13.3.1 The thyroid gland and disorders of thyroid

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areas is autoimmunity, where the follicular gland structure is destroyed by autoreactive T cells. Clinical features—manifests in the adult with the gradual onset of a constellation of symptoms and signs including tiredness, feeling cold, weight gain, hoarseness of the voice, and slow-relaxing tendon reflexes. A goitre may (Hashimoto's thyroiditis) or may not (atrophic thyroiditis/primary myxoedema) be present. Biochemical diagnosis of primary hypothyroidism is confirmed by a high serum TSH and a low free T4, with autoimmune hypothyroidism associated with the presence of thyroid peroxidase autoantibodies. Treatment is with levothyroxine (typically 100–150 µg/day for total hypothyroidism, but beginning with a lower dose in older people or those with heart disease). Myxoedema coma—this is the most dramatic presentation of hypothyroidism and a medical emergency with high mortality: man- agement requires (1) supportive treatment; (2) identification and treatment of any precipitating condition, often infective; (3) paren- teral thyroid hormone replacement. Thyrotoxicosis Aetiology—Graves' disease, which is caused by TSH receptor stimu- lating autoantibodies, is responsible for 60 to 80% of cases, and nodular thyroid disease (toxic multinodular goitre and toxic ad- enoma) accounts for most of the rest. 13.3 Thyroid disorders

13.3.1 The thyroid gland and disorders of thyroid function 2285 Clinical features—presents with a wide range of symptoms and signs including hyperactivity, palpitation, fatigue, weight loss (despite increased appetite), sinus tachycardia (or atrial fibrillation), tremor, and eye signs (including lid retraction and lid lag). Biochemical diag- nosis of primary hyperthyroidism is confirmed by a low serum TSH and a high free T4 and/or T3, with autoimmune hyperthyroidism associated with the presence of thyroid peroxidase autoantibodies in many and anti-TSH receptor antibodies in most patients with Graves' disease. β-blockers can rapidly relieve symptoms, but de- finitive treatment requires antithyroid drugs (usually carbimazole or propylthiouracil), radio-iodine (131I), or surgery. Thyroid-associated ophthalmopathy—this often causes anxiety and social embarrassment, but severe cases are a threat to vision and may require treatment with corticosteroids, radiotherapy, other im- munosuppressive agents, or orbital decompression. Thyrotoxic crisis or storm—this is the most dramatic presentation of hyperthyroidism and a medical emergency with high mortality. Manifestations include fever (>38.5ºC), delirium or coma, seizures, vomiting, diarrhoea, and jaundice. Management requires (1) sup- portive treatment; (2) identification and treatment of any precipitating condition, including infection; (3) antithyroid treatment (e.g. loading dose of carbimazole or propylthiouracil), followed 1 h later by stable iodine (e.g. Lugol's iodine). Other conditions Acute thyroiditis—usually caused by bacterial infection; presents with severe thyroid pain, fever, and malaise; thyroid function is rarely disturbed. Subacute (or de Quervain's) thyroiditis—due to viral infection and commonly presents with thyroid pain; there may be transient thyro- toxicosis, followed by hypothyroidism, before restoration of normal thyroid function; diagnosis depends on demonstration of raised inflammatory markers and low/absent radio-iodine uptake by the thyroid. Amiodarone—inhibits T4 deiodination and hence leads to free T4 levels that are in the upper half of the reference range or mildly elevated; may cause hypothyroidism or hyperthyroidism, the latter being difficult to treat. Structure of the thyroid gland Development The human thyroid develops as a diverticulum in the pharyngeal floor at around 3 weeks of gestation. This median anlage moves caudally and remains connected to the pharynx via the thyroglossal duct, which is subsequently obliterated when the thyroid begins to expand as two distinct lobes at around 2 months of gestation. The foramen caecum marks the point in the tongue where the thyroid develops and there is sometimes an upward extension of thyroid tissue from the isthmus, the pyramidal lobe, arising from the lower part of the thyroglossal duct. At the same time, the lateral anlage ultimobranchial bodies, derived from the fifth branchial pouches, fuse with the

developing thyroid to which they contribute the parafollicular calcitonin-secreting clear cells. Synthesis of thyroid hormone begins at week 12, at the same time as TSH production by the pituitary. There is significant maternal-to-fetal T4 transfer so that babies with no endogenous thyroid hormone production are none- theless protected from the adverse effects of fetal hypothyroidism on development of the brain, lung, and skeleton. Preterm infants may have transient hypothyroxinaemia in the first weeks of life but trials of thyroid hormone supplementation have been inconclusive. Anatomy and histology The adult thyroid weighs 15 to 20 g; each lobe is around 4 cm long and 2 cm wide, although the right lobe is often larger than the left. The isthmus connecting the two lobes lies just below the cricoid car- tilage. The blood supply on each side is derived from the external ca- rotid artery via the superior thyroid artery and from the subclavian artery via the inferior thyroid artery. There is adrenergic and cholin- ergic innervation which regulates blood flow. The thyroid is attached to the trachea by connective tissue, and the recurrent laryngeal nerves lie between the trachea and the posterior aspect of the lobes. The gland is made up of lobules each comprising 20 to 40 spher- ical follicles. The follicles vary considerably in size, but average 200 μm in diameter, and are made up of a single layer of thyroid fol- licular epithelial cells (Fig. 13.3.1.1). The cells are cuboidal when quiescent and columnar when active, and have a microvillous apical membrane. The follicular lumen contains colloid, the principal con- stituent of which is the glycoprotein thyroglobulin secreted by the thyroid cells. Each follicle is surrounded by a rich capillary network. Clear cells lie scattered between follicular epithelial cells or in the interstitium, and account for around 1% of the epithelial mass. Thyroid hormone synthesis and metabolism Synthesis and secretion Thyroid hormone synthesis requires iodide uptake and oxidation, iodination of certain tyrosine molecules on thyroglobulin, and coupling of the iodotyrosines to form the thyroid hormones T3 and T4 (Fig. 13.3.1.2). Iodide is actively transported into the thyroid cell by the Na+/I− symporter, which is also expressed in breast tissue and the salivary glands. Perchlorate, thiocyanate, and pertechnetate are also transported by the same symporter and these anions can Fig. 13.3.1.1 Histology of a normal thyroid. Thyroid epithelial cells are arranged in follicles containing colloid. Original magnification ×200. Photomicrograph by courtesy of Dr K. Suvarna.

 competitively inhibit iodide uptake. The World Health Organization (WHO) recommended daily intake of iodine is 150 μg for adults (250 μg during pregnancy and lactation) but there is wide variation in actual intake with many countries having borderline or frankly deficient intakes of less than 50 to 100 μg. In some parts of western Europe and North America intake has been excessive (up to 750 μg/ day), although there is recent evidence that an increasing number of individuals in these countries remain at risk of iodine deficiency, especially during pregnancy. Iodide is oxidized by thyroid peroxidase, a haem-containing enzyme located at the apical border of the thyroid cell, using hydrogen peroxide generated by dual oxidase (DUOX) and DUOX maturation factor 2, and is then rapidly incorporated into tyro- sine residues to form monoiodotyrosine and di-iodotyrosine. Thyroid peroxidase is also responsible for the coupling of these iodotyrosines, with different sites in the thyroglobulin molecule being responsible for the formation of T3 or T4. Normally, each thyroglobulin molecule contains three or four T4 molecules, but only 20% of thyroglobulin molecules contain a T3 molecule. Thyroglobulin acts as slow turnover reservoir for thyroid hor- mone, thus ensuring maximum use is made of often scarce dietary iodine. Around a 7-week supply of T4 is contained in the normal thyroid. Thyroid hormone is released from the gland after endo- cytosis of colloid and lysosomal hydrolysis of the thyroglobulin to yield T4 and T3, which are secreted from the basal

membrane into the capillaries in a molar ratio of 14:1. Released iodotyrosines are deiodinated for iodide recycling. Thyroid hormone transport Up to 90% of the total T3 in the circulation is derived from per- ipheral conversion of T4 to T3 by deiodinase enzymes (see next) rather than thyroid secretion. Only 0.03% of T4 and 0.3% of T3 in the circulation exist as free hormone that is able to diffuse into tissues; the remainder is protein bound. T4 binds predominantly to T4-binding globulin, and to a lesser extent to transthyretin (or prealbumin); a little is bound to albumin. T3 binds to T4-binding globulin and albumin, with little bound to transthyretin. Alteration in the concentration or binding capacity of thyroid hormone- binding proteins can produce major changes in total but not free thyroid hormone levels (Table 13.3.1.1). Several transporters mediate thyroid hormone uptake by cells; monocarboxylate transporter 8 is particularly important in the uptake of T3 by brain, and mutations in this gene cause severe psychomotor 1 Iodide trapping 2 Oxidation 3 TG iodination 4 Coupling 5 Colloid resorption 6 TG hydrolysis 7 Deiodination of MIT+ DIT 8 Deiodination of T4 9 T3 and T4 secretion Follicular lumen Apical membrane containing TPO, catalysing steps 2–4 Thyroid epithelial cell TG synthesis MIT DIT I− T4 T3 9 8 6 1 I− 2 3 4 TG TG TG I− T3 T4 5 7 T4 T3 DIT MIT Fig. 13.3.1.2 Steps in the synthesis of thyroid hormones. DIT, di-iodotyrosine; MIT, monoiodotyrosine; TG, thyroglobulin; TPO, thyroid peroxidase. Table 13.3.1.1 Conditions in which there is altered binding of thyroid hormones to binding proteins TBG Increased binding Genetic variation in TBG Oestrogens (pregnancy, oral contraception, hormone replacement therapy, tamoxifen) Other drugs (perphenazine, opiates,
5-fluorouracil, clofibrate, mitotane) Hepatitis, cirrhosis Acute intermittent porphyria Decreased binding Genetic variation in TBG Steroids (testosterone, anabolic steroids, glucocorticoids) Acromegaly Nephrotic syndrome Protein malnutrition Acute severe illness L-asparaginase Albumin Decreased binding Any cause of hypoalbuminaemia Increased binding Genetic variation Transthyretin Increased binding Genetic variation Competition for binding sites Drugs Phenytoin Carbamazepine Salicylates and nonsteroidal anti-inflammatory drugs Nonesterified fatty acids TBG, thyroid-binding globulin.

