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hormone (“cold” nodules, see Chap. 397, Fig 397-3A), and these are more likely to be malignant (~5–10%). Whole-body and thyroid scanning is also used in the treatment and, now less frequently, in the surveillance of thyroid cancer. After thyroidectomy for thyroid cancer, the TSH level is raised by either using a thyroid hormone withdrawal protocol or recombinant human TSH injection (Chap. 397). Admin istration of either 131I or 123I (in higher activities than used to image the thyroid gland alone) allows whole-body scanning (WBS) to detect the thyroid remnant. WBS imaging is also performed after therapeutic administration of 131I, which confirms remnant ablation and may reveal iodine-avid metastases. Thyroid Ultrasound Ultrasonography is the most valuable tool for the diagnosis and evaluation of patients with nodular thyroid disease (Chap. 397). Evidence-based guidelines recommend thyroid ultrasonography for all patients suspected of having thyroid nodules by either physical examination or another imaging study. Using 10- to 12-MHz linear transducers, resolution and image quality are excellent, allowing the characterization of nodules and cysts >3 mm. Sonographic patterns that combine suspicious sonographic features are highly sug gestive of malignancy (e.g., hypoechoic solid nodules with irregular borders and punctate echogenic foci >90% cancer risk), whereas other patterns correlate with a lower likelihood of cancer (isoechoic solid nodules, 5–10% cancer risk). Some patterns suggest benignity (e.g., spongiform nodules, defined as those with multiple small internal cys tic areas, or simple cysts, <3% cancer risk) (see Chap. 397, Fig. 397-2). These patterns have been incorporated into validated risk stratification systems (RSSs) for sonographic imaging of thyroid nodules (American College of Radiology [ACR] Thyroid Imaging Reporting and Data System [TI-RADS], American Thyroid Association, European Thyroid Association [EU-TIRADS] and others) (see Chap. 397, Fig. 397-1). These systems are relatively concordant in the classification of thyroid nodules; they differ in size cutoff recommendations for FNA. Not sur prisingly, the RSSs with lower size cutoffs have higher sensitivity and lower specificity for thyroid cancer diagnosis than those with higher cutoffs. Nevertheless, all have been shown to reduce unnecessary FNAs by at least 45%, in part due to the recommendation not to perform FNA of spongiform nodules. In addition to evaluating thyroid nodules, ultrasound is useful for monitoring nodule size and for the aspiration of nodules or cystic lesions. Ultrasound-guided FNA biopsy of thyroid lesions lowers the rate of inadequate sampling and decreases sample error, thereby reduc ing both the nondiagnostic and false-negative rates of FNA cytology. Ultrasonography of the central and lateral cervical lymph node com partments is indispensable in the evaluation of thyroid cancer patients, preoperatively and during follow-up. In addition, the all of the RSSs recommend a survey of the cervical lymph nodes as part of every diag nostic thyroid sonographic examination. ■ ■FURTHER READING Alexander EK et al: 2017 Guidelines of the American Thyroid Asso ciation for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 27:315, 2017. Andersson M, Braegger CP: The role of iodine for thyroid function in lactating women and infants. Endocr Rev 43:469, 2022. Carvalho DP, Dupuy C:

