

## CHAPTER 8

## 8

## The thyroid gland

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## LEARNING OBJECTIVES

- To appreciate the development of the thyroid gland and its clinical consequences
- To understand the regulation, biosynthesis and metabolism of thyroid hormones
- To understand the function of thyroid hormones
- To understand the clinical consequences of underproduction and overproduction of thyroid hormone

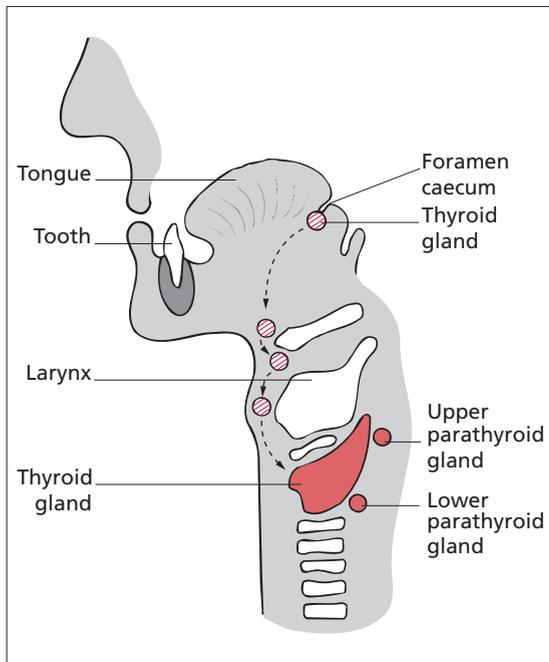
*This chapter integrates the basic biology of the thyroid gland with the clinical conditions that affect it*

The thyroid gland sits in the neck and is responsible for the concentration of iodine and the biosynthesis of thyroid hormones from tyrosine. Thyroid hormones play major roles in regulating the body's metabolism and affect many different cell types. Understanding the basic science and associated clinical conditions of the thyroid gland, therefore, is of major importance.

### Embryology

Understanding the development of the thyroid gland and its anatomical associations allow the correct surgical approach to the gland in the treatment of thyroid overactivity or enlargement. In the fourth week of development, the thyroid begins as a mid-line thickening at the back of the tongue. This endodermal out-pouching of the oral cavity stretches

downward and soon forms a solid mass of cells weighing 1 to 2 mg (Fig. 8.1). This thyroid primordium migrates past the front of the larynx and by 7 weeks is bilobed. It remains attached to its origin by the thyroglossal duct. The descent of the thyroid brings it into close proximity with the developing parathyroid glands (Fig. 8.1; see Chapter 9). In adulthood, these small, pea-sized structures are situated on the back of the thyroid as pairs of upper and lower glands and are responsible for calcium homeostasis. The lower parathyroids start out higher in the neck than the upper glands and only achieve their final position by also migrating downwards. The thyroid gland comes into contact with other cells during its migration. From the lower part of the developing pharynx, the future C-cells that secrete calcitonin mix with the descending thyroid and eventually comprise ~10% of the gland (see Chapter 9).



**Figure 8.1** The thyroid gland and its downward migration. The point of origin in the tongue persists as the foramen caecum. Common sites of thyroglossal cysts (⊗) and the final position of the paired parathyroid glands are indicated (Modified from K. L. Moore, *The Developing Human*, W.B. Saunders, Philadelphia).

Towards the end of the second month, the thyroglossal duct and the thyroid gland lose contact. The duct atrophies in all but ~15% of the population, in whom its lowest portion differentiates into the pyramidal lobe as an upward, finger-like extension of thyroid tissue. Laterally, two distinct lobes form on either side of the trachea. These are connected in the midline by the narrow isthmus in front of the trachea, just below the larynx—a convenient landmark for locating the ‘bowtie-shaped’ thyroid gland during clinical examination (see Box 8.12). The cells are grouped into clusters, which by ~11 weeks have organized themselves into a single layer of epithelial cells surrounding a central lumen. This signals the first ability of the gland to trap iodine (as iodide) and synthesize thyroid hormone, although it only responds to thyroid-stimulating hormone (TSH) from the anterior pituitary towards the end of the second trimester.

### BOX 8.1 Embryological abnormality and clinical consequences

Failure of the gland to develop → congenital hypothyroidism  
*Under or overmigration* of the thyroid → lingual or retrosternal thyroid  
 Failure of thyroglossal duct to atrophy → thyroglossal cyst

On occasion, embryology does not take place normally with several clinical consequences (Box 8.1). Thyroglossal cysts are located in the midline and can be distinguished clinically by upward movement on tongue protrusion. Congenital absence of the thyroid due to mutation in genes, such as *PAX8*, requires immediate detection and treatment with thyroid hormone in order to minimize the severe and largely irreversible neurological damage that could occur in the infant.

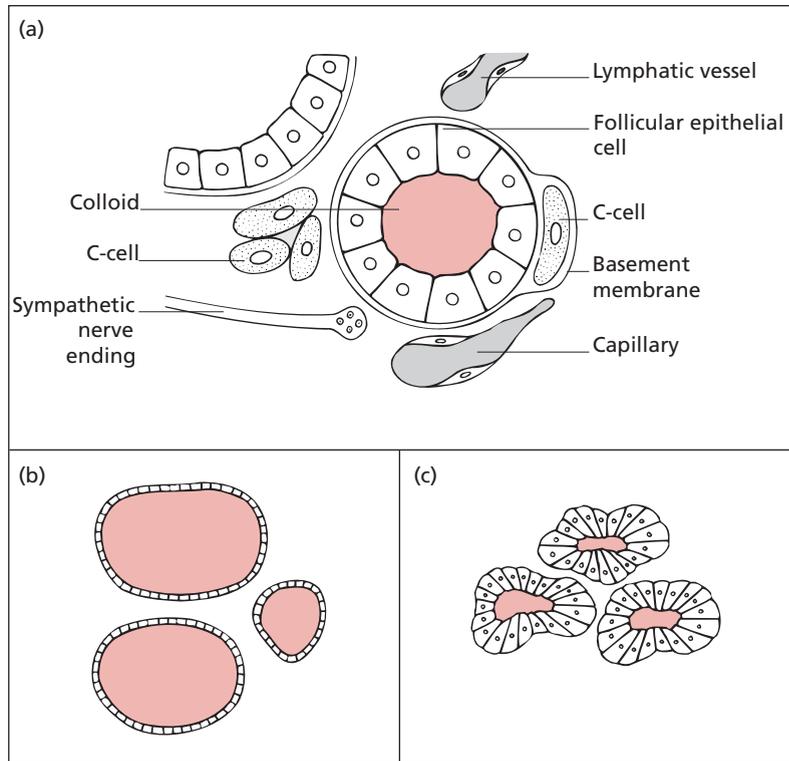
### Anatomy and vasculature

The adult thyroid gland weighs 10 to 20 g. Commonly, the right lobe is larger than the left and the entire gland is bigger in women and in areas of the world with iodine deficiency. It enlarges during puberty, in pregnancy and during lactation.

The outer part of the capsule is not well-defined, but attaches the thyroid to the trachea. The parathyroid glands are situated between this and the inner capsule, from which trabeculae of collagen pervade the gland and carry nerves and a rich vascular supply to the cells (Fig. 8.2). The thyroid receives ~1% of cardiac output from superior and inferior thyroid arteries, which branch off the external carotid and subclavian arteries respectively. Per gram of tissue, this disproportionately large supply is almost twice that of the kidney. Supply is increased further during some conditions of overactivity and may be evidenced by a bruit on auscultation (Box 8.2 and Box 8.12).

Histologically, the functional unit of the thyroid is the follicle (Fig. 8.2). This consists of cuboidal epithelial (‘follicular’) cells arranged as spheres, the central lumen of which contains colloid. Colloid is com-

**Figure 8.2** Histology of the human thyroid gland. (a) Euthyroid follicles are shown, consisting of 'hollow' spheres of cuboidal epithelium, the lumens of which are filled with gelatinous colloid that contains stored thyroid hormones (complexed in thyroglobulin). Surrounding each follicle is a basement membrane enclosing parafollicular C-cells within a stroma containing fenestrated capillaries, lymphatic vessels and sympathetic nerve endings. (b) Underactive follicles with flattened thyroid epithelial cells and increased colloid. (c) Overactive follicles with tall, columnar epithelial cells and reduced colloid.



