REVIEWS

Thyroid disorders—an update

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Patients with thyroid disease are seen in many different general and specialist clinics because of the many and varied modes of presentation. This review will highlight recent developments in aspects of pathophysiology and clinical management of thyroid disorders but will inevitably not be all inclusive. Recent developments in molecular biology have had important effects on our understanding of many areas of thyroidology.

Thyroid hormone action

The thyroid produces 100% of circulating thyroxine but only about 5%–10% of circulating triiodothyronine, the rest being derived from peripheral monodeiodination of thyroxine in tissues such as heart, liver, kidney, and gut mucosa by the type I deiodinase. The type II deiodinase provides intracellular triiodothyronine in specific sites such as central nervous system and pituitary.

Triiodothyronine is the hormone that mediates hormone action at the cell level. After gaining entry to a thyroid responsive cell it binds to a specific nuclear receptor which initiates transcription of messenger RNA leading to new protein production. Three triiodothyronine responsive receptors (TRα1,TRβ1, and TRβ2) have been identified and vary in their tissue distribution. Mutations in the TRβ gene are seen in patients with the syndrome of resistance to thyroid hormone (see below). Thyroid hormones also have extranuclear actions in the cell which will not be further discussed.

During the last decade advances in thyroid biology and immunology have resulted in the identification of the major thyroid autoantigens. The genes for these moieties have been cloned and details of their structure and function have been characterised (table 1).

The prevalence of hyperthyroidism has been reported to be in the region of 2.5–4.7/1000 females. The prevalence is about 10 times more common in women than men. The incidence of the disease is about 1/1000 women annually in north east England and similar figures are seen in Scandinavia, Japan, and the USA.

Hypothyroidism is common. The prevalence in the Whickham survey was 1.5% in women and less than 1% in men. Recent follow up data indicate a continuing risk of developing thyroid failure especially if positive thyroid autoantibodies are present. There is a female/male ratio of about five to one.

Hyperthyroidism

The causes of hyperthyroidism are shown in table 2.

Graves' disease is the commonest cause of hyperthyroidism in the UK and is accompanied by the presence of thyroid stimulating antibodies (TsAb). Recent developments in assay methodology have resulted in a near 100% detection rate in Graves' patients. Although the presence of TsAb is not a very satisfactory predictor of relapse after a course of antithyroid drugs, it is to be hoped that the newer assays may improve this aspect of treatment. Graves' hyperthyroidism has been treated with thionamide antithyroid drugs for the past 50 years or so. In addition to blocking thyroid hormone biosynthesis there is persuasive evidence that they have significant immunosuppressive effects thereby affecting the disease process in Graves' disease. During this time it has been realised that (1) the relapse rate after a course of six to 12 months' therapy may be as high as 50% and that this relates to ambient iodine concentration; (2) there is some evidence that an 18 month course may lessen the relapse rate but this is not universally accepted; (3) prediction of relapse in any one patient is not possible, although goitre size, HLA haplotype, and pretreatment triiodothyronine levels have been found to predict on a group basis; (4) the report that the addition of thyroxine to the antithyroid drug regimen would reduce the relapse rate has not been confirmed by a recent study. Under conditions of iodine deficiency or borderline sufficient iodine a supply of 40 mg methimazole daily (approximately 60 mg carbimazole) will render more patients with Graves' disease euthyroid within the first six weeks of therapy than 10 mg

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Table 1 Features of major thyroid autoantigens

	TSH receptor	*Sodium iodide symporter*	*Thyroid peroxidase*	*Thyroglobulin*
Chromosome	14	19	2	8
Amino acids	743	643	933	274
Protein	G protein	Transmembrane transporter	Haemoprotein enzyme	Iodinated glycoprotein
MW (kDa)	85	65–77	105–110	660
Glycosylation	+	+	+	
Function	Receptor for TSH	Iodide uptake	Iodination and coupling of tyrosine	Storage of thyroxine + triiodothyronine
Homologies	FSH + LH receptor	Na/glucose transporter	Myeloperoxidase	Anticholinesterase

FSH = follicle stimulating hormone; LH = luteinising hormone; MW=molecular weight.