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Hypothyroidism HYPOTHYROIDISM Iodine deficiency remains a common cause of hypothyroidism world wide. In areas of iodine sufficiency, autoimmune disease (Hashimoto’s thyroiditis) and iatrogenic causes (treatment of hyperthyroidism) are most common (Table 395-1). Hypothyroidism CHAPTER 395 ■ ■CONGENITAL HYPOTHYROIDISM Prevalence Hypothyroidism occurs in about 1 in 2000–4000 new borns, and neonatal screening is performed in most industrialized countries. It may be transient, especially if the mother has thyroidstimulating hormone (TSH) receptor (TSH-R)–blocking antibodies or has received antithyroid drugs, but permanent hypothyroidism occurs in the majority. The causes of neonatal hypothyroidism include thyroid gland dysgenesis in 65%, inborn errors of thyroid hormone synthesis in 30%, and TSH-R antibody mediated in 5% of affected newborns. The developmental abnormalities are twice as common in girls. Mutations that cause congenital hypothyroidism are being increasingly identi fied, but most remain idiopathic (Chap. 394). These can be broadly categorized as mutations causing (1) central hypothyroidism because of abnormal hypothalamic-pituitary development or the loss of spe cific components of the thyrotropin-releasing hormone (TRH)/TSH hormonal pathways; (2) abnormal thyroid gland development or dys genesis; or (3) abnormal thyroid hormone synthesis and processing, or dyshormonogenesis (Table 395-2). Transplacental passage of maternal thyroid hormone occurs before the fetal thyroid gland begins to func tion and provides partial hormone support to a fetus with congenital hypothyroidism. TABLE 395-1 Causes of Hypothyroidism Primary Autoimmune hypothyroidism: Hashimoto’s thyroiditis, atrophic thyroiditis Iatrogenic: 131I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer Drugs: iodine excess (including iodine-containing contrast media), amiodarone, lithium, antithyroid drugs, p-aminosalicylic acid, interferon a and other cytokines, aminoglutethimide, tyrosine kinase inhibitors (e.g., sunitinib), immune checkpoint inhibitors (e.g., ipilimumab, nivolumab, pembrolizumab) Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation Iodine deficiency Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel’s thyroiditis Overexpression of type 3 deiodinase in infantile hemangioma and other tumors Transient Silent thyroiditis, including postpartum thyroiditis Subacute thyroiditis Withdrawal of supraphysiologic thyroxine treatment in individuals with an intact thyroid After 131I treatment or subtotal thyroidectomy for Graves’ disease Secondary Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan’s syndrome, trauma, genetic forms of combined pituitary hormone deficiencies Isolated TSH deficiency or inactivity Drugs: bexarotene, mitotane Hypothalamic disease: tumors, trauma, infiltrative disorders, Prader-Willi syndrome Abbreviations: TSH, thyroid-stimulating hormone; TSH-R, TSH receptor.