### BOX 8.2 The adult thyroid gland

- Enlargement = a 'goitre'
- The gland is encapsulated
  - breaching the capsule is a measure of invasion in thyroid cancer
- The thyroid receives a large arterial blood supply
  - may cause a bruit in Graves disease

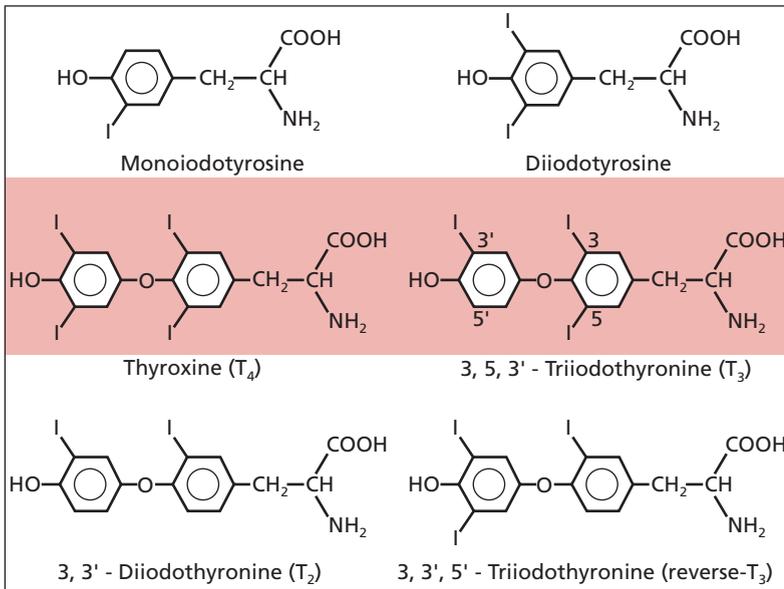
posed almost entirely of the iodinated glycoprotein, thyroglobulin, which turns an intense pink on periodic acid-Schiff (PAS) staining. The normal human follicle varies in diameter from 20 to 900  $\mu\text{m}$ . Many thousands are present in the gland interspersed with blood vessels, an extensive network of lymphatic vessels, connective tissue and the parafollicular calcitonin-secreting C-cells. The blood flow through the fenestrated capillaries is controlled by postganglion-

ic sympathetic nerve fibres from the middle and superior cervical ganglia.

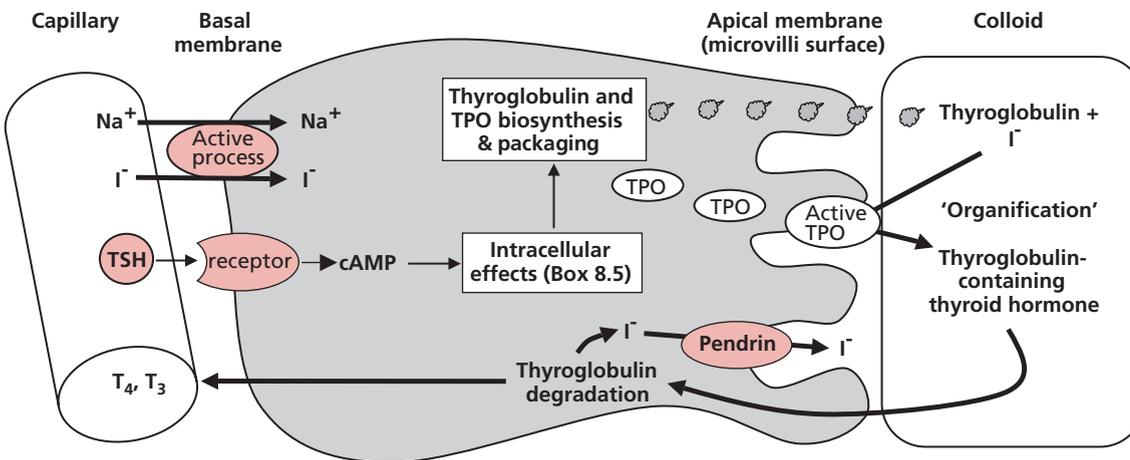
When the gland is quiescent, as occurs in an iodine-deficient hypothyroid state, the follicles are distended with colloid and the epithelial cells are flattened with little cytoplasm. In an overactive gland, the follicular cells are columnar and contain colloid by light microscopy—a sign of intense activity (Fig. 8.2).

### Thyroid hormone biosynthesis

There are two active thyroid hormones: thyroxine (3,3',5,5'-tetraiodothyronine), frequently abbreviated to  $T_4$ , and triiodothyronine ( $T_3$ )—the subscript 4 and 3 representing the number of iodine atoms attached to each thyronine residue (Fig. 8.3). These thyroid hormones are generated from the sequential iodination and coupling of the amino acid tyrosine. They are inactivated by deiodination and modification to 'reverse  $T_3$ ' ( $rT_3$ ; 3,3',5'-triiodothyronine) and



**Figure 8.3** The structures of active and inactive thyroid hormones and their precursors. Monoiodotyrosines and diiodotyrosines are precursors. Thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) are the two thyroid hormones, of which  $T_3$  is the biologically more active. Reverse  $T_3$  and  $T_2$  are inactive metabolites formed by deiodination of  $T_4$  and  $T_3$  respectively. The numbering of critical positions for iodination is shown on the structure of  $T_3$ .



**Figure 8.4** Thyroid hormone biosynthesis within the follicular cell. Active iodide import is linked to a  $\text{Na}^+/\text{K}^+$  ATPase pump. Thyroglobulin is synthesized on the rough endoplasmic reticulum, packaged in the Golgi complex and released from small, Golgi-derived vesicles into the follicular lumen. Its iodination is also known as 'organification'. Cytoplasmic microfilaments and

microtubules organize the return of thyroglobulin as endocytotic vesicles into the cell. The thyroglobulin now contains thyroid hormone, which is released upon degradation. Modified from Williams Textbook of Endocrinology, 10th edition, Saunders, 2003. Chapter 10, page 332.

diiodothyronine ( $T_2$ ). The balance in the formation of these different molecules determines overall thyroid hormone activity. The synthesis of thyroid hormones can be broken down into several key steps described over the next few pages and depicted in Fig. 8.4.

### Uptake of iodide from the blood

The synthesis of thyroid hormone relies on a constant supply of dietary iodine (as iodide). When the element is scarce the thyroid enlarges to form a goitre

(see Box 8.3). Iodide enters the follicular cell by active transport from the circulation through the basal cell membrane. The sodium/iodide ( $\text{Na}^+/\text{I}^-$ ) pump is linked to the activity of an ATP-driven sodium/potassium ( $\text{Na}^+/\text{K}^+$ ) pump. This process concentrates iodide within the thyroid gland ~20 to 100 times that of the remainder of the body. This selectivity allows the organ-specific use of radioiodine both diagnostically and therapeutically (covered in later sections). Several structurally related anions can competitively inhibit the iodide pump. For example,

### BOX 8.3 Iodine deficiency

Some areas of the developing world remain iodine-deficient, which can cause hypothyroidism and particularly large goitres (Plate 8.1, facing p. 246). Thyroglobulin in the normal human thyroid stores ~2 months supply of thyroid hormone. When dietary iodide is limited (<50  $\mu\text{g}$  per day), less is incorporated into thyroglobulin, which consequently releases a higher proportion of the more active  $\text{T}_3$  to  $\text{T}_4$ . However, eventually thyroid hormone biosynthesis can no longer keep up. Diminished negative feedback increases TSH secretion, which induces thyroid enlargement, a compensatory mechanism to increase the capacity for iodide uptake. This may permit sufficient thyroid hormone biosynthesis under normal circumstances; however, during pregnancy, the supply of iodine and thyroid hormones will not be sufficient for a developing fetus. The fetus is at risk from severe neurological damage and may develop a goitre. Postnatally, the syndrome of intellectual impairment, deafness and diplegia (bilateral paralysis) has been termed 'cretinism' and affects many millions of infants worldwide. Decreased iodine intake with a marginal but chronic elevation of TSH may also result in an increased incidence of thyroid cancer, especially if irradiation is involved, as with the Chernobyl accident.

Prophylaxis with iodine supplements has reduced the incidence of cretinism, although tends not to shrink adult goitres very much. Supplementation of common dietary constituents such as salt or bread has been undertaken in many countries but is not always practicable. In extremely isolated communities, depot injections of iodized oils can provide the thyroid with supplies for years.

large doses of perchlorate ( $\text{ClO}_4^-$ ) can be employed clinically as a short-term measure to block iodide uptake by the gland (e.g. in accidental ingestion of radioiodine). The pertechnetate ion incorporating a  $\gamma$ -emitting radioisotope of technetium is also taken up by the iodide pump and allows the thyroid gland to be imaged diagnostically.