Table 2 Aetiology of hyperthyroidism

Disease	*Mechanism*
Graves' disease	Thyroid stimulating IgG antibody
Congenital (neonatal) hyperthyroidism	Transplacental passage IgG antibody
Non autoimmune hereditary hyperthyroidism	Constituitive activation of TSH receptor
Toxic multinodular goitre	Relative excess iodine exposure in previous goitre
	Thyroid stimulating immunoglobulins (?)
Toxic uninodular goitre (adenoma)	Somatic mutation Gsα or TSH receptor
Subacute thyroiditis	Viral destruction
Silent thyroiditis	Lymphocytic infiltrate
Postpartum thyroiditis	Immune destruction (transient)
Iodine induced hyperthyroidism	Increased substrate for biosynthesis
Drug induced hyperthyroidism	Iodine
	Amiodarone
	Lithium (?)
	Radiocontrast agents
Hyperemesis gravidarum	Human chorionic gonadotrophin
	TSH receptor mutation
Molar pregnancy	Human chorionic gonadotrophin
Thyrotoxicosis factitia	Exogenous thyroid hormone
Hamburger toxicosis	Exogenous thyroid hormone
Metastatic differentiated thyroid cancer	Ectopic thyroid hormone production
Struma ovarii	Ectopic thyroid hormone production
Pituitary resistance to thyroid hormone	Mutation thyroid hormone β-receptor
Pituitary adenoma	Autonomous TSH secretion

daily but at the expense of an increased rate of adverse reactions. Remission rates are not dose dependent. The most severe side effect of the thionamide drugs is agranulocytosis which, in life threatening states, has been successfully treated with granulocyte colony stimulating factor but does not always respond to this treatment.

Radioiodine therapy is now widely employed as a cheap effective therapy which can be administered in the outpatient setting. There is still discussion relating to safety issues of radiation exposure to the family of patients receiving radioiodine and considerable variation is noted in these regulations in different European countries. Another controversial area is the relationship between radioiodine administration and development or worsening of ophthalmopathy. Patients who smoke and who have evidence of significant eye involvement should receive prednisone (0.5–1.0 mg/kg) for four to eight weeks at the time of treatment to prevent eye progression.

The management of thyroid associated ophthalmopathy is largely symptomatic in the early phase. Ophthalmic evaluation of diplopia and optic nerve dysfunction should be performed if clinically indicated. Attention should be paid to the avoidance of smoking, and the use of tinted spectacles.

Elevation of the head end of the bed at night, diuretic therapy, and frequent bathing will help to reduce the swelling and periorbital oedema. Many patients with more severe eye changes will respond to high dose prednisone (120 mg/day) and some clinicians add azathioprine as a steroid sparing agent during long term treatment. After favourable reports of orbital decompression operations this procedure should be considered earlier in the disease process than in the past. A combination of orbital radiotherapy and steroids is also effective in reducing proptosis and diplopia in some patients. When the eyes are quiet, corrective muscle surgery may be undertaken for residual diplopia.

Toxic multinodular goitre and toxic adenoma are important causes of thyrotoxicosis and may account for 25% or more, and up to 10% respectively, of a hyperthyroid population depending on the geographic location.

In the past patients with familial hyperthyroidism and diffuse or nodular goitre have been described who did not show autoimmune features. Affected individuals showed thyroid autonomy, negative thyroid stimulating hormone (TSH) receptor antibodies and no thyroid eye disease; however they were noted to have recurrent hyperthyroidism. This familial non-autoimmune hyperthyroidism is autosomal dominantly inherited and is now known to be due to constituitively activating germline mutations in the TSH receptor gene. The diagnosis can be confirmed by mutation analysis of genomic DNA obtained from a venous blood sample. A near total thyroidectomy is recommended in order to avoid relapses. Ablative radioiodine may also be given. Genetic counselling is advised.

Autoimmune thyroiditis

Autoimmune thyroiditis is defined as a state in which the thyroid gland is the site of chronic lymphocytic inflammation leading to progressive destruction and fragmentation of thyroid follicular structure. Clinically this condition is five to six times more common in females, subject to certain HLA haplotype restriction, and is characterised in many patients by the presence of a firm goitre and the presence of circulating thyroid antibodies.These are the antithyroid peroxidase antibody and antithyroglobulin antibody, the former being thought to be more closely involved in the pathogenesis of antibody mediated cytotoxicity partly due to its expression at the follicular luminal surface.