TABLE 395-2 Examples of Genetic Causes of Congenital Hypothyroidism DEFECTIVE GENE PROTEIN TYPE OF HYPOTHYROIDISM INHERITANCE CONSEQUENCES PROP-1 Central, hypothyroidism Homozygous recessive Combined pituitary hormone deficiencies, including thyroid-stimulating hormone (TSH), with preservation of adrenocorticotropic hormone PIT-1 Central, hypothyroidism Homozygous or heterozygous loss of function IGSF1 Central, hypothyroidism X-linked loss of function Loss of TSH receptor (TSH-R) expression, testicular enlargement TSHb Central, hypothyroidism Heterozygous loss of function TSH deficiency TTF-1 (TITF-1) Primary, thyroid dysgenesis Heterozygous loss of function Variable thyroid hypoplasia, choreoathetosis, pulmonary problems PART 12 Endocrinology and Metabolism TTF-2 (FOXE-1) Primary, thyroid dysgenesis Homozygous recessive Thyroid agenesis, choanal atresia, spiky hair PAX-8 Primary, thyroid dysgenesis Heterozygous loss of function Thyroid dysgenesis, kidney abnormalities NKX2-1 Primary, thyroid dysgenesis Heterozygous loss of function Thyroid dysgenesis, brain, lung abnormalities NKX2-5 Primary, thyroid dysgenesis Heterozygous loss of function Thyroid dysgenesis, heart abnormalities GLIS3 Primary, thyroid dysgenesis Homozygous recessive Thyroid dysgenesis, neonatal diabetes, facial abnormalities JAG-1 Primary, thyroid dysgenesis Heterozygous loss of function Thyroid dysgenesis, Alagille syndrome type 1, heart abnormalities TSH receptor Primary, thyroid dysgenesis and dyshormonogenesis Homozygous recessive Resistance to TSH Primary, thyroid dyshormonogenesis Heterozygous loss of function, imprinting GSa (Albright hereditary osteodystrophy) Na+/I– symporter (SLC5A5) Primary, thyroid dyshormonogenesis Homozygous recessive Inability to transport iodide DUOX2 (THOX2) Primary, thyroid dyshormonogenesis Heterozygous loss of function Organification defect DUOXA2 Primary, thyroid dyshormonogenesis Homozygous recessive Organification defect Thyroid peroxidase Primary, thyroid dyshormonogenesis Homozygous recessive Defective organification of iodide Thyroglobulin Primary, thyroid dyshormonogenesis Homozygous recessive Defective synthesis of thyroid hormone Pendrin (SLC26A4) Primary, thyroid dyshormonogenesis Homozygous recessive Pendred syndrome: sensorineural deafness and partial organification defect in thyroid Dehalogenase 1 (IYD) Primary, thyroid dyshormonogenesis Homozygous recessive Loss of iodide reutilization Clinical Manifestations The majority of infants appear normal at birth, and with the use of biochemical screening, few cases are now diagnosed based on clinical features, which include prolonged jaundice, feeding problems, hypotonia, enlarged tongue, delayed bone maturation, and umbilical hernia. Importantly, permanent neuro logic damage results if treatment is delayed. Typical features of adult hypothyroidism may also be present (Table 395-3). Other congenital malformations, especially cardiac, are four times more common in congenital hypothyroidism. Diagnosis and Treatment Because of the severe neurologic con sequences of untreated congenital hypothyroidism, neonatal screening programs have been established. These are generally based on mea surement of TSH or T4 levels in heel-prick blood specimens. When the TABLE 395-3 Signs and Symptoms of Hypothyroidism (Descending Order of Frequency) SYMPTOMS SIGNS Tiredness, weakness Dry skin Feeling cold Hair loss Difficulty concentrating and poor memory Constipation Weight gain with poor appetite Dyspnea Hoarse voice Menorrhagia (later oligomenorrhea or amenorrhea) Paresthesia Impaired hearing Dry coarse skin; cool peripheral extremities Puffy face, hands, and feet (myxedema) Diffuse alopecia Bradycardia Peripheral edema Delayed tendon reflex relaxation Carpal tunnel syndrome Serous cavity effusions

Combined deficiencies of growth hormone, prolactin, TSH Resistance to TSH diagnosis is confirmed, T4 is instituted at a dose of 10–15 μg/kg per d, and the dose is adjusted by close monitoring of TSH levels. T4 require ments are relatively great during the first year of life, and a high cir culating T4

level is usually needed to normalize TSH. Early treatment with T4 results in normal IQ levels, but subtle neurodevelopmental abnormalities may occur in those with the most severe hypothyroidism at diagnosis or when treatment is delayed or suboptimal. If transient hypothyroidism is suspected, or the diagnosis is unclear, treatment can be stopped safely after the age of 3 years followed by further evaluation. ■ ■AUTOIMMUNE HYPOTHYROIDISM Classification Autoimmune hypothyroidism (Hashimoto's thy roiditis) may be associated with a goiter (goitrous thyroiditis) or minimal residual thyroid tissue (atrophic thyroiditis). Because the auto immune process gradually reduces thyroid function, there is a phase of compensation when normal thyroid hormone levels are maintained by a rise in TSH. Although some patients may have minor symptoms, this state is called subclinical hypothyroidism. Later, unbound T4 levels fall and TSH levels rise further; symptoms become more readily apparent at this stage (usually TSH >10 mIU/L), which is referred to as clinical hypothyroidism or overt hypothyroidism. Prevalence The mean annual incidence rate of autoimmune hypo thyroidism is up to 4 per 1000 women and 1 per 1000 men. It is more common in certain populations, such as the Japanese, probably because of genetic factors and chronic exposure to a high-iodine diet. Hypothy roidism typically occurs between 30 and 50 years of age, and the preva lence of increases with age. The mean age at diagnosis is 60 years, and the prevalence of overt hypothyroidism increases with age. Subclinical hypothyroidism is found in 6–8% of women (10% over the age of 60) and 3% of men. The annual risk of developing clinical hypothyroidism is ~4% when subclinical hypothyroidism is associated with positive thyroid peroxidase (TPO) antibodies.