 retardation and hypotonia due to brain-specific hypothyroidism during development. Metabolism of thyroid hormone The half-life of T4 in the circulation is 7 days, contrasting with the much shorter half-life of T3 of 24 h. The most important metabolic pathway for T4 is outer ring (5′) deiodination to T3
(Fig. 13.3.1.3). This is catalysed by type 1 and type 2 deiodinase (EC 1.97.1.10), while type 3 deiodinase (EC 1.97.1.11) catalyses inner ring (5) deiodination leading to hormone inactivation. Type 1 deiodinase can also catalyse inner ring deiodination of T3 and T4. All three enzymes have a selenocysteine moiety as the active catalytic site. Type 1 deiodinase is expressed predominantly in the liver, kidney, thyroid, and brain, type 2 in the pituitary, brain, placenta, skeletal muscle, and heart (tissues critically dependent on thyroid hormone for development or function), and type 3 in the brain, placenta, and skin. The type 1 deiodinase is largely re- sponsible for the generation of circulating T3 from T4, whereas T3 generated by the type 2 enzyme mainly provides intracellular T3 at specific sites. Around 40% of T4 is metabolized to T3 and 40% is converted to reverse T3 by the type 3 deiodinase. This same enzyme is responsible for the main metabolic pathway for T3 which is converted to 3,3′- di-iodothyronine. Starvation, trauma, and drugs (propylthiouracil, amiodarone, glucocorticoids, propranolol) impair T4 to T3 conver- sion and must be borne in mind when interpreting tests of thyroid function (see next). In addition to deiodination, a small proportion of thyroid hormone is metabolized by conjugation of the phenolic hydroxyl group with sulphate or glucuronic acid, which increases water solubility and allows urinary and biliary

excretion. Biliary iodothyronine glucuronides can be reabsorbed, constituting an enterohepatic cycle. Thyroid hormone action Thyroid hormone acts primarily as a transcription regulatory factor, mediated by T3 binding to nuclear receptor isoforms that belong to the same superfamily as steroid and retinoic acid receptors. All such receptors possess a conserved DNA-binding domain containing two zinc fingers, which interact with specific DNA response elem- ents, and a hormone-binding domain. Alternative splicing results in two pairs of thyroid hormone receptors (Fig. 13.3.1.4) whose tissue expression varies during development. Thyroid hormone receptors bind to DNA as homodimers or heterodimers (with the retinoid X receptor). Without ligand, basal gene transcription is in- hibited by a corepressor. When T3 binds, homodimers dissociate releasing corepressor and allowing gene transcription; the stable heterodimer binds coactivators in the presence of T3 with the same outcome. The α2 thyroid hormone receptor does not bind T3 and may act as a natural inhibitor of receptor activity. A cell surface re- ceptor for T3, involving integrin αvβ3 and leading to protein kinase signal transduction, has been delineated and there are further path- ways for thyroid hormone action involving cytoplasmic and mito- chondrial receptors. DI1,DI2 T3 HO I I O CH COOH I DI3,(DI1) reverse T3 HO I I O CH COOH NH2 NH2 I HO I I O CH COOH T4 HO I(5′) I(3′) I(3) O I(5) CH COOH DI3,(DI1) di-iodothyronine (T2) DI1,DI2 NH2 CH2 CH2 CH2 NH2 CH2 Fig. 13.3.1.3 Main deiodination pathway for thyroid hormones. DI, deiodinase enzyme; parentheses denote a minor contribution. Deiodination of T3 also yields 3,5-T2 and deiodination of reverse T3 also yields 3′,5′-T2. T2 is further deiodinated to monoiodothyronine and thyronine. Tissue distribution Brain, muscle fat Brain, testis Liver, kidney Pituitary, hypothalamus 1 2 1 2 410 492 461 514 T3 binding domain DNA binding domain Fig. 13.3.1.4 Structure of the thyroid hormone receptors. The numbers indicate the amino acid content. Homologous areas are shaded; the lack of homology in the T3-binding domain of the α2 receptor (hatched area) prevents T3 binding and the function of this receptor is unknown.

 Regulation of thyroid function The main regulator of thyroid function is TSH (thyrotropin), se- creted by thyrotrophs in the anterior pituitary gland in response to the tripeptide thyrotropin-releasing hormone derived from the hypothalamic supraoptic and paraventricular nuclei. Thyroid hor- mones exert a classic negative feedback effect on thyrotrophs; the acute effect is mediated by T3 in the pituitary which is derived from T4 by type 2 deiodination. Thyroid hormones also inhibit hypo- thalamic thyrotropin-releasing hormone synthesis. TSH secretion stimulated by thyrotropin-releasing hormone is inhibited by dopa- mine and somatostatin, while α-adrenergic activation stimulates TSH release. Cytokines, particularly interleukin-1, interleukin-6, and tumour necrosis factor, inhibit TSH synthesis and may be re- sponsible for the suppression of TSH seen in severe illness. Within the thyroid, TSH binds to the G protein-coupled TSH re- ceptor, leading to intracellular signalling predominantly via cAMP. TSH increases iodide transport and organification, endocytosis of colloid, and thyroid hormone secretion, as well as thyroid follicular epithelial cell division. Autoregulatory mechanisms can modulate thyroid function when TSH levels are constant. The most important is iodine intake. Increased iodide transport transiently decreases organification and reduces thyroid hormone synthesis (the Wolff– Chaikoff effect); after several weeks under normal conditions, the thyroid escapes and resumes hormone production. Sudden in- creases in iodine intake can also acutely block thyroid hormone re- lease. In iodine deficiency, thyroid hormone production is switched to preferential T3 synthesis, but this effect is largely TSH-mediated rather than autoregulatory. Laboratory investigation of thyroid function Determining thyroid status The introduction of sensitive immunoradiometric assays for circu- lating TSH, with a detection level of 0.1 mU/litre or

less, has trans- formed the evaluation of thyroid status. A normal TSH level rules out primary thyroid dysfunction. Low levels of thyroid hormones elevate TSH as a result of negative feedback, while excessive thyroid hormone suppresses TSH. The thyrotropin-releasing hormone test for detecting low TSH levels is now redundant. As well as primary thyroid disorders, other conditions may alter TSH levels and must be borne in mind when using TSH as a screening test for thyroid dysfunction (Table 13.3.1.2), as must the possibility of secondary (pituitary or hypothalamic) disturbances of thyroid function. It is, therefore, essential to confirm thyroid status when TSH levels are abnormal, or when pituitary or hypothalamic abnor- malities are possible, by measuring circulating thyroid hormone levels. Methods which measure total T3 or T4 are prone to artefacts caused by abnormal thyroid hormone binding (Table 13.3.1.1), al- though in the absence of such abnormalities these tests are reliable. When altered binding is suspected or found, compensation can be made by calculation of the free T3 or free T4 index. These indices are derived from the total hormone levels and measurement of the differential distribution of radiolabelled T3 between unoccupied protein binding sites in the sample and an absorbent resin (hence the term ‘resin uptake test’). T4-binding globulin levels can also be measured directly. However, the ready availability of immunoassays for free T3 and free T4 has generally supplanted these methods. The immunoassays rely on the ability of a radiolabelled thyroid hormone analogue to bind to thyroid hormone antibody but not to plasma binding pro- teins. The analogue then competes for antibody binding with the free thyroid hormone in the sample. Despite initial concerns about the theoretical basis and performance of such assays, recent im- provements allow generally reliable estimation of free thyroid hor- mones. In cases of doubt, free hormone levels can be measured by physical separation from bound hormone using ultracentrifugation or equilibrium dialysis. Several indirect methods can be used to determine thyroid status. The thyroidal uptake of radio-iodine (123I, 131I) or 99mTc pertechnetate is increased in hyperthyroidism and decreased in hypothyroidism, but can be affected by excessive dietary iodine and destructive processes in the thyroid so that uptake is low when the patient is thyrotoxic (see ‘Destructive thyroiditis’). Serum thyro- globulin is raised in hyperthyroidism of all types but is also raised in destructive thyroiditis and thyroid cancer. Its main role in inves- tigation is follow-up of treated thyroid cancer (see Chapter 13.3.2). Several non-specific tests have also been used to determine end- organ responses to thyroid hormones, including basal metabolic rate, tendon relaxation time, and serum levels of cholesterol, ferritin, sex hormone-binding globulin, and liver enzymes although these should not be used routinely to determine thyroid status. Thyroid function in nonthyroidal illness and pregnancy Assessing thyroid function in severely ill patients often reveals abnor- malities termed the ‘sick euthyroid syndrome’. Many of the changes are due to cytokine release, but therapeutic agents such as dopamine

Table 13.3.1.2 Causes of abnormal serum TSH concentrations TSH level Cause Free thyroid hormone levels Raised Overt hypothyroidism ↓ Subclinical hypothyroidism N Sick euthyroid syndrome ↓ or N Dopamine antagonists (acute effect) N TSH-secreting pituitary adenoma ↑ Thyroid hormone resistance syndrome ↑ Adrenal insufficiency ↓ or N Lowered Overt thyrotoxicosis ↑ Subclinical thyrotoxicosis N Recently treated hyperthyroidism N Thyroid-associated ophthalmopathy without Graves’ disease N Excessive thyroxine treatment N or ↑ Sick euthyroid syndrome ↓ or N First trimester of pregnancy N or ↑ Pituitary or hypothalamic disease N or ↓ Anorexia nervosa N or ↓ Dopamine, somatostatin (acute effect) N Glucocorticoids N N, normal; TSH, thyroid-stimulating hormone; ↑, increased; ↓, decreased.

 and glucocorticoids also contribute, as do unknown factors. Any major, acute illness or starvation can result in a decrease in circu-

lating T3 (total and free) with normal levels of T4 and TSH. Reverse T3 levels rise. The severity of the illness correlates with the magni- tude of the fall in T3, and in very sick patients total T4 levels also fall. Analogue-based free T4 assays generally produce normal results but sometimes high or low values occur. In 10 to 15% of sick individuals, TSH levels are abnormal (raised or lowered). Psychiatric illness can be associated with raised total and free T4 levels with normal T3. There is no proven benefit from thyroid hormone administration in the sick euthyroid syndrome and the hormone changes may be protective by limiting catabolism (although this view is regularly challenged). The importance of these alterations lies in their potential to cause diagnostic confusion. Thyroid function tests should only be requested in ill patients when thyroid disease is genuinely suspected. Abnormal thyroid function tests due to the sick euthyroid syndrome return to normal after recovery and, therefore, repetition of testing is the simplest way to confirm the reason for unusual results. Pregnancy also affects thyroid function testing. The most obvious change is the rise in T4-binding globulin secondary to high oes- trogen concentrations, which elevates total but not free T3 and T4 levels. In addition, the reference ranges for free T3 and T4 are higher than normal in the first half of pregnancy because placental human chorionic gonadotropin, at high levels, acts as a weak stimulator of the TSH receptor. There is a reciprocal fall in TSH levels during the first trimester, but TSH returns to normal in the second trimester as human chorionic gonadotropin levels decline. Current guidelines advise the use of population and trimester-specific reference ranges during pregnancy. Occasionally, the changes in circulating hormone concentrations are sufficiently pronounced to cause transient ‘ges- tational’ hyperthyroidism associated with high circulating HCG (human chorionic gonadotrophin) concentrations (e.g. in those with hyperemesis) during pregnancy. Antithyroid drugs are usually un- necessary in this condition, and attention should be directed to con- trolling the vomiting and giving parenteral fluids. Renal clearance of iodine is increased in pregnancy, leading to maternal and neonatal goitre and mild hypothyroidism in areas where iodine intake is mar- ginal (50 µg/day). These complications can be prevented by ensuring an adequate iodine intake of 250 µg/day during pregnancy. Determining the cause of thyroid dysfunction The most frequent cause of thyroid dysfunction in iodine-sufficient areas is autoimmunity, and the simplest test for this is measurement of thyroid autoantibodies, particularly those directed against thyroid peroxidase. Antibodies against thyroglobulin are also easily meas- ured but are usually accompanied by thyroid peroxidase antibodies, so testing for the latter alone is usually adequate. Different methods, including haemagglutination, immunofluorescence, radioimmuno- assay, and enzyme-linked immunosorbent assay, give different prevalence rates for thyroid autoantibodies. Almost all patients with autoimmune hypothyroidism and around 75% with Graves’ disease have thyroid peroxidase antibodies. Generally lower levels are found in 5 to 15% of healthy women and 2% of men, and in slightly higher proportions of patients with nodular goitre and thyroid cancer, and results therefore need to be interpreted carefully. Individuals with positive thyroid autoantibodies but normal thyroid function are at increased risk of developing autoimmune hypothyroidism (c.2% per year). Measurement of antibodies to the TSH receptor may be useful to confirm an underlying diagnosis of Graves’ disease and reliable assays to perform this test are now widely available. Thyroid imaging by scintiscanning is useful in determining the aetiology of thyroid disease when this is not obvious clinically, par- ticularly in hyperthyroidism and ectopic thyroid tissue. Its role in the evaluation of a solitary thyroid nodule is considered in Chapter 13.3.2. 99Tcm pertechnetate is usually used as it has a short half-life (6 h) which allows safe administration of high activity and rapid scanning. 123I is not as readily available but is preferable to 131I, especially in children, as it too has a short half-life and does not emit β-radiation. Thyroid ultrasound is being increasingly