While many patients are euthyroid others progress to a hypothyroid state and require thyroxine treatment. The prevalence of thyroid antibodies in women rises to around 10% with age and the progression to hypothyroidism in women with positive antibodies is about 5% per year. In younger people the presence of thyroid antibodies is usually the only indication of potential underlying thyroid autoimmunity as the goitre may not have developed and euthyroidism is present.

It should be noted that autoimmune thyroiditis may coexist with Graves' disease, which is also an autoimmune disorder. Hyperthyroidism caused by Graves' disease will not be considered further.

Hypothyroidism

The causes of hypothyroidism are shown in table 3. Some are dealt with elsewhere in this review.

The commonest cause of primary thyroid failure is Hashimoto's thyroiditis; other frequent causes of primary hypothyroidism include post-radioiodine hypothyroidism, postthyroidectomy, and drugs. Destruction of pituitary thyrotropes by tumour or infiltrative disease results in secondary hypothyroidism and hypothalamic pressure or destruction due to tumour causing reduction or loss of thyrotrophin releasing hormone produces tertiary hypothyroidism.

Table 3 Causes of hypothyroidism (in decreasing order of frequency)

Adult
Hashimoto's disease
^{131}I therapy for hyperthyroidism
Subtotal thyroidectomy for hyperthyroidism or tumour
Previous antithyroid drug therapy
Postpartum (60%–70% transient)
Drugs (lithium, amiodarone, iodides interferon alfa)
Pituitary hypothyroidism (secondary)
Hypothalamic hypothyroidism (tertiary)
Subacute thyroiditis, silent thyroiditis
Iodine deficiency
Generalised resistance to thyroid hormone
Child/neonate
Neonatal hypothyroidism
Thyroid agenesis
Thyroid ectopia
Thyroid dyshormonogenesis
Others
Resistance to thyroid hormone
Isolated TSH deficiency

INVESTIGATION

A high index of clinical suspicion is important. Symptoms such as lethargy, mild depression, variation in menstruation, and weight increase are common and non-specific but may be a pointer to the diagnosis of the hypothyroid state. The plethora of symptomatology means that patients may be referred to a variety of clinics—for example, gynaecology, psychiatry, neurology, cardiology, etc. The duration of the history should be ascertained as this often relates to the time taken to achieve full recovery. A family history of autoimmune endocrinopathy should be obtained. Recent pregnancy may suggest postpartum hypothyroidism.

CLINICAL EXAMINATION

The classic features of hypothyroidism should be assessed. A myotonic ankle jerk is the most discriminatory clinical feature. The thyroid gland should be palpated. The typical Hashimoto gland is firm and lobulated. In secondary or tertiary hypothyroidism the sallow waxy appearance of pituitary hypothyroidism may be apparent.

LABORATORY TESTS

A subnormal total or free thyroxine together with a raised TSH confirms the hypothyroid state. The sensitivity of the modern assays has made the thyrotrophin releasing hormone test redundant. Thyroid autoantibodies (antithyroid peroxidase antibody) should be determined routinely by ELISA or radioimmunoassay. Investigation of pituitary or hypothalamic hypothyroidism will be prompted by the initial finding of a low thyroxine and low TSH. Appropriate pituitary function tests and radiology must be arranged and the same procedures followed for suspected tertiary hypothyroidism. Care must be taken not to confuse apparently subnormal hormone values with a low triiodothyronine or euthyroid sick syndrome (see below). Serum triiodothyronine concentrations are a poor indicator of the hypothyroid state and should not be used.

SICK EUTHYROID SYNDROME

A range of thyroid function test abnormalities may be observed in non-thyroidal illness. The abnormalities are more likely with increasing severity of such diseases. The earliest change is a decreased concentration of free triiodothyronine.

This may be followed by low free thyroxine and TSH concentrations, resulting in transient central hypothyroidism, which has the beneficial effect of preventing excess tissue catabolism. High levels of reverse triiodothyronine are also noted.

Low free triiodothyronine levels are due to decreased concentrations of 5-monodeiodinase, the enzyme which catalyses the conversion of thyroxine to triiodothyronine. High concentrations of cortisol and free fatty acids, present in the sick state, inhibit the activity of this enzyme. Increased activity of the enzyme 5-monodeiodinase results in higher levels of reverse triiodothyronine, useful in distinguishing non-thyroidal illness from true central hypothyroidism. High reverse triiodothyronine levels correlate with increased mortality in severe non-thyroidal illness. Management with thyroid hormones is not beneficial since these biochemical changes are transient.