Pathogenesis In Hashimoto's thyroiditis, there is a marked lym phocytic infiltration of the thyroid with germinal center formation, atrophy of the thyroid follicles accompanied by oxyphil metaplasia, absence of colloid, and mild to moderate fibrosis. In atrophic thy roiditis, the fibrosis is much more extensive, lymphocyte infiltration is less pronounced, and thyroid follicles are almost completely absent. Atrophic thyroiditis usually represents the end stage of Hashimoto's thyroiditis rather than a separate disorder, although a distinct form of marked fibrosis occurs in which the gland is infiltrated with IgG4positive plasma cells. As with most autoimmune disorders, susceptibility to autoimmune hypothyroidism is determined by a combination of genetic and envi ronmental factors, and the risk of either autoimmune hypothyroidism or Graves' disease is increased among siblings. HLA-DR polymor phisms are the best documented genetic risk factors for autoimmune hypothyroidism, especially HLA-DR3, DR4, and DR5 in Caucasians. A weak association also exists between polymorphisms in PTPN22 and CTLA-4, which have immunoregulatory functions, and autoimmune hypothyroidism. All these genetic associations are shared by other autoimmune diseases, which may explain the relationship between autoimmune hypothyroidism and other autoimmune diseases, espe cially type 1 diabetes mellitus, Addison's disease, pernicious anemia, and vitiligo. The role of other contributory loci remains to be clarified. A gene on chromosome 21 may be responsible for the association between autoimmune hypothyroidism and Down's syndrome. The female preponderance of thyroid autoimmunity is most likely due to sex steroid effects on the immune response, but an X chromosome– related genetic factor is also possible and may account for the high frequency of autoimmune hypothyroidism in Turner's syndrome. Envi ronmental susceptibility factors are poorly defined at present. A high iodine or low selenium intake and decreased exposure to microorgan isms in childhood increase the risk of autoimmune hypothyroidism. Smoking cessation transiently increases incidence, whereas alcohol intake seems protective. These factors may account for the increase in prevalence over the past two to three decades. The thyroid lymphocytic infiltrate in autoimmune hypothyroid ism is composed of

activated T cells as well as B cells. Thyroid cell destruction is primarily mediated by the CD8+ cytotoxic T cells, but local production of cytokines, such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interferon γ (IFN-γ), derived from the inflammatory infiltrate may render thyroid cells more susceptible to apoptosis mediated by death receptors, such as Fas, and by oxidative stress. These cytokines also impair thyroid cell function directly and induce the expression of other proinflammatory molecules by the thyroid cells themselves, such as cytokines, human leukocyte antigen (HLA) class I and class II molecules, adhesion molecules, CD40, and nitric oxide. Administration of high concentrations of cytokines for therapeutic purposes (especially IFN-α) is associated with increased autoimmune thyroid disease, possibly through mechanisms similar to those in sporadic disease. Novel anticancer and immunomodulatory treatments, such as tyrosine kinase inhibitors, immune checkpoint inhibitors, and alemtuzumab, can also induce thyroiditis via their effects on T-cell regulation. Antibodies to TPO and thyroglobulin (Tg) are clinically useful mark ers of thyroid autoimmunity, but any pathogenic effect is restricted to a secondary role in amplifying an ongoing autoimmune response. TPO antibodies fix complement, and complement membrane-attack complexes are present in the thyroid in autoimmune hypothyroidism. However, transplacental passage of Tg or TPO antibodies has no effect on the fetal thyroid, which suggests that T cell–mediated injury is required to initiate autoimmune damage to the thyroid. Up to 20% of patients with autoimmune hypothyroidism have anti bodies against the TSH-R, which, in contrast to thyroid-stimulating immunoglobulin (TSI), do not stimulate the receptor but prevent the binding of TSH. These TSH-R-blocking antibodies, therefore, cause hypothyroidism and, especially in Asian patients, thyroid atrophy. Their transplacental passage may induce transient neonatal hypothy roidism. Rarely, patients have a mixture of TSI and TSH-R-blocking antibodies, and thyroid function can oscillate between hyperthyroidism