### The synthesis of thyroglobulin

Thyroglobulin is synthesized within the follicular cell from many tyrosine residues. It is ~1% iodine by weight and serves as the substrate for the synthesis of  $\text{T}_4$  and  $\text{T}_3$ . Thyroglobulin is a glycoprotein and contains ~10% carbohydrate, some of which includes the sialic acid that is responsible for the intense pink PAS staining of colloid. Thyroglobulin is transcribed, translated, post-translationally modified in the Golgi apparatus and then packaged into vesicles within the follicular cell (Fig. 8.4 and review Chapter 2). These vesicles move to the apical membrane, with which they fuse, and then release their contents into the follicular lumen.

### Iodination of thyroglobulin

Thyroid peroxidase (TPO) catalyses the iodination of thyroglobulin. Like thyroglobulin, the enzyme is synthesized and packaged into vesicles at the Golgi complex. At the apical cell membrane, TPO becomes activated. Active TPO binds the iodide and thyroglobulin at different sites. The enzyme oxidizes iodide, which is then transferred to an exposed tyrosine residue of thyroglobulin. The enzyme is particularly efficient at iodinating fresh thyroglobulin; as the reaction proceeds, the efficiency of adding further iodide decreases. Drugs inhibiting TPO and iodination are used to treat hyperthyroidism (Box 8.4).

### BOX 8.4 Antithyroid drugs—effective at suppressing the synthesis and secretion of thyroid hormones

- Carbimazole
- Methimazole (active metabolite of carbimazole; used in USA)
- Propylthiouracil (PTU)

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Some naturally occurring substances, such as chemicals from well water, the milk of cows fed on certain green fodder and the brassicae vegetables (cabbages, sprouts), can inhibit the iodination of thyroglobulin and hence the synthesis of thyroid hormones. Negative feedback is diminished at the anterior pituitary and TSH secretion increases (Fig. 8.5). Prolonged stimulation results in thyroid hyperplasia and a goitre, hence the chemicals are known as 'goitrogens'.

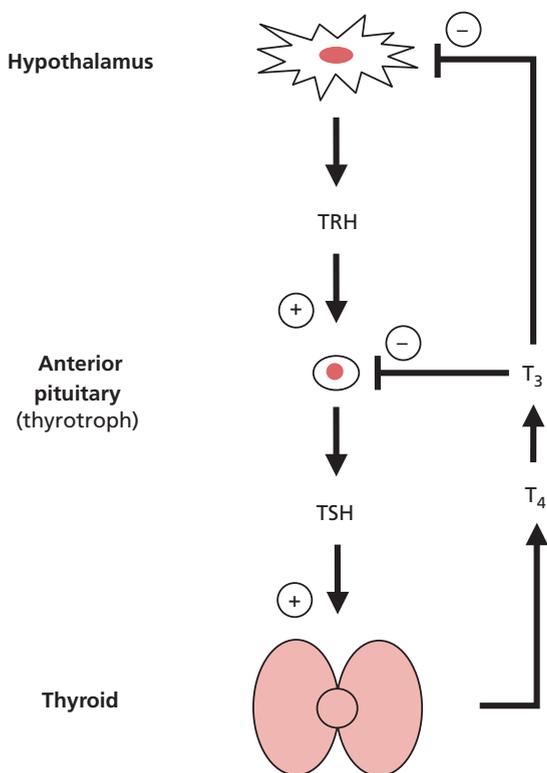
### The production of thyroid hormones

The process of iodination is also important for initiating the formation of thyroid hormones (Figs 8.3 and 8.4). Within the thyroglobulin structure, diiodotyrosine couples to either a monoiodotyrosine (to gener-

ate  $T_3$ ) or to another diiodotyrosine (to generate  $T_4$ ). This coupling occurs during the TPO-mediated iodination reaction so no additional enzyme is necessary. The iodinated thyroglobulin protein now contains thyroid hormone stored as colloid in the lumen of the thyroid follicle.

### The secretion of thyroid hormones

The thyroglobulin-containing thyroid hormone returns into the follicular cell (Fig. 8.4). Microvilli on the apical cell membrane envelop the thyroglobulin ('endocytosis') to form colloid droplets within the cell. The cytoskeleton steers these vesicles away from the apical membrane and facilitates fusion with lysosomes. The enzymes from the lysosomes break down the thyroglobulin, releasing thyroid hormones and degradation products. The latter, including iodide, are recycled within the gland. The transporter, *Pendrin*, moves iodide back into the follicular lumen. Mutations in the *Pendrin* gene cause a congenital form of hypothyroidism (Pendred syndrome). The thyroid hormones move across the basal cell membrane and enter the circulation, ~80% as  $T_4$  and 20% as  $T_3$ .



**Figure 8.5** The hypothalamic–anterior pituitary–thyroid axis. The more active hormone,  $T_3$ , provides the majority of negative feedback.

### Regulation of thyroid hormone biosynthesis

The activity of the thyroid gland is controlled by TSH from the anterior pituitary, which in turn is regulated by thyrotrophin-releasing hormone (TRH) from the hypothalamus (review Chapter 5). Thyroid hormones, predominantly via the more active  $T_3$ , complete the negative feedback loop by suppressing the production of TRH and TSH (Fig. 8.5). TSH binds to its specific G-protein coupled receptor on the surface of the thyroid follicular cell and activates both adenylate cyclase and phospholipase C (review Chapter 3). The former appears to be the dominant effect and the second messenger cAMP mediates most of the actions of TSH (Box 8.5). The net effect increases fresh thyroid hormone stores and, within ~1 h, increases the release of thyroid hormones. The most recently synthesized thyroglobulin is the first to be resorbed as it is nearest to the microvilli. This thyroglobulin has also had less time to be iodinated than the mature, centrally positioned store, such that it releases

**BOX 8.5 Consequences of TSH stimulation on the follicular cell**

- ↑ intracellular cAMP concentration
- ↑ iodination of thyroglobulin
- ↑ microvilli number and length at luminal cell surface
- ↑ in intracellular volume and endocytosis of colloid droplets
- ↑ thyroid hormone release
- ↑ iodide influx into the cell (relatively late effect as activation of the iodide pump requires protein synthesis)
- ↑ cellular metabolism
- ↑ protein synthesis (including thyroglobulin)
- ↑ DNA synthesis (in fact, mitosis and cell division are rather limited in the adult thyroid)

**BOX 8.6 Circulating thyroid hormones**

- Thyroid hormones are almost entirely bound to the following serum proteins (in order of decreasing affinity):
  - thyroxine-binding globulin (TBG)
  - thyroxine-binding prealbumin (TBPA)
  - albumin
- The unbound fraction is tiny, yet critical — *only free thyroid hormone enters cells*:
  - free  $T_4$  ( $fT_4$ ) ~0.015% of total  $T_4$
  - free  $T_3$  ( $fT_3$ ) ~0.33% of total  $T_3$
  - circulating half-life  $T_3$ , ~1–3 days — needs to be given several times a day if used clinically
  - circulating half-life  $T_4$ , ~5–7 days — can be given as single daily dose
  - Both  $fT_4$  and  $fT_3$  are measured by immunoassay (see thyroid function tests later)
- $T_3$  is more potent than  $T_4$  (~2 to 10-fold depending on response monitored)

thyroid hormones with a relatively higher  $T_3$  to  $T_4$  ratio and, consequently, greater activity.

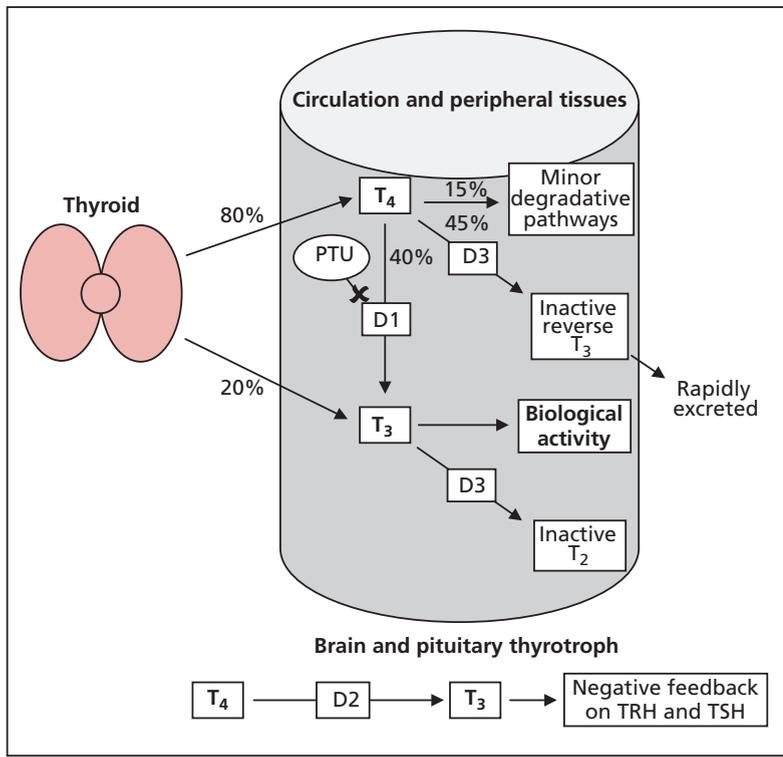
**Circulating thyroid hormones**

Once the serum concentrations of thyroid hormones have settled to constant values ~3 days after birth, little change occurs in normal individuals throughout the remainder of life. Thyroid hormones are strongly bound to serum proteins (Box 8.6). Only the tiny amount of free hormone can enter cells and function.  $T_3$  is bound slightly less strongly than  $T_4$  to each of the three principal serum binding proteins, of which albumin is a relatively nonspecific binder of circulating thyroid hormone. Some drugs, such as salicylates, phenytoin or diclofenac, which structurally resemble the iodothyronine molecule, can compete with thyroid hormone for protein binding. Starvation or liver disease alters the concentration of binding proteins. In either scenario, readjustment of total circulating hormone levels ensures that the free concentrations remain unaltered.