The cause of congenital hypothyroidism should be determined. A thyroid scan using ^{123}I or ^{99m}Tc pertechnetate will indicate the presence or absence of thyroid tissue or any evidence of ectopia. The presence of a rapidly growing large goitre in an elderly hypothyroid patient is suggestive of a thyroid lymphoma and fine needle biopsy is indicated. As a general rule, fine needle aspiration is not performed in patients with hypothyroidism but if there is a goitre with a dominant nodule fine needle aspiration will be necessary to exclude malignancy.

In primary hypothyroidism cardiac evaluation is important especially in middle aged to elderly patients and if angina has been noted or there is evidence of pre-existing heart disease. Usually this will be apparent in the history and an electrocardiogram will show classic low voltage changes with bradycardia. Echocardiographic assessment may be necessary in more severe cases.

TREATMENT

Laevo-thyroxine substitution therapy should be started once the diagnosis is secure. Laevothyroxine is preferred to triiodothyronine because of its longer half life and greater chance of compliance with once a day treatment.

In the absence of severe cardiac manifestations 0.1 mg is a reasonable starting dose in an adult. The patient should be reviewed in six to eight weeks and the dose increased to 0.15 mg/day. Underlying this straightforward approach are two questions: how much reliance can be placed on the patient's perceived response to thyroxine and what level of thyroid hormones (assuming they are measured) is reasonable while the patient is on therapy?

It should be noted that there is considerable variation in patient response to thyroxine

because of differential thyroid hormone receptor isoform tissue concentration. The patient's account of improvement or lack of it with thyroxine therapy should be assessed carefully; serum triiodothyronine concentration during thyroxine therapy must be in the normal range as should that of TSH. Serum thyroxine may exceed the upper limit of normal on thyroxine therapy without ill effect. Often, a high thyroxine and normal triiodothyronine is accompanied by a suppressed TSH (second or third generation assay) but this is not necessarily an indication to reduce the dose of thyroxine if the patient has responded satisfactorily. Clinically, such a response implies a normal pulse rate and complete resolution of presenting symptoms and signs. Occasionally cardiac symptoms such as palpitations will occur with a normal replacement thyroxine dose; in this case a β-adrenergic blocker drug is indicated.

Subclinical hypothyroidism, defined as the presence of a low normal serum thyroxine accompanied by a moderately raised TSH (grade 1, 5–10; grade 2, 10.1–20; grade 3, >20) should nearly always be treated. The patient is questioned carefully about any hypothyroid symptoms and if these are reported, treatment is started. Even asymptomatic patients may respond positively to therapy as shown in a controlled trial.

Apparent lack of response to thyroxine is not uncommon and should raise the possibility of (1) poor compliance with therapy, (2) presence of anaemia, particularly pernicious anaemia, (3) persisting underlying psychiatric abnormality, (4) other autoimmune disease, for example, Addison's disease (this should have been recognised at presentation), (5) other non-thyroid related disease. Hypothyroid myopathy can take up to a year to resolve completely.

As indicated above, the monitoring of thyroxine treatment should ideally be a combination of patient interview and inspection of thyroid hormone concentrations. Where this is not possible or convenient an automated system should be introduced whereby the patient is routinely asked to provide a blood sample for thyroid hormone measurement. Computerisation of the recall system will ensure compliance when dealing with large numbers of patients; this is an important aspect of the long term management as it is known that up to 15% of patients may default on their therapy.

Thyroid disease and pregnancy

It has been known for some time that pregnancy has an appreciable effect on thyroid economy. There are significant changes in iodine metabolism, thyroid hormone transport proteins, serum concentration of thyroid hormones and, especially in iodine deficient areas, thyroid gland size.

The placenta secretes human chorionic gonadotrophin, a glycoprotein hormone which shares an α subunit with TSH but has a unique β subunit, which confers specificity allowing it to act as a TSH agonist.

Pregnancy has a profound effect on the immune system in order to maintain the fetal/maternal allograft, which is not rejected despite displaying paternal histocompatability antigens. The presence of thyroid antibodies is associated with abortion, recurrent abortion, and infertility; fertility is impaired in hypothyroid women with autoimmune thyroid disease.