and hypothyroidism as one or the other antibody becomes dominant. Predicting the course of disease in such individuals is difficult, and they require close monitoring of thyroid function. Bioassays can be used to document that TSH-R-blocking antibodies reduce the cyclic AMP–inducing effect of TSH on cultured TSH-R-expressing cells, but these assays are difficult to perform. Immunoassays for TSH receptor antibodies, which measure whether the patient’s serum contains an antibody that can displace either labeled TSH or a monoclonal TSH receptor antibody from the TSH receptor, do not distinguish between these types of functional antibodies, but a positive result in a patient with spontaneous hypothyroidism is strong evidence for the presence of blocking antibodies. The use of these assays does not generally alter clinical management, although it may be useful to confirm the cause of transient neonatal hypothyroidism.

Hypothyroidism CHAPTER 395 Clinical Manifestations The main clinical features of hypothy roidism are summarized in Table 395-3. The onset is usually insidious, and the patient may become aware of symptoms only when euthy roidism is restored. Patients with Hashimoto’s thyroiditis may present because of goiter rather than symptoms of hypothyroidism. The goiter may not be large, but it is usually irregular and firm in consistency. Rarely, uncomplicated Hashimoto’s thyroiditis is associated with pain. Patients with atrophic thyroiditis or the later stage of Hashimoto’s thyroiditis present with symptoms and signs of hypothyroidism. The skin is dry, and there is decreased sweating, thinning of the epider mis, and hyperkeratosis of the stratum corneum. Increased dermal glycosaminoglycan content traps water, giving rise to skin thickening without pitting (myxedema). Typical features include a puffy face with edematous eyelids and nonpitting pretibial edema (Fig. 395-1). There is pallor, often with a yellow tinge to the skin due to carotene accumula tion. Nail

growth is retarded, and hair is dry, brittle, difficult to manage, and falls out easily. In addition to diffuse alopecia, there is thinning of the outer third of the eyebrows, although this is not a specific sign of hypothyroidism. Other common features include constipation and weight gain (despite a poor appetite). In contrast to popular perception, the weight gain is usually modest and due mainly to fluid retention in the myxedematous tissues. Libido is decreased in both sexes, and there may be oligomenorrhea or amenorrhea in long-standing disease, but FIGURE 395-1 Facial appearance in hypothyroidism. Note puffy eyes and thickened skin.

menorrhagia may occur at an early stage. Fertility is reduced, and the incidence of miscarriage is increased. Prolactin levels are often mod estly increased (Chap. 392) and may contribute to alterations in libido and fertility and cause galactorrhea.