**Metabolism of thyroid hormone: the conversion of  $T_4$  to  $T_3$  and  $rT_3$** 

As already alluded to,  $T_3$  is the more active hormone. However, only 20% of the thyroid's output is  $T_3$ . To

generate more requires the removal of one iodine atom from the outer ring of  $T_4$ , a process called deiodination (Fig. 8.3 and Fig. 8.6). This step is catalysed by selenodeiodinase enzymes, which contain selenium that accepts the iodine from the thyroid hormone. Selenium deficiency in parts of western China or Zaire can be a rare contributory factor to hypothyroidism. The type 1 selenodeiodinase (D1) predominates in the liver, kidney and muscle and is responsible for most of the body's circulating  $T_3$ . It is inhibited by the antithyroid drug propylthiouracil (PTU) (Fig. 8.6). The type 2 enzyme (D2) is predominantly localized in the brain and the pituitary, key sites for regulating  $T_3$  production for negative feedback at the hypothalamus and thyrotroph. There is a third selenodeiodinase, type 3 (D3), which deiodinates the inner ring and catalyses the conversion of  $T_4$  to reverse  $T_3$  ( $rT_3$ ; Fig. 8.3 and Fig. 8.6).  $rT_3$  is biologically inactive and cleared very rapidly from the circulation (half-life ~5 hours). The same degradative action on  $T_3$  is one method by which the similarly inactive  $T_2$  is generated. These combined steps are important. It is suggested that, when a given cell has sufficient  $T_3$  for its metabolic requirements, it switches to produce  $rT_3$ , which is then rapidly cleared. At least in part,  $T_4$  can



**Figure 8.6** Metabolism of thyroid hormone in the circulation. Four times more  $T_4$  is produced by the thyroid gland than  $T_3$ . Under normal 'euthyroid' physiology, ~40% of circulating  $T_4$  is converted to active  $T_3$  by type 1 selenodeiodinase (D1) and ~45% of  $T_4$  is converted to r $T_3$  by the type 3 selenodeiodinase (D3). The remaining 15% of  $T_4$  is degraded by minor pathways, such as deamination. The conversion of  $T_3$  to  $T_2$  by D3 is shown, although other pathways also exist for this reaction. The type 2 selenodeiodinase (D2) is predominantly located in the brain and pituitary gland where it catalyses the production of  $T_3$  for negative feedback within the hypothalamic–anterior pituitary–thyroid axis.

thus be thought of as a 'prohormone', its presence required only to maintain a constant supply of  $T_3$ .

### Function of thyroid hormone

Thyroid hormones affect a vast array of tissue and cellular processes, most obviously increasing the body's metabolic rate. In other species, effects can be more diverse, such as regulating metamorphosis in *Amphibia*.

$T_3$  acts in the nucleus of the target cell where it binds to the thyroid hormone receptor (TR) with 15-fold greater affinity than  $T_4$ . This predominantly explains why  $T_3$  is more potent than  $T_4$ . The consequence is altered gene expression (review Fig. 3.20). In this way, within the anterior pituitary, thyroid hormone can activate growth hormone (GH) production by the somatotroph and repress TSH production by the thyrotroph (part of the negative feedback loop of thyroid regulation). This predominantly genomic action explains why most actions of thyroid

hormone are relatively slow, days rather than minutes-to-hours.

The TR is not identical in all target tissues. There are two predominant isoforms, TR $\alpha$  and TR $\beta$ , each encoded by different genes and each subject to alternative promoter use and/or mRNA splicing (review Fig. 2.2). This creates a number of additional subtypes, all of which perform the basic activities of binding thyroid hormone, binding DNA and influencing target genes. However, they achieve these actions with subtly different efficacy. This layer of complexity helps to explain why different tissues respond differently to the same circulating thyroid hormone. Clinically, this can be evidenced in the very rare condition of thyroid hormone resistance due to mutations mostly located in the TR $\beta$  gene. A striking combination of thyroid overactivity can be observed in some tissues (e.g. tachycardia), while the thyrotroph in the pituitary responds as if thyroid hormone activity is inadequate (i.e. TSH secretion is maintained).

Thyroid hormones influence the actions of other hormones, but these effects can be difficult to discriminate from the generalized increase in cell metabolism. One of the most important effects clinically is the ability of  $T_3$  to synergize with catecholamines to increase heart rate, causing palpitations in thyrotoxicosis.

### Thyroid function tests

Clinical investigation of the thyroid gland hinges upon immunoassay of circulating thyroid hormones and TSH, combined as the 'thyroid function test'. Together, they inform the endocrinologist as to whether the patient's thyroid gland is overactive ('hyperthyroid'), underactive ('hypothyroid') or normal ('euthyroid') (Table 8.1). Now that robust assays are available, thyroid hormones are measured unbound to protein as  $fT_4$  and  $fT_3$ .  $fT_3$  concentrations are ~30% those of  $fT_4$ . Serum TSH is the critical parameter, in the absence of pituitary disease, it illustrates the body's response to its own thyroid hormone

levels. Ideally all three,  $fT_4$ ,  $fT_3$  and TSH, should be measured.

Biochemical assessment can be invaluable as thyroid disease can be insidious, especially primary hypothyroidism in the elderly. Commonly, it is difficult to act on borderline test results, such as subclinical hypothyroidism and hyperthyroidism. These are discussed in the following sections.

Pituitary underactivity can reduce TSH levels and cause hypothyroidism when it is very important to consider the other hormone axes, which might also be underactive. Similar thyroid function test results may be seen in patients suffering from physical (or in some instances psychiatric) illnesses that do not directly involve the thyroid gland. Severe illness in a patient is usually obvious, when total and free  $T_3$  and  $T_4$  may fall below normal without a compensatory increase in TSH. The body's type 1 selenodeiodinase activity is low. This condition is referred to as the 'sick euthyroid' syndrome. Although contentious, treatment is not normally undertaken. If recovery occurs,  $T_3$  and  $T_4$  return to normal of their own accord. In

**Table 8.1** Interpretation of thyroid function tests

Test results			Interpretation
TSH	$fT_4$	$fT_3$	
Normal	Normal	Normal	Euthyroidism
Low	High	High	Primary hyperthyroidism
Low	(High) normal	(High) normal	Subclinical primary hyperthyroidism or pregnancy
Low	Normal	High	$T_3$ -toxicosis
High/normal	High	High	Pituitary (secondary) hyperthyroidism or TR mutation; both exceptionally rare
High	Low	Low	Primary hypothyroidism
High	(Low) normal	(Low) normal	Subclinical primary hypothyroidism
Low	Low	Low	Consider secondary hypothyroidism (assess other pituitary hormone axes)
Normal/low	Low	Low	'Sick euthyroid' syndrome

For simplicity, higher axis disorders have been listed as secondary, i.e. pituitary, although tertiary hypothalamic disease is possible.

In effect, serum TSH = a bioassay of thyroid hormone action in the body.

pregnancy, TSH might decline, particularly in the first trimester, as human chorionic gonadotrophin (hCG) from the placenta is capable of mimicking TSH action.

## Clinical disorders

The major clinical disorders affecting the thyroid gland arise from either too much or too little thyroid hormone, benign goitrous overgrowth causing local symptoms or malignant tumourigenesis.

### Hypothyroidism

Lack of thyroid hormone occurs most commonly due to disease of the thyroid itself (primary hypothyroidism) and, less frequently, from lack of TSH from the pituitary (secondary hypothyroidism) (Box 8.8 and Case History 8.1). Tertiary hypothyroidism, due to hypothalamic dysfunction, is rare.