MANAGEMENT OF HYPERTHYROIDISM AND HYPOTHYROIDISM DURING PREGNANCY

The treatment of hyperthyroidism should preferably be with antithyroid drugs (table 4), although thyroid surgery can be preformed safely during the second trimester. Of the antithyroid drugs carbimazole may result rarely in aplasia cutis and there even have been suggestions of a carbimazole/methimazole specific embryopathy. For these reasons propylthiouracil is preferred. This drug passes into breast milk but less so than carbimazole and breast feeding may be allowed.

Patients already receiving thyroxine for hypothyroidism should increase their dose by at least 50 μg/day after confirmation of pregnancy. Thyroid function should then be tested and further adjustment made as necessary.

Table 4 Management of Graves' hyperthyroidism in pregnancy

Confirm diagnosis
Start propylthiouracil
Render patient euthyroid—continue with low dose antithyroid drugs up to and during labour
Monitor thyroid function regularly throughout gestation (4–6 weekly)
Adjust antithyroid drugs if necessary
Check TsAb at 36 weeks' gestation
Discuss treatment with patient
Effect on patient
Effect on fetus
Breast feeding
Inform obstetrician and paediatrician
Review postpartum—check for exacerbation

Postpartum thyroid disease

In 1948 H E W Roberton, a general practitioner in New Zealand, described the occurrence of lassitude and other symptoms of hypothyroidism relating to the postpartum period and treated them successfully with thyroid extract.

Postpartum thyroiditis (PPT) is characterised by the development of transient hyperthyroidism and/or hypothyroidism or both during the first six months of the postpartum period. The transient hyperthyroidism presents at about 14 weeks postpartum followed by transient hypothyroidism at a median of 19 weeks. PPT is usually associated with the presence of antithyroid peroxidase antibodies detected during pregnancy (in 10% of women at 16 weeks' gestation) and again in the postpartum period. Hypothyroidism is permanent in up to 25%–30% of women.

The disease occurs in 5%–9% of unselected postpartum women. Women with type 1 diabetes have a threefold incidence of PPT compared with non-diabetics. There is an increase of mild to moderate depression in antithyroid peroxidase positive women irrespective of thyroid status compared with controls. This may be seen as early as 6 weeks postpartum. It is possible that antibodies could modulate neurotransmitter function and it is known that there are cytokine receptors in the

brain. The possibility that thyroid antibodies are a marker for a specific genotype related to depression also requires investigation.

Follow up of antithyroid peroxidase positive women (at 16 weeks' gestation) nine years later has shown that the rate of development of hypothyroidism was significantly greater (48% *v* 8%) in those who had had PPT compared with those who were euthyroid antibody positive. There is a 70% chance of developing recurrent PPT after a first attack and 25% chance where the patient is antithyroid peroxidase positive without thyroid dysfunction. These data suggest that it would be beneficial to implement a screening programme for antithyroid peroxidase antibodies at the antenatal booking clinic. In support of this it has also been shown that babies and children born to women found to have thyroid antibodies during pregnancy may have reduced psychomotor performance compared with control children but more data are required to confirm these findings.

Iodine deficiency disorders (IDD)

The disorders induced by iodine deficiency are now recognised as part of a spectrum ranging from mild psychomotor impairment to severe forms of both neurological and myxoedematous cretinism. IDD constitute a major nutritional world problem in that 1.5 billion people in 118 countries are at risk. Around 655 million (about 12% of world population) have goitre. IDD are seen as the world's greatest single cause of preventable brain damage and mental retardation as some 43 million are significantly mentally handicapped (including 11.2 million with overt cretinism) due to IDD. Studies during the past three decades have emphasised the critical importance of circulating maternal thyroxine concentrations during the first trimester to ensure adequate fetal brain development and subsequent maturation. Side effects of iodine supplementation have been reported, the most important one being the occurrence of iodine induced hyperthyroidism, especially after the sudden and uncontrolled introduction of excessively iodised salt in severely iodine deficient populations. Nevertheless it is accepted that the benefits of iodine supplementation by far outweigh the risks.