used as an alternative to scintiscanning. The technique allows accurate determination of thy- roid size, which may be useful in follow-up of goitre, and can help to determine the nature of an atypical neck mass. Its role in evaluating nodular thyroid disease is considered in Chapter 13.3.2. CT scanning is particularly valuable in determining the extent of a retrosternal goitre and assessing tracheal compression (Fig. 13.3.1.5). In contrast, a standard chest radiograph can be misleading in evaluating tracheal compression, particularly in the anterior–posterior plane. Goitre The distribution of thyroid size in any population forms a continuous, positively skewed curve, whose shape depends on the age, sex, and country of residence of the individuals assessed. Hence a precise definition of goitre is impossible. Ultrasound is the most accurate method to assess thyroid size, and estimates of goitre prevalence based on inspection and palpation underestimate the true frequency. However, simple schemes, such as that shown in Box 13.3.1.1, are useful in field studies of goitre prevalence. Fig. 13.3.1.5 CT scan of the chest of a patient with a large retrosternal goitre causing tracheal compression. Box 13.3.1.1 WHO/UNICEF grading of goitre Grade 0 = no visible or palpable thyroid Grade 1 = thyroid enlargement that is palpable but not visible when the neck is in the neutral position Grade 2 = thyroid enlargement that is both visible and palpable when the neck is in the neutral position Grade 3 = goitre visible at a considerable distance

SECTION 13 Endocrine disorders 2290 Of the many causes of goitre (Box 13.3.1.2), those associated with disturbances of thyroid function are considered later. The remainder can be classified broadly as endemic and sporadic nontoxic goitres. Endemic goitre Prevalence Goitre is said to be endemic when the prevalence exceeds 10% in children aged 6 to 12 years, although this figure is arbitrary and it has recently been suggested that a prevalence of more than 5% should be used. Over 200 million people are affected worldwide, especially in the Himalayas, Andes, and parts of Africa, although Eastern and Southern Europe are also involved. Aetiology The main cause is iodine deficiency, with goitre prevalence ex- ceeding 30% in areas with very low iodine intakes (<30 μg/day). However, endemic goitre is not exclusively related to iodine defi- ciency. Naturally occurring goitrogens, such as those in vegetables of the cabbage family and in cassava and millet, exaggerate the effects of iodine deficiency by the action of thiocyanates and fla- vonoids on thyroid hormone synthesis. Where selenium and iodine deficiency coincide, thyroid cell destruction and gland fibrosis min- imize goitre formation. In Japan, endemic goitre actually results from iodine excess, as well as goitrogens in seaweed, and in Kentucky, chemically polluted water from the coal industry is goitrogenic. Clinical presentation Diffuse goitre is more frequent in girls, and gradually becomes nodular with age and increasing iodine deficiency. Endemic goitres can be massive but give few compressive symptoms. In areas of mar- ginal iodine deficiency, such as Belgium, a modest goitre only ap- pears when demands on thyroidal iodide metabolism are increased during puberty or in pregnancy. The major impact of endemic goitre and iodine deficiency on health is the association with endemic cretinism. Two forms of cret- inism can be delineated in separate geographical areas, but there is considerable overlap. First, when maternal iodine intake is severely reduced causing hypothyroidism there is reduced placental transfer of T4 to the fetus, resulting in a profound neurological deficit in the infant, with mental deficiency, deafness, speech defects, and spastic gait. Second, hypothyroidism in the infant after birth produces the typical features of cretinism, in particular stunted growth. The thy- roid in such patients may be enlarged or atrophic and it is clear from field studies that iodine deficiency alone cannot account for the multiple forms of endemic cretinism. Management Iodine supplementation is perhaps the simplest and cheapest of all remedies and it prevents a condition that has devastating con- sequences; it is sobering that iodine deficiency still persists. There are few complications from iodine

supplementation, although thyrotoxicosis may result in a variable proportion of individuals (the Jod–Basedow phenomenon) some of whom have avoided this previously through lack of sufficient iodine. Political, social, and economic inertia are at the heart of continuing iodine defi- ciency. Effective programmes are best targeted at children and women intending pregnancy. Iodization of salt or bread is widely used in developed countries, but intramuscular or oral iodized oil, as a single annual dose, or iodination of drinking water is preferable in areas where distribution of iodized foodstuffs is a problem. Sporadic goitre Prevalence Goitre occurs in around 5% of the iodine-sufficient population and is four times more common in women. However, the preva- lence varies with area and generally declines with age; over 60% of goitres found in adolescents regress over the next 20 years. The character also changes over time, from a diffuse (sometimes called simple) goitre to a multinodular goitre. The presentation of single thyroid nodules is dealt with in Chapter 13.3.2, but it is worth mentioning here that solitary thyroid nodules increase in frequency with age. Aetiology The aetiology of sporadic goitre is largely unknown. Unidentified goitrogens may be responsible in a few patients, and in others mild iodine deficiency in infancy may initiate goitrogenesis which persists despite a subsequently normal iodine intake. A large proportion are probably the result of mild defects in hormone synthesis; compensatory growth ensures normal thy- roid function and current tests cannot identify the nature of the defect. Familial clustering of sporadic goitre supports this idea. Although TSH is the most obvious thyroid growth factor, TSH levels by definition are normal in sporadic goitre, which may therefore be the result of other autocrine and paracrine growth Box 13.3.1.2 Causes of goitre Endemic goitre Iodine deficiency Goitrogens, including drugs with an antithyroid action Sporadic goitre Simple, nontoxic goitre: diffuse or multinodular (colloid goitre) Toxic multinodular goitre Hashimoto’s thyroiditis Graves’ disease Destructive thyroiditis Postpartum thyroiditis Silent thyroiditis Subacute thyroiditis Amiodarone Genetic disorders Dyshormonogenesis Thyroid hormone resistance syndrome McCune–Albright syndrome TSH receptor mutation Infiltration Riedel’s thyroiditis Amyloidosis Sarcoidosis Secondary TSH-secreting pituitary tumour Excessive stimulation from human chorionic gonadotropin in pregnancy or choriocarcinoma

 factors (e.g. insulin-like growth factor-1, epidermal growth factor, fibroblast growth factor). Progression to a multinodular goitre occurs when unencapsulated nodules form in a long-standing diffuse goitre. These nodules con- tain colloid-rich polyclonal follicles and are usually distinct from ad- enomas, which are encapsulated and derived from a single thyroid follicular cell with a somatic mutation conferring growth advan- tage. However, some goitres contain both nodules and adenomas, suggesting a spectrum of pathological changes. Because thyroid follicular cells are heterogeneous, nodules generally develop with varying degrees of function, giving rise to ‘hot’ and ‘cold’ areas on scintiscanning with radio-iodine. Some nodules develop autonomy and may eventually cause hyperthyroidism, completing the evolu- tion from nontoxic to toxic multinodular goitre (see next). Other nodules undergo degeneration with haemorrhage, fibrosis, and cyst formation.
Clinical presentation Patients usually seek attention because of the appearance of the neck or a sensation of pressure or discomfort. Equally, they may be unaware of a long-standing small goitre which is noticed on exam- ination. Careful palpation is sufficient to distinguish true goitre, which moves on swallowing, from a prominent pad of fat over the front of the neck. Very large goitres can cause dysphagia or even stridor when the trachea is compressed, but these symptoms are uncommon. Venous compression at the thoracic inlet is even rarer; this sign is exacerbated by asking the patient to raise his/her arms (Pemberton’s sign). Pain in the thyroid, which radiates to

the jaw, is uncommon and suggests either destructive thyroiditis (see next) or haemorrhage into a cyst in a multinodular goitre. In the latter, the pain is usually unilateral, acute, and associated with a rapid change in thyroid size; symptoms resolve spontaneously in a few days. Investigations Thyroid function should be assessed by checking TSH levels, and then free T3 and T4 levels if the TSH is abnormal to rule out goitre associated with thyroid dysfunction. The presence of thyroid peroxidase antibodies is also useful as a marker of an underlying auto- immune thyroiditis, which occurs in 10 to 20% of multinodular goitres. The use of imaging varies between centres. Ultrasound is useful in determining thyroid size and nodularity accurately and may reassure an anxious patient that the thyroid is not enlarging. Thyroidal uptake of radioisotopes (especially 99Tcm pertechnetate) is indicated if destructive thyroiditis is suspected as a cause of goitre. Otherwise, the major role for imaging is to ensure there is no tra- cheal compression or intrathoracic/retrosternal component in a pa- tient with suggestive symptoms, and a CT scan is then the preferred investigation (Fig. 13.3.1.5). Treatment Most patients with euthyroid sporadic goitre do not require treat- ment. Neck discomfort or cosmetic concerns may prompt inter- vention but it is necessary to take a careful history to ensure that discomfort or difficulty swallowing is indeed caused by the goitre. T4, given at doses to maintain slightly suppressed TSH levels (0.1–0.3 mU/litre), leads to a reduction in goitre size in up to 60% of patients but is unlikely to have any effect on a very nodular goitre or when the TSH level is already low (so-called subclinical hyperthyroidism, discussed next). This treatment is now much less used than previously as there are concerns about the long-term ef- fects of suppressive doses of T4 on the heart and skeleton, and treat- ment must be continued long-term to maintain any improvement. Radio-iodine, by contrast, is increasingly being given to reduce goitre size. Doses of 131I range from 600 to 3400 MBq (hospitalization is required for doses >800 MBq). Recombinant TSH administration may allow lower 131I doses to be given, increasing the potential for outpatient treatment. Goitre size is usually reduced by more than 50% at 2 years, and most of the improvement occurs within 2 to 3 months. Long-term follow-up data are not yet available, although hypothyroidism certainly occurs in 20 to 40% by 5 years. Tracheal compression by a goitre can be treated with 131I despite theoretical concerns over acute worsening due to a radiation thyroiditis. Surgery is used in other centres and is particularly indicated for stridor, severe tracheal compression, or retrosternal goitres and if there is any suspicion of malignancy. Thyroidectomy is the most ef- fective treatment available for goitre, but there may be a recurrence in around 20% of patients within 10 years and is not avoidable by giving T4 replacement. Complications, including recurrent laryn- geal nerve damage, hypoparathyroidism, and hypothyroidism, are more likely with the biggest goitres, near-total thyroidectomy, and reoperation. Hypothyroidism Impaired production of thyroid hormones is usually due to a pri- mary abnormality of thyroid gland or iodine deficiency; occasion- ally it is secondary to pituitary or hypothalamic disorders, dealt with in Chapters 13.2.1 and 13.2.2. The onset of primary hypothyroidism is gradual and may be detected when the TSH is elevated (to com- pensate for impaired thyroid output) but the free thyroid hormone levels are normal. This state is subclinical hypothyroidism (diag- nosis depends on ensuring that the TSH elevation is not due to a sick euthyroid syndrome by repeat measurement after 3 months). As thyroid damage continues, TSH levels rise further but free T4 levels fall. When serum TSH concentrations rise above 10 mU/litre, symp- toms usually become apparent, and the patient is said to have overt or clinical hypothyroidism. Aetiology The causes of hypothyroidism are listed in Box 13.3.1.3. The com-monest cause worldwide is iodine deficiency, discussed earlier. In iodine-sufficient areas, autoimmune hypothyroidism and thyroid damage after radio-iodine or surgical treatment for hyperthyroidism are the major causes. Epidemiology The prevalence of overt hypothyroidism in