Myocardial contractility and pulse rate are reduced, leading to a reduced stroke volume and bradycardia. Increased peripheral resis tance may be accompanied by hypertension, particularly diastolic. Blood flow is diverted from the skin, producing cool extremities. Peri cardial effusions occur in up to 30% of patients but rarely compromise cardiac function. Although alterations in myosin heavy chain isoform expression have been documented, cardiomyopathy is rare. Fluid may also accumulate in other serous cavities and in the middle ear, giving rise to conductive deafness; sensorineural deafness may also occur. Pulmonary function is generally normal, but dyspnea may be caused by pleural effusion, impaired respiratory muscle function, diminished ventilatory drive, or sleep apnea. PART 12 Endocrinology and Metabolism Carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain. On examination, there may be slow relaxation of tendon reflexes and pseu domyotonia. Memory and concentration are impaired. Experimentally, positron emission tomography (PET) scans examining glucose metab olism in hypothyroid subjects show lower regional activity in the amyg dala, hippocampus, and perigenual anterior cingulate cortex, among other regions, and this activity corrects after thyroxine replacement. Rare neurologic problems include reversible cerebellar ataxia, demen tia, psychosis, and myxedema coma. Hashimoto’s encephalopathy has been defined as a steroid-responsive syndrome associated with TPO antibodies, myoclonus, and slow-wave activity on electroencephalog raphy, but the relationship with thyroid autoimmunity or hypothyroid ism is not established, and if a patient is euthyroid, levothyroxine (LT4) therapy has not been shown to be efficacious in treatment. The hoarse voice and occasionally clumsy speech of hypothyroidism reflect fluid accumulation in the vocal cords and tongue. The features described above are the consequence of thyroid hor mone deficiency. However, autoimmune hypothyroidism may be associated with signs or symptoms of other autoimmune diseases, particularly vitiligo, pernicious anemia, Addison’s disease (Schmidt’s syndrome), alopecia areata, and type 1 diabetes mellitus (T1DM). In the polygenic disorder autoimmune polyendocrine syndrome type 2, autoimmune thyroid disease is present in 70–75%, T1DM in 40–60%, and Addison’s disease in 40–50%. Less common associations include celiac disease, dermatitis herpetiformis, chronic active hepatitis, rheu matoid arthritis, systemic lupus erythematosus (SLE), myasthenia Elevated Measure unbound T4 Normal Measure unbound T4 Mild hypothyroidism Primary hypothyroidism TPOAb+ TPOAb– TPOAb+ or symptomatic TPOAb–, no symptoms Autoimmune hypothyroidism Rule out other causes of hypothyroidism Consider T4 treatment Annual follow-up T4 treatment FIGURE 395-2 Evaluation of hypothyroidism. TPOAb+, thyroid peroxidase antibodies present; TPOAb–, thyroid peroxidase antibodies not present; TSH, thyroid-stimulating hormone.

gravis, autoimmune hypoparathyroidism, primary hypogonadism, and Sjögren's syndrome. Thyroid-associated ophthalmopathy usually occurs in Graves' disease (Chap. 396), but in ~5% of patients, it is associated with autoimmune hypothyroidism. Autoimmune hypothyroidism is uncommon in children and usually presents with slow growth and delayed facial and dental maturation. The pituitary may be enlarged due to thyrotroph hyperplasia. Myopa thy, with muscle swelling, is more common in children than in adults. In most cases, puberty is delayed, but precocious puberty sometimes occurs. There may be intellectual impairment if the onset is before 3 years and the hormone deficiency is severe. Laboratory Evaluation A summary of the investigations used to determine the existence and cause of hypothyroidism is provided in Fig. 395-2. A normal TSH level excludes primary (but not secondary or central) hypothyroidism. If the TSH is elevated, a free or unbound T4 level (FT4) is needed to confirm the presence of clinical hypothyroid ism, but T4 is inferior to TSH when used as a screening test because it will not detect subclinical hypothyroidism. Circulating unbound T3 levels are normal in ~25% of patients, reflecting adaptive deiodinase responses to hypothyroidism. T3 measurements are, therefore, not indicated. Once clinical or subclinical hypothyroidism is confirmed, the etiol ogy is usually easily established by demonstrating the presence of TPO and Tg antibodies, which are present in >95% of patients with autoim mune hypothyroidism. Other abnormal laboratory findings in hypo thyroidism may include increased creatine phosphokinase, elevated cholesterol and triglycerides, and anemia (usually normocytic or mac rocytic) depending upon the degree and duration of hypothyroidism. Except when accompanied by iron deficiency or B12 deficiency from concomitant pernicious anemia, the anemia and other abnormalities gradually resolve with thyroxine replacement. Differential Diagnosis An asymmetric goiter in Hashimoto's thy roiditis may be confused with a multinodular goiter (MNG) or thyroid carcinoma, in which thyroid antibodies may also be present. Primary thyroid lymphoma (Chap. 397) is rare but strongly associated with pre existing autoimmune thyroiditis. Ultrasound can be used to show the presence of solitary or multiple nodules rather than the thyroid enlarge ment with heterogeneous echogenicity typical of Hashimoto's thyroid itis. However, ultrasound imaging may also detect pseudonodules, hypoechoic areas likely representing areas of lymphocytic infiltrates, which need to be distinguished from true superimposed nodules as fine-needle aspirate is not warranted for these. Fine-needle aspiration Measure TSH Normal Pituitary disease suspected? Low Yes No No further tests Normal Low No further tests Rule out drug effects, sick euthyroid syndrome, then evaluate anterior pituitary function