Thyroid hormone resistance syndrome

This syndrome, originally described in a family with deaf mutism, stippled epiphyses and goitre, is characterised by a raised serum TSH in the presence of normal or even high thyroid hormone concentrations. The resistance to the action of thyroid hormone is usually generalised, when all tissues are resistant and the patient is euthyroid, or so-called "pituitary resistance" in which the peripheral tissues are normal thus resulting in an hyperthyroid state. The condition is almost always associated with a mutation in the thyroid hormone β-receptor gene. Resistance to thyroid hormone is a rare disorder, there being about 450 cases described, but it is important to recognise so that inappropriate treatment for apparent hyperthyroidism is not given. The condition is an autosomal dominant and the main clinical features include goitre, tachycardia, learning disabilities, and deafness. Growth retardation and delayed bone age are also seen. The diagnosis is made by noting high thyroid hormone levels in the presence of detectable TSH levels after exclusion of other causes of these laboratory findings. These include abnormal thyroid hormone binding proteins, replacement thyroxine therapy, neonatal period, systemic illness, and TSH secreting pituitary adenoma. Treatment to lower the TSH level has employed triiodothyroacetic acid or the D isomer of thyroxine. Symptomatic therapy with β-blockers, antithyroid drugs, and radioiodine can be used.

Drug induced thyroid dysfunction

Although several drugs may cause a wide array of minor alterations in thyroid function, clinically significant abnormalities are caused by only a few agents (see table 5).

AMIODARONE

This very effective antiarrhythmic agent contains approximately 37% iodine by weight. Thus a 200 mg tablet will deliver 6–12 mg of iodine/day, some 40 times the normal recommended intake of the element. The drug has effects on thyroid hormone synthesis as well as thyroid hormone metabolism.There is prevention of uptake and organification of iodine (Wolff-Chaikoff effect) with subsequent resumption of normal thyroid hormone synthesis. The peripheral conversion of thyroxine to triiodothyronine is reduced due to inhibition of the 5' monodeiodinase. This results in a fall in serum triiodothyronine and elevation of serum thyroxine as well as reverse triiodothyronine. The serum TSH is often raised in this situation.

Hyperthyroidism

Hyperthyroidism occurs in 2%–12% of patients on chronic therapy. In general thyrotoxicosis occurs in areas of iodine deficiency while hypothyroidism is seen more in iodine replete locations. Patients with pre-existing thyroid abnormalities develop iodide induced increased thyroid hormone synthesis (similar to jodbasedow) and hyperthyroidism due to Graves' disease or toxic nodular goitre may occur. This is known as type I hyperthyroidism and is to be distinguished from type II hyperthyroidism in which there is a destructive thyroiditis consequent on excess iodide

Table 5 Drugs and thyroid function

Drug	*Free thyroxine*	*Free triiodothyronine*	*TSH*
Amiodarone	↑/↓	↓/→	↑/→/↓
Lithium	↓		↑
Phenytoin	↓	↓	→
Phenobarbitone	↓	↓/→	→
Phenothiazine, NSAIDS	↓	↓	→
β-Blockers	↓	↓	→
Corticosteroids	↓/→	↓/→	↑
Heparin	↑	↑	↓
Aspirin	↑	↑	↓
Radiographic contrast medium	↑	↓	↑

NSAIDS = non-steroidal anti-inflammatory drugs.

Table 6 Aetiology of congenital hypothyroidism

Permanent		
Thyroid dysgenesis		
Thyroid agenesis		
TSH		
Defective synthesis (central hypothyroidism)		
Hyporesponsiveness		
Hyper-responsiveness		
Stimulating G protein deficiency		
Iodide transport defect		
Iodide organification defect		
Thyroglobulin synthesis defect		
Iodotyrosine deiodinase deficiency		
Other gene defects:		
Gene defect	*Mutation*	*Phenotype*
Thyroglobulin	Homozygous	Mouse
	Various complex	Goitrous hypothyroidism
Thyroid peroxidase	Homozygous	
	Heterozygous	
Iodide symporter	Homozygous	Goitre
TSH receptor	Homozygous	Mouse
	Heterozygous	TSH resistance
TTF2	Homozygous	Athyroid
PAX8	Heterozygous	
Transient		
Maternal antithyroid drug ingestion		
Excess maternal iodide ingestion (for example, amniofetography)		
TSH receptor blocking antibodies		
Extreme prematurity		
Transient hyperthyrotrophinaemia		

Table 7 Classification of thyroid cancer

Follicular cell tumours
Papillary carcinoma
Follicular carcinoma
Anaplastic carcinoma
C cell tumours
Medullary cell carcinoma
Other
Malignant lymphoma
Sarcoma
Secondary tumours

exposure. Clinical features may be masked by α and β blocking properties of the drug. Treatment of type 1 includes withdrawal of the drug if possible, administration of antithyroid drugs including potassium perchlorate if necessary, and the use of prednisone. Type 2 disease is managed with steroids similar to that used in other cases of thyroiditis.