white populations is around 2% in women and 0.2% in men, with a mean age of 60 at diagnosis: rates are lower among black and Asian/Pacific Islander populations. Subclinical hypothyroidism is even more common (6–8% of women and 3% of men). Around 4% of these individuals progress to overt hypothyroidism annually if thyroid peroxidase antibodies accompany the elevated TSH. Half this number progress in the absence of thyroid peroxidase antibodies. Focal lympho- cytic infiltration of thyroid associated with thyroid autoantibody

SECTION 13 Endocrine disorders 2292 positivity occurs in up to 15% of healthy women and 2% of men without an elevated TSH level, representing the earliest manifest- ation of thyroid autoimmunity; 2% of these people progress to overt hypothyroidism annually. Congenital hypothyroidism occurs in about 1 in 3000 births and this high frequency has led to the widespread introduction of neonatal screening; recent increases in prevalence are likely to be due to the inclusion of milder cases. Pathogenesis Autoimmune hypothyroidism is primarily the result of auto reactive T-cell-mediated cytotoxicity directed against thyroid follicular cells. Cytokines derived from the locally infiltrating T cells, macrophages, and dendritic cells impair thyroid cell func- tion and enhance T-cell-mediated cytotoxicity. The role of thyroid autoantibodies in thyroid cell destruction is unclear, but thyroid peroxidase antibodies fix complement and may cause secondary damage. In 10 to 20% of patients, antibodies which block the TSH receptor are partially or wholly responsible for hypothyroidism, and transplacental passage of these antibodies (but not thyroid peroxidase antibodies) occasionally causes transient neonatal hypothyroidism. Genetic and environmental factors are in- volved in the aetiology but, as with most autoimmune disorders, the complex interaction of these factors has so far prevented a full understanding. Polymorphisms in HLA-DR, CTLA4 and other immunoregulatory genes are associated with autoimmune hypothyroidism, and a high iodine intake may be an important environmental factor in some cases. Congenital hypothyroidism is caused by thyroid aplasia or hypoplasia in 60% of cases and in 30% there is an ectopic gland. Mutations in thyroid-specific transcription factors have been found in some of these cases. In the remaining 10%, hypothyroidism is due to dyshormonogenesis (see Box 13.3.1.3). Clinical features The cardinal features in adults with hypothyroidism are shown in Box 13.3.1.4. However, the ready availability of reliable screening tests for hypothyroidism, especially TSH assays, has led to the recog- nition of many patients in whom there are only vague or nonspecific symptoms, such as tiredness, weight gain, and poor concentration. The differential diagnosis is accordingly vast, but the high frequency of hypothyroidism should prompt its exclusion when any suggestive features are present, particular in middle-aged women with chronic fatigue or depression. Autoimmune hypothyroidism may present with a goitre (Hashimoto’s thyroiditis) or without (atrophic thyroiditis or primary myxoedema); these entities represent the ends of a spectrum of pro- gressive thyroid destruction. When present, the goitre is of variable size but is often hard and irregular, sometimes giving rise to a sus- picion of malignancy, which then requires exclusion by fine needle aspiration biopsy. Primary lymphoma of the thyroid is a rare but important association (Chapter 13.3.2). Thyroid pain due to auto- immune thyroiditis is also a rare complication. Patients may notice a Hashimoto goitre before any thyroid dysfunction has developed and annual follow-up is then needed. The most dramatic presentation of hypothyroidism is myxoe- dema coma, which is fortunately rare. In addition to the usual fea- tures, there is hypothermia (as low as 23 °C) and coma, sometimes with seizures. Mortality is 30–50% even with intensive treatment. Patients are typically older and either previously undiagnosed or poorly compliant with medication. There is generally an additional precipitant, such as respiratory depression due to drugs, chest infec- tion, heart failure, stroke, blood loss, or exposure to cold. Box

13.3.1.3 Causes of hypothyroidism Primary Iodine deficiency Autoimmune hypothyroidism Hashimoto’s thyroiditis Primary myxoedema Iatrogenic 131I treatment Subtotal or total thyroidectomy External irradiation for lymphoma or cancer involving the neck Drugs Iodine-containing contrast media Amiodarone Lithium Antithyroid drugs p-Aminosalicylic acid Interferon-α and other cytokines Aminoglutethimide Tyrosine kinase inhibitors (e.g. sunitinib) Congenital hypothyroidism Absent or ectopic thyroid gland Dyshormonogenesisa TSH receptor mutation Destructive thyroiditis Postpartum thyroiditis Silent thyroiditis Subacute thyroiditis Infiltrative disorders Amyloidosis Sarcoidosis Haemochromatosis Scleroderma Cystinosis Riedel’s thyroiditis Consumptive hypothyroidism due to increased type 3 deiodinase ex- pression (e.g. infantile haemangiomas) Secondary Hypopituitarism Pituitary tumours Trauma (head injury) Pituitary surgery or irradiation Infiltrative disorders Infarction Isolated TSH deficiency or inactivity Hypothalamic disease Idiopathic Drugs Bexarotene a The following types of dyshormonogenesis are due to mutations in the genes encoding the proteins given in parentheses: iodide transport defect (Na+/I− symporter), defective iodide organification (thyroid peroxidase, dual oxidase 2, pendrin), loss of iodide reutilization (dehalogenase), deficient thyroid hormone synthesis (thyroglobulin). Defects in monoiodotyrosine coupling also occur but are, so far, poorly characterized.

13.3.1 The thyroid gland and disorders of thyroid function 2293 Autoimmune hypothyroidism is frequently associated with other autoimmune conditions. In the type 2 autoimmune polyglandular syndrome, autoimmune thyroid disease (hypothyroidism or Graves’ disease) is associated with type 1 diabetes and/or Addison’s disease. This syndrome is autosomal dominant with variable penetrance. In the rare, autosomal recessive type 1 autoimmune polyglandular syn- drome (chronic mucocutaneous candidiasis, Addison’s disease, and hypoparathyroidism), autoimmune hypothyroidism is found in 5 to 10% of patients. Other commoner associations include pernicious anaemia, vitiligo, and alopecia areata, and there is a significant ex- cess of autoimmune hypothyroidism in coeliac disease, dermatitis herpetiformis, chronic active hepatitis, premature ovarian failure, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren’s syndrome. Breast cancer patients and individuals with Down’s and Turner’s syndromes have a higher than expected frequency of thy- roid autoimmunity. Around 5% of patients with thyroid-associated ophthalmopathy, discussed later in this chapter, have autoimmune hypothyroidism and 15% of patients with Graves’ disease success- fully treated with antithyroid drugs develop hypothyroidism 10 to 20 years later. This relationship with Graves’ disease is further em- phasized by rare patients who oscillate between hyperthyroidism and hypothyroidism over a period of months. The likely explanation is fluctuation in the relative levels of TSH receptor stimulating and blocking antibodies, but the cause of these changes is unknown. Juvenile hypothyroidism is uncommon. The features of adult hypothyroidism (Box 13.3.1.4) may be present, but the diagnosis is usually suggested by retarded growth and dentition, and an infantile face. Myopathy with muscle enlargement is common. Puberty is usually delayed, although sometimes it is precocious. Congenital hypothyroidism is typically unrecognizable at birth but, if not iden- tified by screening, gives rise to prolonged jaundice, failure to thrive, impaired growth, feeding difficulties, constipation, and hypotonia. Left untreated, even for a few weeks after birth, there is permanent neurological damage resulting in intellectual impairment. Pathology In Hashimoto’s thyroiditis there is a prominent diffuse and focal lymphocytic infiltrate with germinal centre formation. The thyroid follicles show varying degrees of destruction and little or no colloid. The remaining thyroid follicular cells have an increased number of mitochondria, giving rise to oxyphil metaplasia (Askanazy or

Hürthle cells). There is a variable degree of fibrosis. In atrophic thyroiditis, fibrosis is the most prominent feature, with a less ob- vious lymphocytic infiltrate than in Hashimoto's thyroiditis. Thyroid follicles are usually sparse, reflecting the later stage at which this form of autoimmune hypothyroidism is diagnosed. Whether there is a natural progression from Hashimoto's to atrophic thyroiditis is unclear, although the goitre usually decreases with T4 replacement.

Laboratory diagnosis Measuring serum TSH is the first step in diagnosing hypothyroidism, with the important caveat that this approach will miss most cases of secondary hypothyroidism in which the serum TSH measured by immunoassays may be low, normal, or even slightly raised, due to the secretion of bioinactive forms of the hormone. If secondary hypothyroidism is suspected, for instance in the follow-up of a pa- tient with treated pituitary disease, it is essential to check the free T4 level. The TSH is elevated in other settings besides primary overt hypothyroidism (Table 13.3.1.2). It is therefore important to confirm the diagnosis by measuring the free T4 in all samples in which the TSH is elevated. Measurement of free T3 adds nothing to the diagnosis, es- pecially as values may be within the reference range in a quarter of hypothyroid patients due to extrathyroidal conversion of T4. If myxoedema coma is expected, it is essential that treatment is initiated immediately without awaiting confirmation of the diagnosis. These patients often have dilutional hyponatraemia, hypoglycaemia, and electrocardiography changes (low voltage, prolonged QT interval, flat or inverted T waves, and heart block). Other nonspecific features which may be found in any patient with hypothyroidism are elevation in serum liver and muscle enzymes (raised creatine phosphokinase concentrations particularly may cause unnecessary concern), raised cholesterol, and anaemia. The anaemia is usually normocytic or macrocytic, but microcytosis oc- curs when hypothyroidism is accompanied by menorrhagia. The aetiology is usually easily established. In the absence of a his- tory of treated hyperthyroidism or iodine exposure, most juvenile or adult onset primary hypothyroidism in iodine-sufficient countries is due to autoimmune hypothyroidism. Transient hypothyroidism due to destructive thyroiditis is considered later. The diagnosis of auto- immune hypothyroidism is confirmed by the presence of thyroid peroxidase antibodies, usually at high levels, although occasionally these antibodies are absent. Cytological diagnosis of Hashimoto's thyroiditis is possible using fine needle aspiration biopsy, but is only necessary if there is uncertainty over the cause of a nodular goitre. Once congenital hypothyroidism is diagnosed by routine testing after birth, it is usual to initiate T4 immediately. The aetiology can be Box 13.3.1.4 Clinical features of hypothyroidism Symptoms Tiredness, weakness Dry skin Altered facial appearance Feeling cold Hair dry, unmanageable, and thinning Poor memory and concentration Constipation Weight gain with poor appetite Dyspnoea Hoarse voice Menorrhagia (later, oligomenorrhoea or amenorrhoea), decreased libido Paraesthesias Deafness Signs Dry coarse skin Cool peripheries Puffy face, hands, and feet Yellow skin due to carotene accumulation Diffuse alopecia Bradycardia Peripheral oedema Slow-relaxing tendon reflexes Carpal tunnel syndrome Serous cavity effusions Galactorrhoea (raised prolactin) Enlarged salivary glands Rarely: ataxia, dementia, psychosis, coma