(FNA) biopsy should be performed for all true nodules meeting FNA criteria (Chap. 397). Other causes of hypothyroidism are discussed below and in Table 395-1 but rarely cause diagnostic confusion. ■ ■OTHER CAUSES OF HYPOTHYROIDISM Iatrogenic hypothyroidism is a common cause of hypothyroidism and can often be detected by screening before symptoms develop. In the first 3–4 months after radioiodine treatment for Graves' disease, tran sient hypothyroidism may occur due to reversible radiation damage. Low-dose thyroxine treatment can be withdrawn if recovery occurs. Because TSH levels are suppressed by hyperthyroidism, unbound T4 levels are a better measure of thyroid function than TSH in the months following radioiodine treatment. Mild hypothyroidism after subtotal thyroidectomy or lobectomy may also resolve after several months, as the gland remnant is stimulated by increased TSH levels. Iodine deficiency is responsible for endemic goiter and cretinism but is an uncommon cause of adult hypothyroidism unless the iodine intake is very low or there are complicating factors, such as the con sumption of thiocyanates in cassava or selenium deficiency. Although hypothyroidism due to iodine deficiency can be treated

with thyroxine, public health measures to improve iodine intake should be advocated to eliminate this problem. Iodized salt or bread or a single bolus of oral or intramuscular iodized oil have all been used successfully. Paradoxically, chronic iodine excess can also induce goiter and hypothyroidism. The intracellular events that account for this effect are unclear, but individuals with autoimmune thyroiditis are especially susceptible. Iodine excess is responsible for the hypothyroidism that occurs in patients treated with amiodarone (Chap. 396). Other drugs, particularly lithium, may also cause hypothyroidism. Transient hypo thyroidism may also be caused by thyroiditis (Chap. 396). Secondary or central hypothyroidism is usually diagnosed in the context of other anterior pituitary hormone deficiencies; isolated TSH deficiency is very rare (Chap. 391). TSH levels may be low, normal, or even slightly increased in secondary hypothyroidism; the latter is due to secretion of immunoactive but bioinactive forms of TSH. The diagnosis is confirmed by detecting a low unbound T4 level. The goal of treatment is to maintain free T4 levels in the upper half of the reference interval because TSH levels cannot be used to monitor therapy. TREATMENT Hypothyroidism CLINICAL HYPOTHYROIDISM If there is no residual thyroid function, the daily replacement dose of LT4 is usually 1.6 μg/kg body weight (typically 100–150 μg), ide ally taken at least 30 min before breakfast. In many patients, how ever, lower doses suffice until residual thyroid tissue is destroyed. In patients who develop hypothyroidism after the treatment of Graves' disease, there is often underlying autonomous function, necessitat ing lower replacement doses (typically 75–125 μg/d). Adult patients under 60 years old without evidence of heart disease may be started on 50–100 μg of LT4 daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH, ideally in the lower half of the reference range. TSH responses are gradual and should be measured about 6–8 weeks after instituting treatment or after any subsequent change in LT4 dosage. The clinical effects of LT4 replacement are slow to appear. Patients may not experience full relief from symptoms until several months after normal TSH levels are restored. Adjustment of LT4 dosage is made in 12.5- or 25-μg increments if the TSH is high; decrements of the same magnitude should be made if the TSH is suppressed. Patients with a suppressed TSH of any cause, including LT4 overtreatment, have an increased risk of atrial fibrillation and reduced bone density. About 10–15% of patients may have persistent symptoms despite restoration of euthyroidism with LT4 for reasons that remain unclear. Although desiccated animal thyroid preparations (thyroid extract USP) are available, they are not recommended because the