Hypothyroidism

Hypothyroidism is usually associated with thyroid antibodies and is managed with standard thyroxine treatment. There is no necessity to withdraw amiodarone.

LITHIUM

This drug is used in the management of bipolar affective disorders. Thyroidal side effects have been described during the last 30 years. The clinical effects of the thyroidal actions of lithium are goitre and hypothyroidism, occurring in about 15%–20% and 5% of patients respectively.

Clinically the goitre is smooth and nontender. It may develop within weeks of starting lithium therapy but in other cases it may take months to years of lithium treatment before goitre occurs. Hyperthyroidism caused by lithium has been recorded but is uncommon. Thyroid function should be obtained before starting lithium and thereafter at six monthly intervals. It may be helpful to measure thyroid antibodies as well before therapy. If hypothyroidism develops thyroxine in normal therapeutic dose should be given. There is no indication for lithium withdrawal in this case.

Congenital hypothyroidism

Congenital hypothyroidism is the commonest metabolic abnormality in the Western hemisphere occuring in approximately one in 4000 live births (see table 6).

The advent of neonatal screening by examination of heel prick blood spot TSH or, in some cases, thyroxine has allowed early treatment of these infants with thyroxine thereby substantially, but not entirely, avoiding subsequent neuropsychomotor problems. Interestingly it has been noted that congenital hypothyroidism is often associated with other congenital malformations raising the possibility of discrete genetic defects in the aetiology. The discovery of genes relating to development of the thyroid has resulted in the description of at least one specific mutation associated with thyroid agenesis (table 6). Further analysis of cases of congenital hypothyroidism is awaited.

Thyroid cancer

The classification of thyroid cancer is shown in table 7.

The incidence of thyroid cancer is low in most countries and varies between 1–4/100 000/year. Although the overall incidence of thyroid cancer does not vary, the ambient iodine concentration influences significantly the distribution of different histological types (papillary, follicular, anaplastic). In iodine sufficient areas the most common type is papillary whereas in iodine deficient areas the follicular type exceeds or is as common as papillary. In iodine sufficient areas papillary accounts for about 65%–80% and follicular around 15%–30% with anaplastic rarely exceeding 5%. The ratio of papillary to follicular cancer ranges from as high as 6.5 in high iodine locations to as low as 0.19 in iodine deficient regions. Special mention should be made of the now well accepted highly significant increase in the incidence of thyroid cancer resulting from the Chernobyl nuclear power station accident in 1986. The increase affected those persons who were children in 1986 and the tumours, which are often aggressive in their behaviour, are thought to be related to the huge amounts of ^{131}I released at the time of the disaster.

While radiation exposure may be an important aetiological factor in thyroid cancer, major advances have been made in the past decade or so in the understanding of the molecular mechanisms involved in the initiation and progression of thyroid carcinoma. Genes thought to be involved in papillary and follicular carcinoma include the gsp, ret, trk, ras, met, and p53 oncogenes. Activation of the ret proto-oncogene located on chromosome 10 is critical in the initiation of papillary and medullary cancer while the p53 and N-ras may be important for progression of well differentiated thyroid carcinomas.