 established by scintiscanning and/or ultrasound: if the exact cause is not established at birth, treatment can be stopped without neuro- logical consequences at age 3 to 4 years to repeat imaging and establish whether life-long T4 replacement is necessary. Dyshormonogenesis, suspected when there is detectable thyroid tissue and a family his- tory, requires specialized investigation to establish the diagnosis and increasingly this is possible by direct analysis of gene mutations. The commonest of these defects is Pendred's syndrome in which there are mutations in the pendrin gene (SLC26A4) encoding a chloride/ iodide transporter present

in the thyroid and cochlea, leading to goitre, mild hypothyroidism, and deafness. The thyroid abnormal- ities usually appear in the second or third decade, rather than at birth. The diagnosis can be made easily by the perchlorate discharge test, which shows an excessive decline of radioactivity in the thyroid when potassium perchlorate is given 2 to 3 h after allowing the thy- roid to take up a tracer dose of radio-iodine. Treatment In adult patients without heart disease and below the age of 65, treat- ment can begin with the estimated replacement dose of T4. If there is no remaining thyroid tissue (indicated by a very high TSH level and very low or undetectable free T4), the daily replacement dose is 1.6 μg T4/kg body weight, which is around 100 to 150 μg/day. In practice, the typical starting dose is 50 to 100 μg T4 daily, the lower dose being re- served for patients with mild to moderate biochemical abnormalities and those with significant cardiac disease. Dosage changes should be based on TSH levels measured 2 to 3 months after starting treatment, the main goal of treatment being to normalize the TSH. A similar period is required to assess the effect of any change to the dosage, made as 25 or 50 μg increments or decrements depending on the degree of abnormality of the TSH. Treatment is usually straightfor- ward, although if there is only partial thyroid failure when treatment is begun, the dose of T4 may require adjustment over many months. Once on a full replacement dose, TSH levels should be checked an- nually. Fluctuating or elevated TSH levels in a previously stable patient, or T4 requirements in excess of 200 μg/day, usually indicate adher- ence problems. It is important to rule out malabsorption, including coeliac disease, Helicobacter pylori infection, excessive soya intake, or interactions with drugs: cholestyramine, ferrous sulphate, lovastatin, aluminium hydroxide, rifampicin, amiodarone, carbamazepine, and phenytoin all alter the absorption or clearance of T4. A common cause for poor adherence is worsening angina. Optimization of antianginal treatment is then required, although some patients may simply prove intolerant of full T4 replacement if their coronary artery disease is ex- tensive and irremediable. It is important to remind poorly adherent patients that, because of the long half-life of T4, missed tablets should always be taken and that this is safe. It should be emphasized that, in the absence of coronary artery disease, T4 has no adverse effects when given at doses that return TSH levels to normal. In older patients or in individuals with heart disease, the usual starting dose is 25 μg T4 daily (or on alternate days when there is severe angina), although in the elderly person without any car- diac comorbidity such caution is probably unnecessary. Dosage should be increased slowly with increments of 12.5 to 25 μg T4. Proportionately higher doses of T4 are needed during the first year of life than in adults, and the starting daily dose of T4 for con- genital hypothyroidism is 8–15 μg/kg body weight. There is a con- tinuing debate on the benefit of T4 in subclinical hypothyroidism. It is reasonable to commence T4 when (i) the TSH levels are above 10 mU/litre or (ii) above 5 mU/litre prior to and during pregnancy. When TSH levels are below 10 mU/litre, routine treatment is not indicated, but this could be considered if patients have symptoms suggestive of hypothyroidism or positive TPO antibodies. Modest improvements in mental function and lipid levels occur when T4 is given to some patients with subclinical hypothyroidism, but con- clusive long-term studies on the benefits of treatment have not been conducted. All patients with subclinical hypothyroidism or positive thyroid peroxidase antibodies should be offered annual testing for the development of overt hypothyroidism if T4 is not given. Another problem is posed by the occasional patient with overt hypothyroidism who continues to feel unwell or who fails to lose weight after the TSH is normalized with T4 replacement. It can take around 3 months from achieving full replacement for all symptoms to disappear, and weight gained during hypothyroidism will gener- ally only be lost by following an appropriate diet. It is sensible to en- sure that the TSH level is in the lower half of the reference range and sometimes a small increment of T4 can achieve this, improving symp- toms

but not suppressing the TSH. Higher doses of T4 that suppress the TSH should be avoided, as there is an increased risk of atrial fibril- lation due to subclinical thyrotoxicosis. The other recognized adverse effect of excessive T4 is a decrease in bone mineral density, particu- larly in postmenopausal women who have previously had hyperthy- roidism and therefore already have a low skeletal mass. Changes in bone mineral density are modest but an increase in fracture rate has been reported as a result of T4 given at supraphysiological doses in those aged over 65. There has some recent interest in the concept that thyroid hormone replacement should consist of both T4 and T3, based on the observation that deiodinase activity varies between tis- sues, suggesting that in some organs the level of the active thyroid hormone, T3, is insufficient when only T4 is given. The short half-life of current T3 preparations makes T3 alone unsuitable for replacement and there is no evidence of any consistent benefit from trials of com- bined T4 and T3 treatment. Treatment of myxoedema coma is a medical emergency (see Box 13.3.1.5). Prognosis T4 treatment is usually life-long and, properly taken, restores normal health and lifespan. Occasional patients may discontinue T4 and re- main euthyroid. Errors in initial diagnosis account for some of these; in others, a spontaneous decline in TSH receptor blocking antibody levels may be responsible. There is no easy means of ascertaining whether a patient continues to need T4, short of stopping it and measuring the TSH 6 weeks later. Because remission is uncommon and of uncertain duration, few endocrinologists attempt T4 with- drawal once started. Special problems in pregnant women Untreated hypothyroidism impairs fertility and increases the risk of miscarriage. Children born to such mothers have varying degrees of intellectual impairment. It is therefore essential that T4 replacement is monitored closely in women with hypothyroidism who intend to become or who are pregnant. Ideally TSH and free T4 should be checked prior to conception, and then every 4 weeks once preg- nancy is confirmed up to mid-pregnancy. The requirement for T4 can increase by up to 50% during pregnancy but reverts to normal

 after delivery. Women can be advised to anticipate this by taking two extra doses of T4 each week as soon as pregnancy is confirmed. The TSH should be maintained below 2.5 mU/litre during the first tri- mester. There are no implications for breastfeeding. Areas of uncertainty or needing further research Although present combination regimens of T3 and T4 have shown no additional benefit compared to T4 alone, development of a sus- tained release preparation of T3 would be worth assessment. Because hypothyroidism is frequent, routine screening of certain groups or even the entire population has been advocated (Box 13.3.1.6), but the cost–benefit of setting up new screening programmes is unclear. If widely adopted, screening will turn up many individuals with subclinical hypothyroidism for whom the benefits of early treat- ment with T4 have not yet been fully established. Recent data show that there is an increased risk of miscarriage in thyroid peroxidase antibody-positive women who are euthyroid and this may be re- duced by T4 treatment, but more work is needed to confirm whether this is due to a subtle defect in thyroid hormone levels or a conse- quence of autoimmunity. Thyrotoxicosis Thyrotoxicosis is defined as the state produced by excessive thyroid hormone. Hyperthyroidism exists when thyrotoxicosis is caused by thyroid overactivity but there are several types of thyrotoxicosis that are not due to hyperthyroidism, the most obvious being ad- ministration of excessive T4. Aetiology The causes of thyrotoxicosis are shown in Box 13.3.1.7. Graves’ disease is responsible for 60 to 80% of cases and nodular thyroid disease (toxic multinodular goitre and toxic adenoma) accounts for most of the rest. Destructive thyrotoxicosis is dealt with in the next section. Epidemiology The prevalence of thyrotoxicosis in white people is 2 to 3% in women and 0.2 to 0.3% in men and higher still in black and Asian/Pacific Islander people. The

peak age of onset for Graves' disease is between 20 and 50 years of age, whereas toxic multinodular goitre occurs more often in later life. Box 13.3.1.5 Treatment of myxoedema coma • Thyroid hormone replacement — A single intravenous bolus of 200–400 μg T4; thereafter 50–100 μg T4 daily — Some centres add a supplementary bolus of T3 5–20 μg, followed by 2.5–10 μg T3 every 8 h, with lower doses in older people or those with heart disease • Supportive treatment — Ventilation usually required — Space blankets for hypothermia — Intravenous infusion of hypertonic saline or glucose as required — Parenteral hydrocortisone 50 mg every 6 h • Identify and treat underlying precipitant (including any cause of re- spiratory depression, infection, cardiac and renal failure, and myocar- dial infarction) • Broad-spectrum antibiotics if infection suspected Box 13.3.1.6 Indications for screening for hypothyroidism Established Congenital hypothyroidism Previous treatment for hyperthyroidism Previous neck irradiation (e.g. for lymphoma) Pituitary tumours, including follow-up after surgery or irradiation Treatment with lithium or amiodarone Subclinical hypothyroidism Worthwhile Antepartuma in type 1 diabetes Three months postpartum after a prior episode of postpartum thyroiditis Unexplained infertility Nonspecific symptoms in women over 40 years of age Refractory depression or bipolar affective disorder with rapid cycling Turner's syndrome Down's syndrome Autoimmune Addison's disease Uncertain Patients with a family history of thyroid autoimmunity Dementia or obesity without other evidence of thyroid disease Antepartum to detect unsuspected hypothyroidismb Breast cancer a Also measure thyroid peroxidase antibodies; screen euthyroid antibody- positive women 3 months postpartum for postpartum thyroiditis. b It is also uncertain whether all pregnant women should be checked for thy- roid peroxidase antibodies as predictors of postpartum thyroiditis. Box 13.3.1.7 Causes of thyrotoxicosis Primary hyperthyroidism Graves' disease Toxic multinodular goitre Toxic adenoma Drugs: iodine excess (Jod–Basedow phenomenon), lithium, amiodarone (type 1 amiodarone-induced thyrotoxicosis) Thyroid carcinoma or functioning metastases Activating mutation of the TSH receptor Activating mutation of the Gsα protein (McCune–Albright syndrome) Struma ovarii (ectopic thyroid tissue) Thyrotoxicosis without hyperthyroidism Ingestion of excess thyroid hormone (factitious thyrotoxicosis) Subacute thyroiditis Silent thyroiditis Other causes of thyroid destruction: amiodarone (type 2 amiodarone- induced thyrotoxicosis), 131I or external irradiation (acute effect), in- farction of an adenoma Secondary hyperthyroidism TSH-secreting pituitary tumour Chorionic gonadotropin-secreting tumours Gestational thyrotoxicosis Thyroid hormone resistance (usually euthyroid)

 Pathogenesis Graves' disease is caused by TSH receptor stimulating antibodies, clearly demonstrated by the occurrence of transient, neonatal thyro-toxicosis in babies born to mothers with Graves' disease whose antibody levels are high enough for transplacental transfer to affect the fetus. As with autoimmune hypothyroidism, genetic factors, including HLA-DR, CTLA4, and TSHR gene polymorphisms, are associated with the disease; the concordance rate in monozygotic twins is about 20% and much less in dizygotic twins. A high iodine intake, smoking, and stress have all been identified as environmental factors, but in many patients the genetic and environmental trig- gers remain elusive. Immune reconstitution after alemtuzumab and highly active antiretroviral therapy are associated with Graves' dis- ease. Smoking is a major risk factor for the development of thyroid- associated ophthalmopathy. These eye signs are due primarily to swelling of the extraocular muscles, the result of fibroblast activa-tion by cytokines released by infiltrating T cells and macrophages, leading to glycosaminoglycan accumulation, oedema, and fibrosis. The close correlation between ophthalmopathy and thyroid disease is best explained by a shared orbital and thyroid autoantigen (prob- ably the TSH receptor).

