

Normally, about 80% of the thyroid hormone produced is thyroxine (T4), a pre-hormone. T4 is activated to triiodothyronine (T3) in the liver, predominantly, but also in peripheral tissues. T3 is about four times more potent than T4 and is the active hormone used by the body. About 10% of the hormone produced by the thyroid is T3. Small amounts of minor hormones, such as 3,3’-diiodothyronine (T2) and reverse-T3, are also released by the thyroid gland.

The thyroid gland is regulated by the anterior pituitary, which, in turn, is regulated by the hypothalamus. Negative feedback ensures that, when circulating T3 and T4 levels drop too low, the hypothalamus increases secretion of thyrotrophin releasing hormone (TRH). This acts on the anterior pituitary, which, in turn, releases thyroid stimulating hormone (TSH). TSH stimulates the thyroid gland to release T3 and T4. This feedback loop ensures appropriate production of thyroid hormones (see Figure 1, p324).

Assessing thyroid function
Thyroid function tests — blood tests measuring serum TSH, free T4 (FT4) and free T3 (FT3) levels — are used to diagnose thyroid disorders and to assess response to therapy. In certain patient groups periodic thyroid monitoring should be undertaken (see Box 1, p324).

Most circulating T3 and T4 is bound to thyroid binding globulin (TBG). Free (unbound) thyroid hormones are the biologically active fraction of the total circulating thyroid hormone pool. Therefore, measuring the amounts of free hormones provides a more accurate means of diagnosing thyroid dysfunction than measuring total hormone concentrations. In the first instance TSH and FT4 are measured since results of these tests should identify most cases of thyroid dysfunction. Additional tests, such as FT3, may be required in certain situations (e.g., hyperthyroidism caused by amiodarone treatment, or where hyperthyroidism is suspected clinically and TSH is suppressed but FT4 is not.

### SUMMARY
The thyroid produces thyroxine (T4) and tri-iodothyronine (T3), both of which are essential for normal metabolism. Hyperthyroidism — a condition in which the body overproduces thyroid hormones — is characterised by palpitations, agitation, tremor, anorexia and weight loss. Patients with hypothyroidism do not produce sufficient amounts of thyroid hormone. This results in symptoms such as depression, fatigue, constipation, weight gain and hypothermia.

Thyroid disorders are diagnosed, primarily, by measuring serum levels of thyroid stimulating hormone (TSH) and free thyroxine (FT4). However, other investigations, such as thyroid scans, may also be required.
elevated). Measurement of FT₃ is not required for diagnosing hypothyroidism.

A TSH value within the reference range (0.4–4.5mU/L) excludes most cases of primary overt thyroid dysfunction. The normal reference range for FT₄ is 9–23pmol/L and for FT₃ is 3.5–7.8pmol/L.

Other tests that may be required include:
- TBG — this can be measured in cases where the cause of hyper- or hypothyroidism is unclear
- TRH test — in healthy people, an injection of TRH will stimulate the production of TSH (the normal baseline level of 0.4–4.5mU/L will increase to 10–20mU/L); hyperthyroid patients will not show an increase in TSH, hypothyroid patients will show an increase of greater than 40mU/L
- Thyroid antibodies — these are present in the serum of patients with immune-mediated thyroid disorders, such as Hashimoto’s disease and Graves’ disease
- Thyroid scans — can be used to assess iodine uptake by the thyroid, detect benign or malignant nodules, measure the size of goitres (see Box 2, p326), monitor patients after thyroid surgery or locate thyroid tissue outside the neck; radioactive iodine is administered orally and images are obtained subsequently using a gamma camera or computerised rectilinear thyroid scanner

Certain medicines can interfere with the synthesis, secretion, binding and metabolism of TSH and thyroid hormones. Some drugs can alter thyroid function and others can cause abnormal thyroid function test results in otherwise euthyroid people. In general, medicines are more likely to affect levels of thyroid hormones than they are to affect levels of TSH (although corticosteroids and high-dose dopamine inhibit TSH release).² The effects of specific drugs on thyroid hormones are summarised in Box 3 (p326).

**Hypothyroidism**

Hypothyroidism refers to any state in which thyroid hormone production is inadequate. In the UK the annual incidence of hypothyroidism is approximately 1–2%, with the incidence for women (particularly older women) around six times greater than that for men.³ Typically the onset of hypothyroidism is insidious. Patients will often experience several non-specific symptoms, which can vary depending on the severity and duration of the deficiency. This often results in a delayed diagnosis. The most common signs and symptoms are shown in Box 4 (p329). Hypothyroidism can often be reversed by the administration of levothyroxine (see accompanying article, p330).

Hypothyroidism can be categorised as primary or secondary, depending on the cause.

**Primary hypothyroidism** Primary hypothyroidism is caused by failure of the thyroid gland to produce thyroid hormones. Usually, the condition has an autoimmune origin (eg, Hashimoto’s disease), but it can also be caused by dietary deficiency of iodine, antithyroid medicines, thyroidectomy or adverse drug reactions (see Box 3, p326).⁴ Up to a third of cases arise from removal or destruction of the thyroid gland (see accompanying article, p330).