#### Primary hypothyroidism

The commonest presentation of thyroid underactivity in the western world is from autoimmune destruction of the gland. It is sixfold more common in women and incidence increases with age (up to 2% of adult women). Attempts have been made to classify the disorder according to goitre with its presence signifying 'Hashimoto thyroiditis', its absence 'primary myxoedema' or 'atrophic thyroiditis'. As we understand more about the pathogenesis, this clinical distinction becomes blurred; indeed, the disease process even overlaps with that of hyperthyroidism due to Graves disease (see later). This common genetic predisposition to thyroid disease also extends to other conditions (Box 8.7).

In autoimmune hypothyroidism, an extensive lymphocytic infiltration is accompanied by autoantibodies directed against thyroglobulin and thyroid peroxidase. Some additional antibodies may block the TSH receptor. Progressive destruction of thyroid follicular tissue results in hypothyroidism. Riedel thyroiditis is rare and due to progressive fibrosis that causes a hard goitre.

Congenital disorders of the thyroid (~1/4000 births), more likely to present to the paediatric endocrinologist, include failure of thyroid gland formation, migration or hormone biosynthesis. Causes

#### BOX 8.7 Examples of organ-specific autoimmune diseases — risk is increased for some individuals

- Graves disease
- Autoimmune hypothyroidism
- Pernicious anaemia
  - pernicious anaemia arises from autoimmune destruction of the parietal cell, loss of intrinsic factor secretion and consequently, vitamin B<sub>12</sub> deficiency
- Addison disease (Chapter 6)
- Autoimmune atrophic gastritis
- Type 1 diabetes mellitus (Chapter 12)

#### BOX 8.8 Causes of hypothyroidism

##### Goitre

- Autoimmune thyroiditis (possibly no goitre)
- Iodine deficiency (see earlier)
  - 'cretinism'
- Drugs (e.g. lithium)

##### No goitre

- Postradioiodine ablation or surgery (see treatment of hyperthyroidism)
- Post-thyroiditis (transient)
- Congenital hypothyroidism
- Hypothalamic or pituitary hypothyroidism

of the latter, collectively called 'thyroid dysmorphogenesis', usually present with goitrous hypothyroidism early in life.

It is important to recognize and exclude transient causes of thyroid upset. Excessive iodine intake, such as from radiocontrast dyes, can transiently block synthesis and hormone release. Lithium, used in the treatment of manic depression/bipolar disorders, can do the same. Indeed, lithium and Lugol's iodine can be used to control hyperthyroidism in certain circumstances (see next section). Viral infection, for instance by Echo or Coxsackie virus, can cause painful inflammation and release of stored hormone. A brief thyrotoxicosis is followed by transient hypothyroidism and is known as 'De Quervain's subacute thyroiditis'.

*Symptoms and signs.* The effects of hypothyroidism in adults are largely the result of a lowered metabolic rate. The classic symptoms and signs are listed in Box 8.9. The facial appearance and the potential for carpal tunnel syndrome are due to the deposition of glycosaminoglycans in the skin. Children tend to present with obesity and short stature (Fig. 8.7). The distinction between permanent (treatment needed) and transient (treatment not needed) disorders is important. Short-lived symptoms (less than a few months) preceded by a sore throat or upper respiratory tract infection may indicate transient hypothyroidism. Permanent hypothyroidism is more likely if other family members have thyroid disease. A drug history should be taken.

*Investigation and diagnosis.* A diagnosis of primary hypothyroidism should not be made without biochemical evidence. A thyroid function test (serum TSH, ideally accompanied by free thyroid hormone levels) is needed (Table 8.1). Four scenarios are commonly encountered.

1. Raised TSH at least twice normal upper limit (can be more than 10-fold increased) plus thyroid hormone levels clearly below the normal range. This diagnosis of primary hypothyroidism is clear-cut.

#### **BOX 8.9 Symptoms, signs and features of hypothyroidism**

- Weight gain
- Cold intolerance, particularly at extremities
- Fatigue, lethargy
- Depression
- Coarse skin and puffy appearance (possible carpal tunnel syndrome)
- Dry hair
- Hoarse voice
- Constipation
- Menstrual irregularities (altered LH/FSH secretion)
- Possible goitre
- 'Slow' reflexes, muscles contract normally, but relax slowly
- Generalized muscle weakness and paraesthesias
- Bradycardia (with reduced cardiac output)
- Cardiomegaly (with possible pericardial effusion)

When accompanied by long-standing symptoms, underactivity will be permanent.

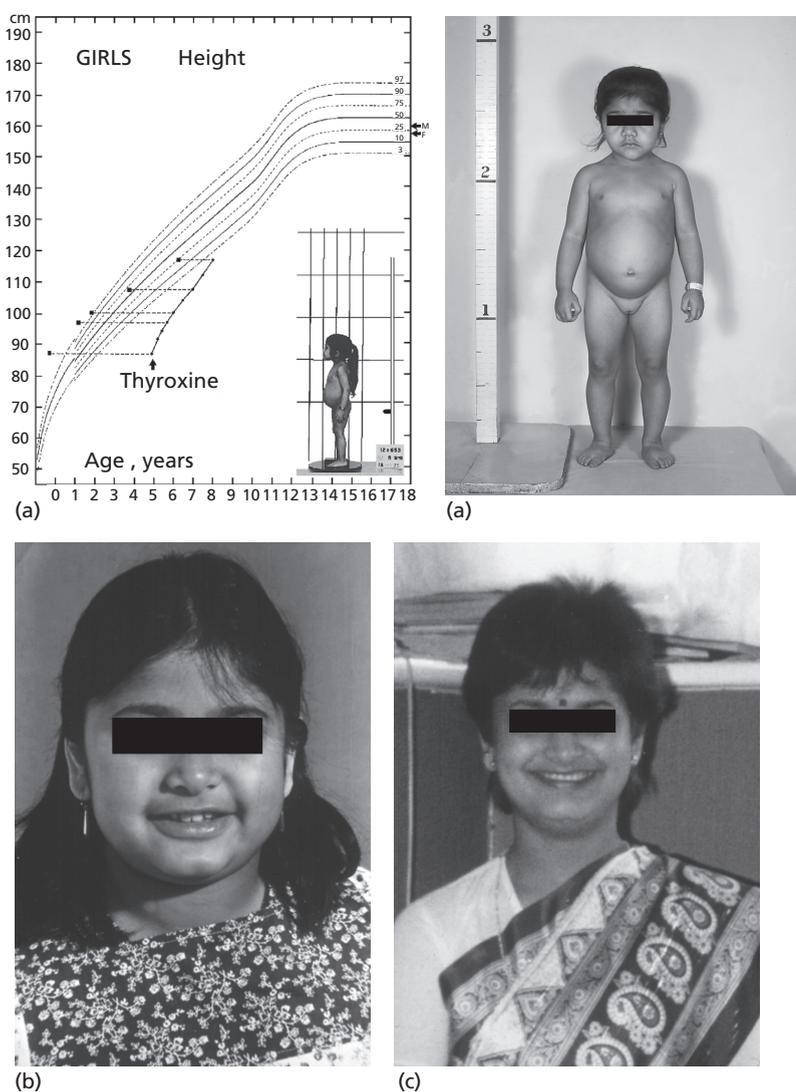
2. Raised TSH at least twice normal upper limit with normal thyroid hormone levels. This implies biochemical compensation. With significant symptoms, treatment is worthwhile; as subclinical hypothyroidism, treatment with thyroxine can still be justified, as ultimately the gland is likely to fail and produce frank hypothyroidism, especially if autoantibodies are detected.

3. TSH is only moderately raised and thyroid hormone levels are normal. This scenario is more difficult. These patients have an increased progression to frank hypothyroidism and, in the presence of significant symptoms, a therapeutic trial of thyroxine is one option. If the results are an incidental finding, repeat testing over the following months is an alternative, especially if there is concern over a transient viral hypothyroidism.

4. Thyroid function tests are unequivocally normal. **Do not treat with thyroxine, regardless of symptoms, as the patient is not hypothyroid.**

Other investigations are commonly not needed; however, if measured, a raised titre of thyroid antibodies may be detected. Creatinine kinase may be elevated. Dyslipidaemia is common with raised LDL-cholesterol. Prolactin may be elevated (stimulated by increased TRH secretion, see Chapter 5).