Toxic multinodular goitre evolves from a nontoxic sporadic goitre (see earlier) and is particularly likely when iodine intake increases, ei- ther gradually as a result of changes in the diet, or acutely when iodine- containing agents (amiodarone, some contrast media) are given. More than 50% of toxic adenomas are due to a somatic activating mutation in the genes encoding the TSH receptor or the associated Gsα protein, and a similar but unknown mechanism leading to constitutive activa- tion of a clone of thyroid cells must underlie the remainder. Clinical features The typical features of thyrotoxicosis from any cause are shown in Box 13.3.1.8, but their presence and severity depend on the duration of disease and the age of the patient. Occasionally there are para- doxical manifestations, such as the weight gain that can occur in up to 10% of patients when the increase in appetite exceeds the effects of increased metabolism, and apathetic or masked thyrotoxicosis in older patients which mimics depression. The most dramatic but rare presentation is thyrotoxic crisis or storm, with a mortality rate of 10 to 30% even with treatment. Patients typically are previously undiagnosed or partially treated and have an acute exacerbation of thyrotoxicosis precipitated by acute illness (infection, stroke, dia- betic ketoacidosis) or trauma, especially directly to the thyroid (sur- gery or radio-iodine). Exact diagnostic criteria for thyrotoxic crisis are not agreed and its frequency is sometimes exaggerated. There is marked fever (>38.5 °C), delirium or coma, seizures, vomiting, diar- rhoea, and jaundice, with death being caused by arrhythmias, heart failure, or hyperthermia. The differential diagnosis of thyrotoxicosis includes any cause of weight loss, anxiety, and phaeochromocytoma, but simple biochem- ical testing can readily distinguish thyrotoxicosis from these con- ditions. Once the diagnosis of thyrotoxicosis is made, it is essential to determine the cause (see Box 13.3.1.7), as this determines treat- ment. Graves' disease is usually clinically distinctive; there is a small to moderate, diffuse, firm goitre and around one-half of these pa- tients have signs of thyroid-associated ophthalmopathy (Fig. 13.3.1.6 and Table 13.3.1.3). There may be evidence of another autoimmune disorder, in the patient or his/her family, with the same associ- ations as autoimmune hypothyroidism just described. Less than 1% of patients have pretibial myxoedema, which is better called thy- roid dermopathy as it can occur anywhere, especially after trauma Box 13.3.1.8 Clinical features of thyrotoxicosis of any cause Symptoms Hyperactivity, irritability, altered mood Heat intolerance, sweating Palpitations Fatigue, weakness Weight loss with increased appetite Diarrhoea, steatorrhoea Polyuria Oligomenorrhoea, amenorrhoea, loss of libido Signs Sinus tachycardia, atrial fibrillation in older patients Fine tremor Warm, moist skin Goitre Palmar erythema, onycholysis, pruritus, urticaria, diffuse pigmentation Diffuse alopecia Muscle weakness and wasting, proximal myopathy, hyperreflexia Eyelid retraction or lag Gynaecomastia Rarely: chorea, periodic paralysis (usually in Asian men), psychosis, im- paired consciousness (a) (b) Fig. 13.3.1.6 Thyroid-associated ophthalmopathy. (a) Upper lid retraction, periorbital oedema, and scleral injection. (b) Chemosis (conjunctival oedema) and proptosis.

 (Fig. 13.3.1.7). These patients almost always have moderate-to-severe ophthalmopathy and 10 to 20% have clubbing (thyroid acropachy). Thyroid dermopathy most commonly occurs as nonpitting plaques with a pink or purple colour but no inflammatory signs. Nodular and generalized forms, the latter mimicking elephantiasis, also occur. Hyperplasia of lymphoid tissue, including splenomegaly and thymic enlargement, is rarely found in Graves' disease. The absence of these features of Graves' disease and the pres- ence of a multinodular goitre strongly suggest toxic multinodular goitre, although nodular thyroid disease is so common that occa- sional patients with Graves' disease may cause confusion when their thyrotoxicosis arises in a pre-existing multinodular gland. In toxic adenoma,

the solitary thyroid nodule is usually readily palpable. Other, rare causes of thyrotoxicosis can usually be easily identified from the history and biochemical investigations. Pathology In Graves' disease, there is thyroid hypertrophy and hyperplasia. The follicles show considerable folding, contain little colloid, and are composed of tall columnar cells. Gland vascularity increases. There is a focal and diffuse lymphocytic infiltrate and lymphoid hyper- plasia may occur in the lymph nodes, spleen, and thymus. These changes are all reversed by antithyroid drugs. Toxic multinodular goitre comprises a mixture of areas of follicular hyperplasia and nodules filled with colloid. There is a variable degree of fibrosis, haemorrhage, and calcification. Toxic adenomas are encapsulated and cellular, sometimes with little evidence of follicle formation, and occasionally containing unusual cell forms suggesting malignant change. However, capsular invasion is absent and this is the cardinal feature which distinguishes a follicular adenoma from carcinoma. Laboratory diagnosis Measuring the serum TSH is the simplest way to exclude primary thyrotoxicosis. A normal or slightly raised TSH level can rarely be associated with secondary hyperthyroidism in the case of a TSH- secreting pituitary adenoma. A low TSH level is not always the re- sult of thyrotoxicosis (see Table 13.3.1.2), therefore the diagnosis of thyrotoxicosis must be confirmed by measuring thyroid hor- mone levels. Free hormone assays are preferable to those for total hormone, to eliminate binding protein effects (see Table 13.3.1.1). Measuring free T4 alone is adequate in most cases of thyrotoxicosis, which can be confirmed by the presence of a suppressed TSH and elevated free T4 level. However, in up to 5% of patients, only free T3 levels are elevated (T3 toxicosis), especially during the earliest phase of the disorder. Therefore, if both free T3 and T4 are not measured routinely by a laboratory, it is essential to request free T3 analysis in any sample showing a suppressed TSH but normal free T4 level. Rarely, the free T4 is elevated but the free T3 is normal. This usu- ally arises when Graves' disease or nodular thyroid disease is pre- cipitated by the administration of excess iodine (the Jod–Basedow phenomenon). TSH receptor antibodies can be measured by methods which test the ability of such antibodies to inhibit the binding of TSH to its re- ceptor, thus called TSH binding inhibiting immunoglobulin (TBII) assays. The presence of these antibodies in a thyrotoxic patient proves the existence of Graves' disease; TBIIs are also detectable in patients with hypothyroidism caused by TSH receptor blocking anti- bodies. Thyroid peroxidase antibodies are present in around 75% of patients with Graves' disease. In cases of diagnostic uncertainty or when TBII assays are not available, a thyroid scintiscan will dem- onstrate a diffuse goitre with high isotope intake in Graves' disease and reveal nodular thyroid disease, as well as ectopic thyroid tissue in the extremely rare struma ovarii. In destructive and factitious

Table 13.3.1.3 Clinical features of thyroid-associated ophthalmopathy Signs and symptoms Assessment Approximate frequencya (%) Lid lag, lid retraction Measure lid fissure width 50–60 Grittiness, discomfort, excessive tearing, retrobulbar pain, periorbital oedema Self-assessment score by patient; activity score by clinician 40 Proptosis Exophthalmometry or CT/MRI-based measurement 20 Extraocular muscle dysfunction (typically causing diplopia looking up and out) Hess chart or similar; CT/MRI scan to detect muscle size 10 Corneal involvement, causing exposure keratitis Rose bengal or fluorescein staining <5 Loss of sight due to optic nerve compression Visual acuity and fields, colour vision; CT/MRI scan <1 a In patients with Graves' disease. Patients often have multiple signs and in 5–10% of them signs are unilateral. Fig. 13.3.1.7 Thyroid dermopathy (pretibial myxoedema) affecting the lateral aspect of the shin and the dorsum of the foot; the patient also had thyroid acropachy.

 thyrotoxicosis, the thyroid scan shows virtually no isotope uptake and the diagnosis of factitious thyrotoxicosis can be confirmed by measuring serum