A low FT₄ and high TSH indicates primary hypothyroidism, since the pituitary is compensating by overproducing TSH in an attempt to increase thyroid hormone levels.

**Secondary hypothyroidism** Secondary hypothyroidism occurs due to pituitary or hypothalamic dysfunction, which results in inadequate release of TRH and TSH.⁵ This reduces the stimulation of the thyroid gland to produce thyroid hormones.

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**Box 1: Screening for thyroid dysfunction**

Widespread screening for thyroid dysfunction is not thought to be cost-effective; however, it is valuable for certain patient groups. Periodic thyroid function tests are recommended for patients who:
- Take amiodarone or lithium
- Are diabetic
- Have atrial fibrillation
- Have hyperlipidaemia
- Have Down’s syndrome, Turner’s syndrome or Addison’s disease

Pregnant women with type 1 diabetes should have their thyroid function tested in the first trimester and after delivery. Women with a history of postpartum thyroiditis should have their thyroid function monitored regularly.
Although not every case of secondary hypothyroidism has a clear cause, it is usually due to damage to the pituitary gland caused by radiation, surgery or the presence of a tumour. FT4 and TSH levels are low in secondary hypothyroidism.

**Hyperthyroidism**

Hyperthyroidism occurs when the thyroid gland produces excessive amounts of thyroid hormones. The annual incidence is 0.8 per 1,000 for females and less than 0.1 per 1,000 for males. The most common cause of hyperthyroidism is Graves’ disease (also termed “diffuse toxic goitre”). Less common causes include subacute thyroiditis, excessive doses of levothyroxine or liothyronine, high iodine intake, postpartum thyroiditis and malignancy. Hyperthyroidism can also be induced by amiodarone treatment.

Common signs and symptoms of hyperthyroidism are listed in Box 5. In overt hyperthyroidism, TSH is low and FT4 and/or FT3 are raised. In sub-clinical hyperthyroidism, TSH is persistently low, with normal FT3 and FT4 concentrations. Thyroid scans can help diagnose the underlying cause.

**Graves’ disease**

Graves’ disease is the most common form of hyperthyroidism. It is an autoimmune condition, in which TSH receptor-stimulating antibodies (TRAbs) cause local tissue inflammation and fluid accumulation, resulting in excessive levels of thyroid hormones. The same immune reaction can occur in the skin and orbital tissues, resulting in exophthalmos (protrusion of the eyes) and, sometimes, ocular dysfunction. Exophthalmos occurs in 25–50% of patients with Graves’ disease and affects an estimated 400,000 patients in the UK. Most signs and symptoms of Graves’ disease result from the direct and indirect effects of hyperthyroidism, involving most body systems (Box 5, p329). The severity is related to the duration of the disease and the magnitude of the thyroid hormone excess.

**Thyroiditis**

The term “thyroiditis” describes inflammation of the thyroid gland. This inflammation can damage thyroid cells, leaving them incapable of meeting the body’s demand for thyroid hormones. Initially symptoms can be subclinical and go unnoticed. However, excessive amounts of thyroid hormone can pass into the bloodstream from the inflamed thyroid gland causing temporary hyperthyroidism, followed by hypothyroidism. The most common cause of thyroiditis is Hashimoto’s disease (also known as chronic lymphocytic thyroiditis) — an autoimmune condition in which lymphocytes produce antibodies that damage thyroid cells. It is usually diagnosed in patients who are over 40 years of age.

Other types of thyroiditis include postpartum thyroiditis and de Quervain’s disease (a subacute or “silent” thyroiditis that shows microscopic changes). Rarely, thyroiditis can develop into a bacterial infection termed acute suppurative thyroiditis. Thyroiditis can be self-limiting, resolving in two to six months with no adverse effect on thyroid function, but more commonly it is a chronic condition.

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**Box 2: Goitre**

A highly recognisable symptom of thyroid dysfunction is goitre, which is characterised by swelling of the thyroid or formation of one or more nodules. Goitre can be associated with hypo- and hyperthyroidism, but in some cases the patient will be euthyroid. Worldwide, iodine deficiency is the most common cause of goitre.

Goitre can vary widely in size and type, yet most are painless. However, a large goitre can cause difficulties with breathing or swallowing if it is pressing on a person’s trachea or oesophagus. Treatment depends on the cause, size and resulting symptoms.