*Treatment.* Hypothyroidism is treated by oral thyroxine (i.e.  $T_4$ , therefore a hormone replacement rather than drug treatment); 100  $\mu\text{g}/\text{day}$  is the standard adult replacement dose ( $\sim 100 \mu\text{g}/\text{m}^2$  per day in children). The goal of replacement is to normalize TSH. The correct dose is determined by repeat serum analysis after 6 weeks as the pituitary responds sluggishly to acute changes in thyroid hormones. In primary hypothyroidism, replacement will be for life. In patients with long-standing hypothyroidism and co-existing ischaemic heart disease, graded introduction of replacement therapy over several weeks is frequently used. A final caveat to initiating treatment is to be confident of excluding Addison disease (review Chapter 6), a clue to which might be hyperkalaemia. Increasing basal metabolic rate with thyroxine only increases the body's demand for an already inadequate cortisol supply and can send a patient into Addisonian crisis. The rare, yet high



**Figure 8.7** Hypothyroidism. At the age of 6 years, this girl (a, upper panels) presented with short stature and extremely delayed skeletal maturation. Circulating thyroid hormone levels were very low and TSH grossly elevated, as were titres of thyroid autoantibodies. A diagnosis of primary hypothyroidism was made. The response to thyroxine treatment is shown by rapid catch-up growth. Learning problems were not evident, as the condition was not congenital but acquired after major development of the brain was complete. Three (b) and eight (c) years later, as a result of continued hormone replacement, she has now gained a normal appearance.

mortality clinical scenario of myxoedema coma is summarized in Box 8.10.

**Monitoring.** Once stable, thyroid function tests should be measured annually although replacement rarely changes. Compliance issues can be encountered where  $fT_4$  is normal (patient took tablet prior to clinic) but TSH is raised (chronically, the patient is taking inadequate thyroid hormone). Despite large trials, no convincing evidence has ever been presented that treatment with  $T_3$  is better than with

$T_4$ .  $T_3$  needs to be taken three times daily and usually only precipitates worse compliance.

### Secondary hypothyroidism

If the anterior pituitary thyrotrophs are underactive, TSH-dependent processes in the thyroid gland will fail. This translates as thyroid hormone deficiency. The causes are covered in Chapter 5. The principles of thyroxine replacement therapy are similar, although TSH is no longer a reliable marker of adequate replacement. The easiest approach is to treat

with sufficient thyroxine so that  $fT_4$  is in the upper half of the normal range (and  $fT_3$  is also within the normal range).

### Hyperthyroidism

Hyperthyroidism is overactivity of the thyroid gland. This produces the clinical effects of increased

circulating thyroid hormones, called thyrotoxicosis. Note the difference: release of stored hormone in viral infection or overdose of thyroxine will cause transient thyrotoxicosis but is not actually hyperthyroidism. Most commonly, true hyperthyroidism has an autoimmune origin, is 10-fold more common in women, and is named after its discoverer, Thomas Graves. Other causes are associated with amiodarone use and overproduction of hormone from an autonomous thyroid nodule. These are considered in turn. Overactivity from excess TSH is incredibly rare.

#### BOX 8.10 Myxoedema coma: very severe hypothyroidism, usually in the elderly

- Diminished mental function → confusion → coma
  - Hypothermia
  - Low cardiac output/cardiac failure
  - Pericardial effusion
  - Hyponatraemia and hypoglycaemia
  - Hypoventilation
- Even with treatment, it still carries a high mortality
- Identify any precipitating cause (e.g. infection)
  - Gradual rewarming
  - Supportive ITU management (protect airway in coma, oxygen, broad-spectrum antibiotics, cardiac monitoring, glucose, monitor urine output)
  - Take blood for thyroid function tests
  - Treat with hydrocortisone until hypoadrenalism excluded
  - Thyroid hormone replacement — both oral and i.v.  $T_4$  and  $T_3$  have been advocated with no clear consensus

### Graves disease

Autoimmune hyperthyroidism affects ~2% of women in the UK and is due to thyroid-stimulating IgG antibodies that activate the TSH receptor on the follicular cell surface. This results in all the consequences of cAMP generation (Box 8.5) and, in many cases, goitre formation.

*Symptoms, signs and biochemical profile.* The natural history of Graves disease is one of waxing and waning. However, identifying the disorder is important, as its symptoms are unpleasant, potentially serious and yet amenable to treatment. Many of the classic symptoms are due to an increased basal metabolic rate and enhanced  $\beta$ -adrenergic activity (Box 8.11 and Case History 8.2). Additional features are specific to Graves disease and represent the autoimmune disease process affecting other sites in the body. Thyroid acropachy and pretibial myxoedema are caused by cytokines that stimulate the deposition of glycosaminoglycans.

#### CASE HISTORY 8.1

A 45-year-old woman attended her doctor feeling 'not quite right' for the last 6 months. She was tired and her hair had been falling out. She had noticed her periods being heavy and rather erratic and wondered whether she was entering the menopause. She had put on 5 kg during the last 6 months. The doctor did some blood tests:  $Na^+$  134 mmol/L,  $K^+$  3.8 mmol/L, urea 4.2 mmol/L, creatinine 95  $\mu$ mol/L, TSH 11.2 mU/L,  $fT_4$  7.4 pmol/L, Hb 112 g/L, gonadotrophins were normal.

- What is the endocrine diagnosis and why?
- What is the treatment?
- Is she menopausal?
- What is the potential significance of the haemoglobin level?

*Answers, see p. 145*

**BOX 8.11 Symptoms and signs of thyrotoxicosis plus features associated with Graves disease**

- Weight loss despite full, possibly increased, appetite
  - Tremor
  - Heat intolerance and sweating
  - Agitation and nervousness
  - Palpitations, shortness of breath/tachycardia +/- atrial fibrillation
  - Amenorrhoea/oligomenorrhoea and consequent subfertility
  - Diarrhoea
  - Hair loss
  - Easy fatigability, muscle weakness and loss of muscle mass
  - Rapid growth rate and accelerated bone maturation (children)
  - Goitre—diffuse, reasonably firm +/- bruit in Graves disease (Fig. 8.8)
- Specific features associated with Graves disease
- Thyroid eye disease, also called Graves orbitopathy (Fig. 8.8)
  - Pretibial myxoedema—thickened skin over the lower tibia
  - Thyroid acropachy (clubbing of the fingers)
  - Other autoimmune features, e.g. vitiligo



**Figure 8.8** Hyperthyroidism. Graves disease in a 4-year-old. Note the goitre and eye signs.

Efficient clinical assessment of thyroid status is commonly required in the outpatient clinic (Box 8.12).

*Diagnosis.* Thyrotoxicosis requires biochemical proof of suppressed TSH and raised free thyroid hormone levels (Table 8.1). In the absence of extra-thyroidal features, additional tests may help to distinguish between Graves disease and a toxic adenoma (the latter possibly part of a multinodular goitre). Antithyroglobulin and/or antithyroid peroxidase antibodies are easier to measure than anti-TSH receptor antibodies (the real 'pathogen') and may be elevated. Thyroid ultrasound has a characteristic appearance in Graves disease due to increased vascularity and blood flow in the overactive gland (the same features that cause the bruit on auscultation). Diffuse uptake on a radionuclide scan indicates Graves disease, while patchy uptake

indicates toxic multinodular goitre; a single toxic nodule will show clearly as a 'hot' nodule. Transient hyperthyroidism will appear normal on ultrasound and have normal isotope uptake.

*Treatment.* There are three options to treatment:

1. *Antithyroid drugs* (Box 8.4). Since Graves disease waxes and wanes, a valid approach to treatment is to block the hyperthyroidism until remission. It is common to maintain patients on antithyroid drugs for 12 to 18 months and then to withdraw treatment to test for spontaneous remission. During this period, thyroid function tests are needed to ensure biochemical euthyroidism. The correct dose of drug, most commonly carbimazole, can be titrated or used at high dose (e.g. 40 mg) in combination with thyroxine (100 µg; 'block and replace'). Very rarely, antithyroid drugs can cause agranulocytosis and the patient must be warned to attend for a blood neutrophil

**BOX 8.12 A 3-minute clinical assessment of thyroid status**

- General inspection
  - Is there an obvious goitre or thyroid eye disease?
  - Is the patient appropriately dressed for the temperature?
  - Is the patient underweight, normal or overweight?
- Start with the hands
  - Are they warm and sweaty? Is there onycholysis or palmar erythema?
  - Is there thyroid acropachy?
  - Place sheet of paper on outstretched hands to assess tremor
  - Assess rate and rhythm of the radial pulse
  - Briefly assess character of pulse at the brachial artery
- Inspect front of neck, ask patient to swallow with the aid of a sip of water; is the neck painful?
- Move behind patient to palpate neck—is there a goitre? If so:
  - Assess size and movement on swallowing
  - Can the lower edge be felt (if not, it may extend retrosternally)?
  - Assess quality (e.g. firm, soft, hard)
  - Is it symmetrical?
  - Palpate for lymphadenopathy, especially if there is a goitre in a euthyroid patient
- Percuss for retrosternal extension
- Auscultate for a bruit
- Examine for other features of Graves disease (thyroid eye disease, pretibial myxoedema)

count in the event of sore throat or fever. Rash is a common side-effect and may settle with hydrocortisone cream. The success of this approach can be broken down into three categories: one-third of patients remits and remains well; one-third remits but relapses at some future time; and one-third relapses soon after stopping the drug and requires further treatment. The risk of falling into the last group is increased for males, having a high fT4 or large goitre at diagnosis and for those in whom TSH remains suppressed during treatment.