thyroglobulin levels, which are suppressed in con- trast to the raised levels in all other causes of thyrotoxicosis. When a TSH-secreting pituitary adenoma is suggested biochemically, the diagnosis is made by demonstrating both an elevated level of the α- subunit common to glycoprotein hormones including TSH and a pi- tuitary tumour on CT, or preferably MRI. Prolonged thyrotoxicosis can cause several nonspecific biochemical abnormalities, especially abnormal liver function tests, hypercalciuria, and elevated serum levels of ferritin. Less commonly, serum calcium and phosphate may be raised, glucose intolerance or diabetes may occur, and rarely there may be a microcytic anaemia or thrombocytopenia. Treatment Definitive diagnosis is the most important determinant of treat- ment selection for thyrotoxicosis. In particular, antithyroid drugs only achieve a cure in Graves' disease. When due to a subacute or silent thyroiditis, discussed next, spontaneous resolution of thyro- toxicosis is expected and symptomatic treatment with β-blockers such as propranolol, 20 to 80 mg three times daily, is indicated. Although β-blockers will rapidly alleviate symptoms in all types of hyperthyroidism, definitive treatment is also necessary, and when euthyroidism is restored β-blockers can be gradually withdrawn. There are three types of treatment for Graves' disease: antithyroid drugs, radio-iodine (131I), and surgery. Local policy and patient age dictate the order of their use. For young or middle-aged adults, antithyroid drugs are generally used initially in Europe and Japan, whereas radio-iodine is preferred in North America. Surgery is par- ticularly useful in patients with a large goitre, but is less frequently used in North America than elsewhere. The local availability of an experienced surgeon is crucial. There is more international agree- ment over the preferential use of radio-iodine for a recurrence after antithyroid drugs and as first-line treatment in older people with Graves' disease. The main antithyroid drugs are carbimazole, its active metabolite methimazole and propylthiouracil. All exert their principal action by inhibiting iodide oxidation and organification by thyroid peroxidase. Propylthiouracil additionally inhibits the activity of type 1 deiodinase, reducing T3 formation in many tissues, but this activity is only of clin- ical importance in very severe hyperthyroidism, and more frequent dosing is necessary with this drug. However, propylthiouracil may induce toxic effects on the liver, particularly in children, in whom it is contraindicated unless no other therapy is available. Two regimens are used to avoid antithyroid drug-induced hypothyroidism and achieve the best chance of remission, which oc- curs in 40 to 50% of patients and is inversely proportional to dietary iodine intake. The first method is to titrate the dose of antithyroid drug, giving carbimazole (or methimazole) 20–40 mg once daily, and then lowering the dose every 3 to 4 weeks or so, based on free T4 measure- ments, until a maintenance dose of 5 to 10 mg once daily is achieved. Equivalent starting and maintenance doses of propylthiouracil are 100 to 200 mg 2 to 3 times daily and 50 mg once or twice daily. Maximum remission rates occur after 18 to 24 months of treatment. The second regimen is to start with the same dose of antithyroid drug but then to add 100 μg T4 daily after 3 to 4 weeks when free T4 levels are usually becoming normal, rather than lowering the dose of drug. Thereafter the patient is maintained on 40 mg carbimazole or methimazole once daily (alternatively, 100 to 150 mg propylthiouracil three times daily) and T4, the latter being adjusted if necessary 4 weeks after starting to achieve normal free T4 levels. This block–replace regimen achieves the same remission rate as the titra- tion regimen within 6 months; continuation beyond this time is not necessary but can be used if a patient wishes to ensure euthyroidism for a particular period of time. Patients with the biggest goitres al- most always relapse after antithyroid drug treatment, and reduced cure rates have been described in those with detectable anti-TSH receptor antibodies at completion of a course of antithyroid drugs, in males and in younger patients. However not all studies are con- sistent and there are no reliable predictors of which other patients will relapse. It is therefore usual practice to follow patients closely (e.g. every 3 months)

in the first year after stopping treatment. Thereafter, an annual check of thyroid function is warranted as re- currence occurs in 10 to 20% 1 to 5 years after treatment, and auto- immune hypothyroidism may supervene in around 15%. The side effects of antithyroid drugs are shown in Box 13.3.1.9; most occur in the first 3 months of treatment and there is a moderate dose dependency. Substituting propylthiouracil for carbimazole or methimazole usually reverses the common side effects but further antithyroid drugs should be avoided if bone marrow disturbance de- velops. Lower doses of antithyroid drugs can be used in areas of low iodine intake. Lithium and potassium perchlorate have antithyroid actions and are alternatives when antithyroid drugs are not toler- ated, but these drugs are difficult to use, their side effects are serious, and they are given as a last resort. Anticoagulation with warfarin or newer anticoagulants should be considered in all patients with atrial fibrillation; only 50% of patients revert to sinus rhythm when euthyroidism is restored. In the remainder, attempts at cardioversion should be made, ideally when hyperthyroidism has been defini- tively treated with radio-iodine. Digoxin is useful to control atrial fibrillation acutely, but higher doses than normal are needed in the thyrotoxic state. Box 13.3.1.9 Side effects of antithyroid drugs Common Rash (typically maculopapular) Urticaria Arthralgia Fever, sometimes with malaise Rare Gastrointestinal symptoms Abnormal taste and smell Arthritis Agranulocytosisa Very rare Thrombocytopenia Aplastic anaemia Hepatitis and liver failure (propylthiouracil; avoid in children) Cholestasis (methimazole, carbimazole) Lupus-like syndrome, vasculitis Hypoglycaemia due to the insulin autoimmune syndrome a All patients must be warned in writing, before treatment commences, to seek immediate medical advice and stop medication if features suggesting agranulocytosis (fever, mouth ulcers, sore throat) develop.

13.3.1 The thyroid gland and disorders of thyroid function 2299 Accurate dosimetry for radio-iodine administration, based on uptake tests, has now largely fallen out of favour as the results have been little or no better than more empirical methods of dose calcula- tion. Typical 131I doses are 400 to 600 MBq in uncomplicated Graves' disease, but local policies vary, not least because less 131I is needed when iodine intake is low. Around 5 to 10% of patients treated this way require a second dose of 131I, while hypothyroidism rates are 40–60% after 1 year and 5 to 10% annually thereafter, depending on the dose of 131I administered. Close follow-up is needed in the first year after treatment, and an annual test of thyroid function there- after is recommended. Transient cytoplasmic, rather than nuclear, damage may cause hypothyroidism in the first 2 to 3 months after 131I treatment, which then resolves. It is usual to delay a second dose of 131I for 6 months after the first, as hyperthyroidism is controlled only slowly by radiation-induced nuclear damage. Antithyroid drugs or β-blockers are useful in the interim. Radio-iodine is contraindicated in pregnancy and breastfeeding. There are no teratogenic risks if men or women attempt concep- tion 6 months or more after treatment. Overall mortality rates from cancer are not increased by radio-iodine. There is a theoretical risk of an increase in the frequency and aggressiveness of thyroid cancer in children, which makes some endocrinologists reluctant to use 131I, but this view is gradually changing with increasing usage of radio-iodine in this group. Another concern is the precipitation of thyrotoxic crisis by 131I, but in practice this is extremely rare. To minimize the risk, antithyroid drugs can be given for up to 4 weeks or more prior to radio-iodine, particularly in older people who are at special risk, but should be stopped 3–5 days before radio-iodine administration. Thyroid-associated ophthalmopathy may appear or worsen after radio-iodine, especially if the patient smokes. A 6-week tapering course of prednisolone, starting with 0.2 mg/kg bw daily at the time of 131I administration, will prevent such worsening but an extended course of antithyroid drugs, with scrupulous maintenance of euthyroidism, may be preferable to radio-iodine in the case

of any severe and active ophthalmopathy until this becomes inactive. Surgery for Graves' disease consists of near-total or total thyroidectomy, and in the best centres achieves cure in more than 99% of patients but with a hypothyroidism rate similar to radio- iodine. Lower rates of hypothyroidism are inevitably associated with a higher recurrence rate. Patient preference is the main determinant of when surgical treatment is used to treat relapses after antithyroid drugs. Euthyroidism must be achieved with a further course of these drugs prior to surgery to avoid thyrotoxic crisis. Stable iodine (e.g. Lugol's iodine three drops three times daily) is often also given for 7 to 10 days prior to surgery to block hormone synthesis acutely. Specific complications of surgery include haemorrhage leading to laryngeal oedema, damage to the recurrent laryngeal nerves, and hypopara- thyroidism. These problems occur in less than 1% of patients in experienced hands and the last two problems are often transient. The management of thyroid-associated ophthalmopathy is sum- marized in Box 13.3.1.10. Symptoms and signs are usually mild to moderate, although still capable of creating considerable anxiety and disturbance of social function. Severe ophthalmopathy is fortu- nately rare (1–5% of cases) and requires specialist ophthalmological management. Signs usually stabilize 12 to 18 months after onset, and may improve thereafter in 30 to 50% of patients, although improve- ment is less likely for marked proptosis or diplopia. Corrective sur- gery for diplopia or cosmetic problems should only be considered in this stable phase. Thyroid dermopathy is usually left untreated and often resolves spontaneously. Meticulous control of thyroid func- tion and compression stockings may help. Surgical removal typically worsens the situation and, when troublesome, the best treatment is topical, high-potency corticosteroids. Toxic multinodular goitre is usually managed by radio-iodine treatment. Antithyroid drugs will control the hyperthyroidism but relapse is inevitable when the drugs are stopped. Long-term use of antithyroid drugs may be indicated in the very old or frail, or when incontinence poses an insuperable problem for the safe dis- posal of excreta after 131I. The therapeutic dose of 131I used for toxic multinodular goitre is generally higher than for Graves' disease (500–800 MBq) because there is uneven uptake of the isotope and usually a large goitre. Surgery is sometimes used as an alternative in patients with a retrosternal goitre or if there is any suspicion of a ma- lignancy. Toxic adenoma is also usually treated with 131I (500 MBq) and the rate of subsequent hypothyroidism is low because the func- tion of the normal thyroid tissue is suppressed at the time the patient is hyperthyroid and therefore receives little irradiation. When there is a large (>5 cm) nodule or in young patients, surgical excision is preferable and subsequent hypothyroidism is uncommon. Treatment of rare forms of primary hyperthyroidism is by surgical removal of the source of thyroid hormone or by radio-iodine. TSH-secreting pituitary adenomas causing secondary hyperthyroidism are usually treated by trans-sphenoidal surgery, with radiotherapy for any re- sidual tumour. Octreotide can also be used to lower TSH secretion. Thyrotoxic crisis is a medical emergency (Box 13.3.1.11). Prognosis Although spontaneous remission occurs in Graves' disease, its exact frequency is unknown and is unlikely to be more than 10%, with no guarantee of persistence. Remission does not occur in other types of hyperthyroidism. Mortality rates in untreated hyperthyroidism are also uncertain but are probably around 30%. Even after successful Box 13.3.1.10 Treatment of thyroid-associated ophthalmopathy Mild to moderate disease Reassurance and explanation Avoid hypothyroidism and hyperthyroidism Stop smoking Protect eyes from dust and bright light Artificial tears; simple eye ointment at night Sleep with more pillows or the head of the bed elevated Diuretics Stick-on prisms Severe disease (worsening diplopia, exposure keratitis, sight loss) Corticosteroids (e.g. pulse therapy with 500 mg methylprednisolone once weekly for 6 weeks, then 250 mg once weekly for 6 weeks) Radiotherapy (10 fractionated doses of 2 Gy) Immunosuppressive agents (azathioprine, ciclosporin A, rituximab)

Intravenous immunoglobulin Orbital decompression (usually transantral) Stable, burnt-out disease Prisms Surgery to extraocular muscle Cosmetic eyelid surgery