**Box 3: Drug effects on thyroid hormones**

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in TSH secretion</td>
<td>Dopamine (high-dose); corticosteroids; octreotide</td>
</tr>
<tr>
<td>Decreased secretion or synthesis of thyroid hormones (T3, T4)</td>
<td>Lithium; iodine; amiodarone; carbimazole; propylthiouracil</td>
</tr>
<tr>
<td>Increased secretion or synthesis of thyroid hormones (T3, T4)</td>
<td>Iodine; amiodarone; lithium (rare)</td>
</tr>
<tr>
<td>Displacement of thyroid hormone from plasma proteins</td>
<td>Carbimazole; propylthiouracil; lithium</td>
</tr>
<tr>
<td>Impaired conversion of T4 to T3</td>
<td>Beta-blockers; corticosteroids; amiodarone; propylthiouracil; radiocontrast dyes</td>
</tr>
<tr>
<td>Increased clearance of T4</td>
<td>Phenytoin; carbamazepine</td>
</tr>
<tr>
<td>Increased thyroid binding globulin, total T3 and total T4</td>
<td>Dextrogestren; tamoxifen; methadone; raloxifene</td>
</tr>
<tr>
<td>Decreased thyroid binding globulin, total T3 and total T4</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Modified action of thyroid hormones</td>
<td>Amiodarone</td>
</tr>
</tbody>
</table>

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Thyroid emergencies

**Myxoedema crisis** Myxoedema crisis is a state of decompensated hypothyroidism characterised by:

- Altered mental state — patients can be entirely unconscious or may be roused by stimuli; usually lethargy and drowsiness have been present for many months
- Defective thermoregulation — hypothermia (as low as 23°C) or the absence of fever despite infection
- Presence of a precipitating event — such as infection, drugs (e.g., diuretics, sedatives, analgesics), trauma, stroke, heart failure, gastrointestinal bleeding, cold exposure

It is a rare but life-threatening condition that requires immediate treatment. Despite optimum treatment, mortality rates of up to 50% have been reported; mortality is higher if myxoedema crisis progresses to a coma and multi-organ failure. Persistent hypothermia is significantly associated with a fatal outcome within one month of treatment. Generally, myxoedema crisis occurs in elderly women and is rarely seen in patients aged under 60 years.

A diagnosis of myxoedema crisis should be considered for all unconscious patients with hypothermia, especially if chronic renal insufficiency and hypoglycaemia can be excluded as causes. Most patients have reduced responsiveness of the respiratory system to hypoxia and hypercapnia. Bradycardia, hypotension and electrocardiographic changes are also common. Biochemical abnormalities include hyponatraemia and anaemia (normocytic or macrocytic).

Markedly increased TSH and low total T4 and FT4 confirm the diagnosis of myxoedema crisis (although TSH levels can be normal or low for patients with secondary hypothyroidism).

**Thyroid storm** The terms “thyroid storm” or “thyrotoxic crisis” describe an acute, life-threatening, hypermetabolic state that affects multiple systems and results from excessive release of thyroid hormones in people with hyperthyroidism. This is a rare condition and early diagnosis is essential since it has a mortality rate over 90% if left untreated. With early treatment the adult mortality rate drops to less than 20%.

Because no specific diagnostic tests are available, the diagnosis of thyroid storm is largely clinical. The clinical picture reflects severely exaggerated effects of thyroid hormones. Heat intolerance and sweating are commonly associated with simple hyperthyroidism. However, in thyroid storm this manifests as hyperpyrexia — temperature can exceed 41°C. Hypermetabolism also increases oxygen and energy demands.

Cardiac findings range from mild-to-moderate sinus tachycardia in hyperthyroidism to accelerated tachycardia, hypertension, arrhythmias and high-output cardiac failure in thyroid storm. Similarly, irritability and restlessness in hyperthyroidism progress to severe agitation, delirium, seizures and coma in thyroid storm.

Several factors may precipitate the progression of hyperthyroidism to thyroid storm. These include:

- Infection/sepsis
- Radioactive iodine therapy
- Surgery
- Diabetic ketoacidosis
- Direct trauma to the thyroid gland
- Medication (e.g., treatment with amiodarone, cessation of antithyroid drugs)

With regard to biochemical tests, hyperglycaemia, leucocytosis, mild hypercalcaemia and abnormal liver function tests can be present. Impairment of adrenal reserve may also occur.

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**Box 4: Clinical features of hypothyroidism**

<table>
<thead>
<tr>
<th>Clinical features of hypothyroidism include:</th>
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</thead>
<tbody>
<tr>
<td>Facial swelling</td>
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<tr>
<td>Hair loss</td>
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<tr>
<td>Dry, pale skin</td>
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<tr>
<td>Bradycardia</td>
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<tr>
<td>Husky voice</td>
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<tr>
<td>Hyperthermia</td>
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<td>Goitre</td>
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<td>Constipation</td>
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<tr>
<td>Psychosis</td>
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<td>Delayed deep tendon reflexes</td>
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<td>Fatigue</td>
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<td>Weight gain</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Menorrhagia</td>
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<tr>
<td>Hearing impairment</td>
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<tr>
<td>Hyponatraemia</td>
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</tbody>
</table>

**Box 5: Hyperthyroidism signs and symptoms**

Common signs and symptoms of hyperthyroidism include:

- Tremor
- Tachycardia
- Warm, moist skin
- Weight loss and muscle weakness
- Agitation
- Sweating and heat intolerance
- Goitre
- Hunger and thirst
- Exophthalmos (protrusion of the eyeballs in their sockets)
- Atrial fibrillation
- Anorexia
- Diarrhoea

References