2. *Surgery.* If drugs fail or if a prompt definitive outcome is required (e.g. in pregnancy), subtotal

thyroidectomy can be used so long as the patient is adequately blocked preoperatively. Failure to achieve this runs the risk of 'thyroid storm' when handling the gland at operation can release huge stores of hormone and cause raging, life-threatening thyrotoxicosis. Carbimazole can be used to achieve biochemical euthyroidism or Lugol's iodine/potassium iodide can acutely block thyroid hormone release. Subtotal thyroidectomy leaves a small amount of tissue to try and minimize the risk of postoperative hypothyroidism (Box 8.8). Complications include: damage to the recurrent laryngeal nerve controlling the laryngeal muscles and voice; transient or permanent hypoparathyroidism due to damage or removal of the parathyroids; and bleeding. The scar, parallel to natural skin creases, is usually neat.

3. *Radioiodine.* Iodine-131 ( $I^{131}$ ) can be used to treat thyroid overactivity in the absence of thyroid eye disease, which it aggravates, and pregnancy, where it is contraindicated. It requires the same preparation as surgery to avoid thyroid storm. In the UK,  $I^{131}$  has tended to be reserved for women who have completed their family, although evidence of increased tumour risk or diminished fertility is poor. It is used more liberally in Europe, except in children. It carries no risk to surrounding structures but it is highly likely to induce permanent hypothyroidism, for which the patient needs preoperative counselling, postoperative monitoring and, in all likelihood, lifelong replacement therapy.

For all of these approaches, beta-blockers, most commonly propranolol can be used to moderate the symptoms of adrenergic excess, especially as antithyroid drugs take 2 weeks to have much effect.

*Graves disease in pregnancy.* Autoimmune disorders, including Graves disease, tend to ameliorate during pregnancy. A common scenario is one of relative subfertility while hyperthyroidism is undiagnosed, followed by pregnancy once treatment becomes effective. Antithyroid drugs cross the placenta more efficiently than thyroxine and block the fetal thyroid. The minimum dose possible should be used and 'block and replace' avoided. Carbimazole increases the risk of aplasia cutis (a congenital scalp defect) and other abnormalities, so propylthiouracil (PTU) is preferred. In ~1% of mothers with Graves disease, past or present, high levels of thyroid-stimulating

antibodies cross the placenta and cause fetal thyrotoxicosis, which is easy to forget when the mother has been treated by previous thyroidectomy. Fetal heart rate is a useful guide to its thyroid status. If needed, treatment is with antithyroid drugs. After birth, the symptoms recede with a time course that reflects the clearance of the maternal antibodies. If surgery is required during pregnancy, it is best planned for the second trimester. Postpartum, the mother is no longer 'protected' from Graves disease and may relapse. Monitoring with thyroid function tests is warranted.

### Thyroid eye disease (Graves orbitopathy)

The same autoimmune infiltration that affects the thyroid can also affect the extraocular muscles of the orbit (Table 8.2). Although most commonly timed close to the thyroid disease process, it is possible for thyroid eye disease to run an entirely separate course. However, its presence with thyrotoxicosis confirms the diagnosis of Graves disease. For reasons that are unclear, thyroid eye disease is much worse in smokers.

Some symptoms of 'grittiness' are common, for which liquid teardrops are effective. All but minor

thyroid eye disease warrants referral to an ophthalmologist. Detecting patients who can no longer close the eye due to proptosis is important because the cornea becomes at risk of ulceration. Taping the eyelids closed may be necessary at night. Although cosmetically undesirable, proptosis acts as a safeguard, relieving the retro-orbital pressure from swollen muscles. A relatively normal external appearance associated with retro-orbital pain or visual disturbance is far more concerning; there is risk of pressure on the optic nerve that can cause loss of vision.

The degree of retro-orbital inflammation and compression is assessed by magnetic resonance imaging (so-called 'stir' sequence MRI). If needed, treatment begins with cessation of smoking. Carbimazole probably possesses immunosuppressive qualities, so block and replace (see earlier) may be useful if there is coexisting thyroid disease. Radioiodine is contraindicated during active orbitopathy. Glucocorticoids are certainly immunosuppressive and can be used with steroid-sparing agents (e.g. azathioprine). The efficacy of orbital radiotherapy is contentious. Surgery can relieve sight-threatening compression. The natural history is for the disease to 'burn out'. Diplopia may remain from fibrosed mus-

Symptoms and signs	Gritty, weepy, painful eyes Retro-orbital pain Difficulty reading Diplopia Loss of vision 'Staring' appearance Periorbital oedema and chemosis (redness) of the conjunctiva Injection over the insertion point of lateral rectus Lid retraction Proptosis (forward displacement of the orbit)
Examination	Inspect from the front for signs of inflammation and lid retraction Is the sclera visible around the entire eye (Fig. 8.8) Inspect from the side for proptosis Assess eye movements from the front asking the patient to report double vision Assess visual fields Ask the patient to look away while retracting the lateral portion of each eyelid in turn. The insertion point of lateral rectus is visible. Is it inflamed? Assess whether the patient can close the eyelids completely

**Table 8.2** Symptoms, signs and examination of thyroid eye disease

cles, however, at this late stage, corrective surgery is highly effective.

### Amiodarone-associated thyroid disease

Amiodarone is frequently used in cardiology to treat arrhythmias. It contains a lot of iodine and has a half-life longer than 1 month. It causes disordered thyroid function tests in up to half of patients as well as frank hyperthyroidism and hypothyroidism in up to 20% (Box 8.13).

### Toxic adenoma

Hyperthyroidism, which is not autoimmune in origin, is usually due to thyroid autonomy associated with either a single adenoma (a 'toxic nodule') or a dominant nodule within a multinodular goitre (see below). Both are virtually always benign. Occasionally, adenomas secrete a predominant excess of  $T_3$  to cause 'T<sub>3</sub>-toxicosis' with normal  $fT_4$  levels. This may require a special request to the laboratory to ensure that  $fT_3$  is assayed.

#### BOX 8.13 Amiodarone can affect the thyroid gland and the thyroid function test

D1 and D2 are Types 1 and 2 selenodeiodinase respectively (review Fig. 8.6)

Effects on peripheral hormone metabolism and thyroid function tests:

- $fT_3$  slightly decreased
  - $fT_4$  slightly increased
  - $rT_3$  formation increased
  - Transient TSH increase
- } inhibition of D1 and D2 activity

Amiodarone-associated hypothyroidism:

- Iodine content may inhibit hormone synthesis and release

Amiodarone-associated hyperthyroidism:

- Amiodarone may be directly toxic to the thyroid
- Iodine excess may stimulate overactivity in susceptible individuals

Inflammation may provoke transient thyrotoxicosis followed by hypothyroidism

Treatment:

- Uptake can be difficult as the thyroid is already loaded with iodine
- Try carbimazole
- If drugs fail, surgery can be considered

Such patients will not have the diffuse and symmetrical goitre characteristic of Graves disease, nor will they have signs of Graves eye disease. Ultrasound and uptake scans will demonstrate the lesion. Unlike Graves disease, spontaneous remission does not occur and definitive treatment with surgery or radioiodine is indicated. With thyroid lobectomy or with radioiodine (when most of the gland is quiescent and will not take up the  $I^{131}$ ), the risk of post-treatment hypothyroidism is low.

### Multinodular goitre

The pathogenesis of multinodular goitre, where many colloid-filled follicular nodules develop, is unclear. Frequency is increased in females, with age and with iodine deficiency. The case for treatment is pressed if autonomous functioning of a dominant nodule causes thyrotoxicosis, if local compressive symptoms occur (e.g. on the trachea) or if cosmetic disfigurement prevails. Surgery is best for cosmetic improvement of the largest goitres; otherwise  $I^{131}$  is effective, especially in the frail. As with toxic adenoma, the risk of hypothyroidism post- $I^{131}$  treatment is relatively low.