SECTION 13 Endocrine disorders 2300 treatment, there is a threefold increased risk of death from osteo- porotic fracture and a 1.3-fold increased risk of death from cardio- vascular disease and stroke. It is important that the patient with Graves' disease understands that the course of ophthalmopathy is sometimes independent of the thyroid disorder; eye signs appear one or more years before or after the onset of hyperthyroidism in one-quarter of patients and progression of the orbital disease can occur despite restoration of euthyroidism. Special problems in pregnant women Graves' disease during pregnancy is usually treated with propy lthiouracil, especially in the antenatal period and in the first trimester of pregnancy, as carbimazole and methimazole have been associated with fetal aplasia cutis and other fetal abnormalities. The block– replace regimen is contraindicated in pregnancy, as preferential pla- cental transfer of antithyroid drug will cause fetal hypothyroidism. Instead, the dose of antithyroid drug should be titrated to the lowest dose that results in maternal free T4 levels in the upper part of the reference range. TSH receptor stimulating antibodies decline during pregnancy and it is usually possible to stop treatment in the second or third trimester. Subtotal thyroidectomy can be performed in the second trimester for women intolerant of antithyroid drugs. Transplacental passage of TSH receptor antibodies causes fetal and neonatal thyrotoxicosis in 1 to 5% of mothers with Graves' disease, and can be predicted by demonstrating a high level of these antibodies in the maternal circulation at 20 weeks of gesta- tion. Poor intrauterine growth and a high fetal heart rate also sug- gest this diagnosis. Fetal thyrotoxicosis is treated by giving the mother antithyroid drugs and the neonate requires treatment for 1 to 3 months after delivery. Failure to treat intrauterine and neo- natal thyrotoxicosis causes low birth weight, premature closure of the sutures, and intellectual impairment. Breastfeeding is safe with low doses of antithyroid drugs, but when high doses are needed (e.g. 20 mg or more carbimazole daily) thyroid function should be checked monthly in the baby. Patients with Graves' disease who have entered remission prior to or during pregnancy have an increased risk of relapse around 3 to 6 months after delivery and should be offered thyroid function testing at this time. Areas of uncertainty or needing further research The pathogenesis of thyroid-associated ophthalmopathy is poorly understood, and this remains an obstacle to developing better treat- ments. Outcome after antithyroid drug treatment in Graves' dis- ease cannot yet be predicted, but improved assays for TSH receptor antibodies may permit better assessment in the future. Antithyroid drugs modulate the autoimmune response favourably in those pa- tients whose Graves' disease remits, indicating the potential for more specific immunotherapy aimed at the cause of the disease, which would be preferential to present treatments which merely block or destroy the thyroid. The evolution of hyperthyroidism is gradual and patients with multinodular goitre in particular are now recognized at the stage of subclinical hyperthyroidism (i.e. with a low or suppressed TSH but normal free T3 and T4 levels). Their optimum management is uncer- tain. There is a twofold to threefold increased risk of atrial fibrilla- tion over 10 years in subclinical thyrotoxicosis, as well as deleterious effects on bone mineral density, but no clinical trials have been per- formed to show a clear benefit from early intervention. Many endo- crinologists simply follow such patients carefully if the TSH is still detectable (i.e. >0.1 mU/litre) and if they are less than 65 and in otherwise good health, electing to treat when overt hyperthyroidism is shown by an abnormal free T3 level (T3 usually increases before T4). However, in older patients, those with known cardiac disease or those who are symptomatic with a persistent TSH value less than 0.1 mU/litre, there is an increasing shift to the use radio-iodine for subclinical

hyperthyroidism. Destructive thyroiditis Acute thyroiditis is rare and is usually caused by bacterial infection of the thyroid via a pyriform sinus connecting the gland with the oropharynx. Most such patients are children or young adults. There is severe thyroid pain with fever and malaise, but thyroid function is rarely disturbed. Diagnosis is made by fine needle aspiration biopsy with culture of the specimen, and treatment consists of antibiotics, surgical drainage of any abscess, and excision of the sinus which is identified by barium swallow. Immunocompromised patients may also develop acute thyroiditis. Subacute (or de Quervain's) thyroiditis is due to thyroid infec- tion by any of several viruses, especially mumps, Coxsackie, influ- enza, adenoviruses, and echoviruses. The most prominent symptom is pain in the thyroid, often radiating to the ears. A small, tender goitre can be palpated which is usually diffuse, but there can be asymmetrical involvement. Systemic upset with fever is variable but sometimes profound, and symptoms of a prodromal viral infec- tion several weeks earlier may be recalled. Serum C-reactive protein levels and the erythrocyte sedimentation rate are elevated. There is a granulomatous thyroid inflammation with follicular destruc- tion and the release of thyroid hormones often results in a transient thyrotoxicosis lasting 1 to 4 weeks. Continuing thyroid destruction then leads to a phase of hypothyroidism once stored hormone is de- pleted. This lasts 4 to 12 weeks before euthyroidism is restored, but relapses occur in 10 to 20% of patients. Sometimes only one phase of thyroid disturbance is seen. Confirmation of the clinical diagnosis is made by finding an elevated erythrocyte sedimentation rate and low or absent radio-iodine uptake by the thyroid. Thyroid function requires continuous monitoring as the disease evolves. Mild cases Box 13.3.1.11 Treatment of thyrotoxic crisis ('thyroid storm') • Antithyroid treatment — Propylthiouracil 500–1000 mg as a loading dose; then 250 mg every 4 h, given orally, by nasogastric tube, or per rectum — Stable iodine given 1 h after starting propylthiouracil (e.g. Lugol's iodine five drops every 6 h); ipodate 500 mg every 12 h is an al- ternative with additional deiodinase blocking activity but the avail- ability of this agent is limited — Propranolol 60 mg orally or 2 mg intravenously every 4 h to con- trol heart rate; careful monitoring necessary in heart failure — Severe cases may respond to plasmapheresis or dialysis • Supportive treatment • Oxygen • External cooling • Intravenous saline • Hydrocortisone 300 mg bolus intravenously, then 100 mg every 8 h • Diuretics and digoxin for heart failure • Identify and treat underlying precipitant (including trauma, infection, diabetic ketoacidosis, and myocardial infarction) — Broad-spectrum antibiotics if infection suspected

13.3.1 The thyroid gland and disorders of thyroid function 2301 may resolve spontaneously with paracetamol or a nonsteroidal anti- inflammatory drug as symptomatic treatment, but most patients benefit from prednisolone 15–40 mg daily as this rapidly alleviates the pain. The dose is tapered over 6 to 8 weeks depending largely on symptoms. Propranolol may be useful for thyrotoxic symptoms, and temporary T4 replacement is sometimes needed during the hypo- thyroid phase. Permanent late-onset hypothyroidism may develop in around 15% of patients. Silent thyroiditis is an autoimmune disorder in which there is a transient but painless thyroid destruction, giving rise to the same kind of thyroid function disturbances as subacute thyroiditis. As well as the absence of thyroid pain, there is no sign of a systemic in- flammatory response (including normal C-reactive protein levels and erythrocyte sedimentation rate) and the two conditions are therefore readily distinguished. The commonest setting for silent thyroiditis is in the postpartum period in women with pre-existing thyroid peroxidase antibodies and a mild autoimmune thyroiditis, exacerbated for unknown reasons at this time. Such postpartum thyroiditis is common, being detectable in up to 5% of women 3 to 6 months after delivery when repeated biochemical testing is done, although in many of these women the changes in thyroid function are mild and asymptomatic. Postpartum thyroiditis is three times more common in type 1 diabetes. Thyroid

uptake tests are useful in the postpartum period to distinguish thyrotoxicosis due to postpartum thyroiditis from Graves' disease. 99mTc pertechnetate is used in pref- erence to 131I and only requires cessation of breastfeeding for a day. Treatment is with propranolol for thyrotoxic symptoms and T4 for hypothyroidism. As 90% of women recover normal thyroid function, T4 should be withdrawn 1 year after delivery and thyroid function tested 6 weeks later. However, annual follow-up is needed as around 20% of these women have permanent hypothyroidism 5 years later. The condition usually recurs in subsequent pregnancies. Riedel's thyroiditis is a rare disorder which, in some patients, may be with associated with IgG4-related systemic disease causing multi- focal fibrosclerosis (retroperitoneum, mediastinum, biliary tree, orbit). The typical presentation is a hard, painless goitre suggestive of malignancy, often with symptoms due to compression of the oe- sophagus, trachea, neck veins, or recurrent laryngeal nerves. Some cases respond to corticosteroids or tamoxifen, and surgery can re- lieve compressive symptoms. Amiodarone inhibits T4 deiodination, and in all amiodarone- treated patients free T4 levels are in the upper half of the reference range or mildly elevated. Several months to years after starting amiodarone, however, effects on the thyroid may become manifest. In patients with mild thyroid dysfunction, especially autoimmune thyroiditis and positive thyroid peroxidase antibodies, the excessive iodine released from the drug causes hypothyroidism. This is treated as usual with levothyroxine. Paradoxically, the high level of iodine causes hyperthyroidism in other subjects who are predisposed to this because of an underlying multinodular goitre or incipient Graves' disease (Jod–Basedow phenomenon). This is called type 1 amiodarone-induced thyrotoxicosis; type 2 amiodarone-induced thyrotoxicosis is due to thyroid destruction via drug-induced lyso- somal activation. Colour-flow Doppler thyroid scanning shows an increase in vascularity in type 1 but not type 2 amiodarone- induced thyrotoxicosis, but mixed forms sometimes make an exact diag- nosis impossible. Treatment of amiodarone-induced thyrotoxicosis can be diffi- cult and biochemical changes are often out of proportion to the symptoms. Amiodarone should be stopped if possible, but often this cannot be done and in any case the drug has a very long half- life. Antithyroid drugs alone can be very slow to take effect in type 1 amiodarone-induced thyrotoxicosis; High doses are often re- quired and potassium perchlorate may need to be added, 200 mg 4 or 5 times daily. There is a high frequency of agranulocytosis (up to 1%) with this drug. Prednisolone can also be used at doses of 40 to 60 mg daily and is particularly helpful in type 2 amiodarone- induced thyrotoxicosis. Thyroidectomy is another alternative in severe cases. Thyroid hormone resistance syndrome Mutations in one allele of the β thyroid hormone receptor gene (Fig. 13.3.1.4) cause thyroid hormone resistance. The mutations af- fect the hormone-binding domain and the mutant receptor inhibits the activity of normally encoded receptors, so-called dominant negative inhibition, resulting in an autosomal dominant pattern of inheritance. The condition is usually discovered during screening for a goitre, but children may sometimes present with short stature, hyperactivity, or mild learning difficulties. Thyrotoxic features in some patients were originally ascribed to selective pituitary resist- ance to thyroid hormone, leading to increased thyroid hormone secretion and therefore thyrotoxicosis in the peripheral tissues. However, the same receptor mutations occur in generalized and pituitary resistance syndromes, and although differential tissue ex- pression of receptor subtypes presumably underlies the occasional expression of thyrotoxic signs and symptoms, the exact molecular basis is unknown. The diagnosis is suggested by the presence of a normal or elevated TSH level with elevated free T3 and T4 levels. Biochemical changes of thyrotoxicosis such as elevated ferritin, sex hormone-binding globulin, and liver enzymes are absent. The main differential diag- nosis is a TSH-secreting adenoma. Thyroid hormone resistance can be confirmed by direct mutational analysis. Treatment is usu- ally not required as reducing thyroid hormone levels to normal causes hypothyroidism. If thyrotoxic symptoms do occur, treat-

ment is with β-blockers or thyroid hormone analogues (e.g. tri- iodothyroacetic acid) aimed at lowering TSH secretion. Recently, mutations in the α thyroid hormone receptor gene have been identified; patients have early-onset severe hypothyroidism with a normal TSH level, low or normal T4 levels and normal or elevated T3 levels. FURTHER READING Akamizu T, et al. (2012). Diagnostic criteria, clinical features, and in- cidence of thyroid storm based on nationwide surveys. Thyroid, 22, 661–74. Alexander EK, et al. (2017). 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid, 27, 315–89. Bahn RS (2010). Graves' ophthalmopathy. N Engl J Med, 366, 726–38. Beck-Peccoz P, et al. (2013). 2013 European Thyroid Association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J, 2, 76–82.

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