ratio of T3 to T4 is nonphysiologic. The use of LT4 combined with liothyronine (triiodothyronine, T3) has been investigated, but ben efit has not been confirmed in prospective studies. There is no place for liothyronine alone as long-term replacement, because the short half-life necessitates three or four daily doses and is associated with fluctuating T3 levels.

Once full replacement is achieved and TSH levels are stable, fol low-up measurement of TSH is recommended at annual intervals. It is important to ensure ongoing adherence as patients do not feel any symptomatic difference after missing a few doses of LT4, and this sometimes leads to self-discontinuation. Hypothyroidism CHAPTER 395 In patients of normal body weight who are taking ≥200 μg of LT4 daily, an elevated TSH level is often a sign of poor adherence to treatment. This is also the likely explanation for fluctuating TSH levels, despite a constant LT4 dosage. Such patients often have normal or high free T4 levels, despite an elevated TSH, because they remember to take medication for a few days before testing; this is sufficient to normalize T4, but not TSH levels. It is impor tant to consider variable adherence because this pattern of thyroid function tests is

otherwise suggestive of disorders associated with inappropriate TSH secretion (Chap. 394). Because T4 has a long half-life (7 days), patients who miss a dose can be advised to take two doses of the skipped tablets at once. Other causes of increased LT4 requirements must be excluded, particularly malabsorption (e.g., celiac disease, small-bowel surgery, atrophic or Helicobacter pylori–related gastritis), oral estrogen-containing medications or selective estrogen receptor modulator therapy, ingestion with a meal, and drugs that interfere with T4 absorption or metabolism such as bile acid sequestrants, ferrous sulfate, calcium supplements, sevelamer, sucralfate, proton pump inhibitors, lovastatin, aluminum hydroxide, rifampicin, amiodarone, carbamazepine, phenytoin, and tyrosine kinase inhibitors. SUBCLINICAL HYPOTHYROIDISM Subclinical hypothyroidism refers to biochemical evidence of thy roid hormone deficiency in patients who have few or no appar ent clinical features of hypothyroidism. There are no universally accepted recommendations for the management of subclinical hypothyroidism, but LT4 is recommended if the patient is a woman who wishes to conceive or is pregnant or when TSH levels are

> 10 mIU/L. Most other patients can simply be monitored annually. A trial of treatment may be considered when young or middle-aged patients have symptoms of hypothyroidism or risk of heart disease. It is important to confirm that any elevation of TSH is sustained over a 3-month period before treatment is given. Treatment is administered by starting with a low dose of LT4 (25–50 µg/d) with the goal of normalizing TSH. SPECIAL TREATMENT CONSIDERATIONS Rarely, LT4 replacement is associated with pseudotumor cerebri in children. Presentation appears to be idiosyncratic and occurs months after treatment has begun. Because maternal hypothyroidism may both adversely affect fetal neural development and be associated with adverse gestational outcomes (miscarriage, preterm delivery), thyroid function should be monitored to preserve euthyroidism in women with a history or a high risk of hypothyroidism. Although epidemiologic studies have demonstrated the association of miscarriage and preterm delivery with the presence of thyroid autoantibodies detected either during or prior to gestation in euthyroid women, randomized controlled multicenter trials evaluating LT4 therapy prior to conception in this population have not demonstrated benefit. Because of the known increase in thyroid hormone requirements during preg nancy in hypothyroid women, LT4 therapy should be targeted to maintain a serum TSH in the normal range but <2.5 mIU/L prior to conception. In women without evidence of thyroid dysfunction, serum TSH decreases in the late first trimester, and if trimester-specific ranges are not available, an appropriate range for 7–12 weeks’ gestation can

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