As a sign of autonomy in multinodular goitres, TSH is often suppressed, yet  $fT_4$  and  $fT_3$  are in the normal range. Long-term, this subclinical overactivity increases mortality from cardiovascular disease. Treatment may also benefit seemingly minor symptoms. If treatment is decided against, annual progression to frank thyrotoxicosis in such patients is ~1% and occurs particularly in goitres with a dominant nodule greater than 2 cm diameter. In this scenario, annual monitoring of thyroid function is indicated.

### Thyroid cancer

There are various types of thyroid cancer with quite different prognoses. Details here are restricted to clinically significant disease; it is relatively common to find small foci of papillary cancer ('microcarcinoma'), of dubious significance, upon histological examination of multinodular goitre. A general approach to the patient is given in Box 8.14.

In a patient with a goitre, diagnosing hyperthyroidism reduces the likelihood of thyroid malignancy. Fine needle aspiration is the investigation of choice for investigating 'cold' nodules and is ideally

**CASE HISTORY 8.2**

A 32-year-old man attended his doctor having lost 10 kg in weight and with poor sleep. He felt on edge and had had difficulty concentrating at work. He smokes five cigarettes per day. Colleagues had commented that he always looks like he is staring or glowering at them. The doctor completes the history and examination and takes a blood test. He knew the likely diagnosis beforehand, however the results provided proof: TSH <0.01 mU/L, fT<sub>4</sub> 82.7 pmol/L, fT<sub>3</sub> 14.2 pmol/L.

What is the biochemical diagnosis and why?

What features of the examination could have suggested the diagnosis for the doctor without the blood test?

What is the most likely treatment plan and with what advice?

What definitive treatment is not appropriate at present?

*Answers, see p. 145*

**BOX 8.14 Approach to diagnosing thyroid malignancy**

Although there is a female predominance, given the much-increased incidence of all thyroid disease in women, goitre in a male increases the relative risk of malignancy.

Suspicious features in the history:

- Rapid growth
- Alteration of the voice or dysphagia
- Previous irradiation of the neck
- Familial tumour predisposition syndrome (e.g. multiple endocrine neoplasia; see Chapter 10)

Suspicious features on examination:

- Firm, irregularly shaped goitre with euthyroidism
- Tethering to other structures
- Local lymphadenopathy

Investigation:

- 'Cold' nodule (decreased uptake in comparison to normal tissue) on radioiodine scanning
- Fine needle aspiration or biopsy
- Histological diagnosis

performed under ultrasound guidance; ~12% of cold nodules prove to be malignant. It tends to produce four results: clear malignancy, suspicion, normality, or 'nondiagnostic'. Endocrinologists vary in how follow-up is conducted of normal results. Clear malignancy requires total thyroidectomy. Suspicious results in high-risk individuals are probably best managed by local resection to provide a clear tissue diagnosis—malignancy then proceeding to total thyroidectomy. Repeated nondiagnostic aspirations and biopsies are relatively common and, if clinical suspicion is high, local surgery is probably the best option (as for suspicious biopsies). Despite the link to familial syndromes (Table 8.3), most medullary carcinoma is sporadic. Calcitonin serves as a circulatory marker. It is covered in greater detail in Chapter 10.

Papillary cell thyroid cancer carries a good prognosis. Spread is characteristically by the lymphatic system. Following thyroidectomy, doses of replacement thyroxine are given that suppress TSH. Thyroglobulin acts as a very sensitive marker of persisting or recurrent disease, to which radioactive

**Table 8.3** Some characteristics of thyroid malignancies

Type	% of thyroid malignancies	Groups affected	Outcome
Follicular cell origin			
Papillary carcinoma	70–75	Young women	Good
Follicular carcinoma	15–20	Middle-aged women	Good
Anaplastic	5	Older people	Very poor
C-cell origin			
Medullary carcinoma	<10	Can be part of MEN	Poor
Others			
e.g. lymphoma, sarcoma	<10		Can be good

**KEY POINTS**

- $T_3$  and  $T_4$  are produced from the thyroid gland in response to TSH stimulation
- The thyroid stores significant amounts of hormone compared to other endocrine organs
- $T_3$  is the major, active thyroid hormone
- The effects of thyroid hormone are enacted rather slowly by virtue of its action on gene expression
- TSH levels are particularly important to the diagnosis of hypothyroidism and hyperthyroidism
- Overactive and underactive thyroid disease is common, especially in women
- Most thyroid swellings/goitres are benign
- The vast majority of thyroid malignancy has a good outcome

iodine ablation can be administered. Follicular carcinoma also carries a good prognosis. It consists of a mixture of neoplastic colloid-containing follicles, empty acini and alveoli of neoplastic cells. Intriguingly, follicular carcinomas predominate in geographical areas with low dietary iodine. Treatment and postoperative follow-up are similar to papillary carcinoma. In contrast, anaplastic carcinoma is almost always fatal and represents a fast-growing, poorly differentiated tumour, for which there is a mean survival from diagnosis of only 6 months.

**Answers to case histories****Case history 8.1**

The woman has primary hypothyroidism, which probably accounts for the tiredness and the hair loss. TSH is more than twice the upper limit of normal and  $fT_4$  levels are below the normal range.  $fT_3$  has not been measured but is unnecessary in this instance. The slightly low serum sodium is probably associated with the hypothyroidism. Treatment should be with oral thyroxine. The dose required is the one that normalizes the TSH on repeat thyroid function tests, which should be performed 6 weeks to 2 months after starting treatment. It is most likely to be a single daily tablet of 100  $\mu\text{g}$ , which in the UK does not currently attract a prescription charge. Treatment is lifelong. She could start on this dose straightaway.

She is highly unlikely to be menopausal as gonadotrophins are normal. She has mild anaemia, possibly due to iron deficiency from the menorrhagia, which might also contribute to the hair loss. Alternatively, hypothyroidism can cause anaemia,

most probably normochromic normocytic, but possibly associated with mild macrocytosis. A finding of macrocytosis should also raise concern over pernicious anaemia, of which this patient is at increased risk. The mean cell volume should be measured and the anaemia should be investigated further by examining iron stores. If low, then a course of ferrous sulphate would be appropriate. The full blood count should be reinvestigated with the future thyroid function test.

Finally, the patient should be advised that restoring euthyroidism by itself will not necessarily cause loss of the weight gain. However, alongside careful diet and exercise, this should be attainable.

**Case history 8.2**

The thyroid function tests reveal thyrotoxicosis. TSH is undetectable and both free thyroid hormones are ~threefold the normal upper limit.

The scale of these blood results is very unlikely to be due to transient hyperthyroidism and the history contains no clues of recent viral infection. The diagnosis is clinched by the presence of thyroid eye disease. The staring appearance is due to the entire sclera being visible because of lid retraction and possible proptosis. In combination with the thyrotoxicosis, this diagnoses primary hyperthyroidism due to Graves disease. The other relevant feature of the examination could have been the detection of a thyroid bruit on auscultation over each lobe of the gland. A characteristic goitre is strongly suggestive of Graves disease; however, the bruit, indicative of diffusely increased vascularity, confirms the diagnosis. Although rare, pretibial myxoedema would also

indicate that the thyrotoxicosis is due to Graves disease. Less specifically, a positive family history for autoimmune thyroid disease would be supportive.

The patient should be referred to an endocrinologist. However, treatment could be initiated with antithyroid drugs to attain biochemical euthyroidism. The most likely treatment plan is their use for 12 to 18 months, followed by withdrawal. In the UK, the most common agent is carbimazole at a starting dose of ~40 mg once daily. The prescription should be issued with a warning over the rare side-effect, agranulocytosis, and the need for urgent consultation in the event of sore throat or fever. Rash is a more common side-effect and may settle after a few days. Propranolol 40 mg three times daily could be prescribed to control symptoms, certainly during the 2 weeks or so that the carbimazole takes to begin its effect. Endocrinologists vary in their follow-up strategy, by either titrating the dose of carbimazole or using 'block-and-replace' (see earlier text in this chapter). By either approach, TSH would most likely remain undetectable at first; however, in time, it

would be anticipated to rise back towards the normal range. Biochemical hypothyroidism should be avoided.

As a male with high levels of free thyroid hormones at diagnosis, he is already at higher risk of failure to remit and the need for definitive treatment with surgery. Persistently undetectable TSH during treatment and a large goitre would increase this risk further.

Further assessment of the thyroid eye disease is needed. The patient should be advised to stop smoking. If symptoms are limited to minor 'grittiness', the patient can close his eyes completely, and the remainder of the eye examination is largely unremarkable (e.g. vision normal, no retro-orbital pain), then observation would suffice. However, if the disease is any more significant, then referral should be made to an ophthalmologist.

Radioiodine would be contraindicated for definitive treatment of the thyroid disease, as, especially in an active smoker, it would be likely to exacerbate the eye disease.