Treatment of differentiated thyroid cancer usually involves surgical resection of the tumour followed in many cases by radiotherapy. The measurement of serum thyroglobulin is used routinely as a tumour marker in the follow up of these patients. The thyroglobulin measurement may be subject to interference by the presence of thyroglobulin antibodies thus giving misleading clinical information (for example, assumption of remission due to false low thyroglobulin levels). If serum thyroglobulin is raised thyroxine suppressive therapy is withdrawn to allow for a radioiodine tumour localising scan to be performed.The recent advent of recombinant

Multiple choice questions in thyroid disorders

1. The incidence of congenital hypothyroidism in the Western hemisphere is:
(A) 1:500 live births
(B) 1:10 000 live births
(C) 1:2000 live births
(D) 1:1 000 000 live births
(E) 1:4000 live births

2. Amiodarone:
(A) Amiodarone tablets contain 37% iodine by weight
(B) Amiodarone induced thyrotoxicosis is common in iodine replete areas
(C) Amiodarone induced hypothyroidism is common in iodine replete areas
(D) The destructive thyroiditis caused by amiodarone is usually treated with antithyroid drugs
(E) In amiodarone induced hyperthyroidism, clinical features may be masked by the α and β-blocking properties of the drug

3. Thyroid disease and pregnancy:
(A) Human chorionic gonadotrophin shows a similar β subunit with TSH
(B) Fertility is impaired in women with autoimmune hypothyroidism
(C) The drug of choice for treatment of hyperthyroidism in pregnancy is methimazole
(D) Propylthiouracil causes aplasia cutis and embryopathy
(E) In the management of Graves' hyperthyroidism in pregnancy, thyroid stimulating antibody (TsAb) levels should be checked at 36 weeks' gestation

4. Graves' disease:
(A) Is the commonest cause of hyperthyroidism in the UK
(B) The presence of TsAb may predict relapse after treatment with antithyroid drugs
(C) The remission rate of Graves' hyperthyroidism is dependent on the dose of antithyroid drugs employed
(D) Agranulocytosis complicating thionamide use invariably responds to administration of granulocyte colony stimulating factor
(E) The optimum initial dose of carbimazole in Graves' hyperthyroidism should not exceed 10 mg daily

5. Autoimmune thyroiditis:
(A) Histology shows thyroid follicles infiltrated by eosinophils
(B) 5% of women with positive thyroid antibodies develop hyperthyroidism per year
(C) Is clinically more common in males than females
(D) Is usually associated with the presence of antithyroid peroxidase and thyroglobulin antibodies
(E) May coexist with Graves' disease

6. Hypothyroidism and pregnancy:
(A) Hypothyroid patients who become pregnant may be required to increase their dose of thyroxine by 50 μg daily
(B) Postpartum thyroiditis may present as frank hyperthyroidism
(C) Depression is not a feature of postpartum thyroiditis
(D) Children of poorly controlled hypothyroid mothers may have inferior psychomotor performance
(E) The hypothyroidism of postpartum thyroiditis may persist in 20%–30% of cases

7. Thyroid cancer:
(A) The incidence in most countries varies between 1–4/100 000/year
(B) Papillary cancers are the commonest variety in iodine deficient areas
(C) Follicular cancers are the commonest variety in iodine sufficient areas
(D) Radiation exposure may be an important aetiological factor
(E) Measurement of serum thyroglobulin is used routinely as a tumour marker

8. Iodine deficiency disorders (IDD):
(A) IDD are not now a major world nutritional problem
(B) IDD are the greatest single cause of preventable brain damage and mental retardation
(C) Over a 10th of the world's population have a goitre
(D) Adequate maternal thyroxine levels in the first trimester are required for fetal brain development
(E) Iodine deficiency still exists in some parts of Europe

TSH will result in a much shorter period of hypothyroidism when thyroxine is withdrawn and thus represents a significant advance in management.

While there have been encouraging advances in understanding the aetiology and management of differentiated thyroid cancer and some progress in medullary cancer including multiple endocrine neoplasia no similar reports are available for anaplastic cancer. This tumour, although rare, is the most aggressive solid tumour known. The spindle and giant cell variants are resistant to treatment and trials of multimodal therapy are difficult because of small numbers of cases.

Reading material

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Answers: true (T)/false(F)

1. (A) F, (B) F, (C) F, (D) F, (E) T; 2. (A) T, (B) F, (C) F, (D) F, (E) T; 3. (A) F, (B) T, (C) F, (D) F, (E) T; 4. (A) T, (B) F, (C) F, (D) F, (E) F; 5. (A) F, (B) T, (C) F, (D) T, (E) T; 6. (A) T, (B) T, (C) F, (D) T, (E) T; 7. (A) T, (B) F, (C) F, (D) T, (E) T; 8. (A) F, (B) T, (C) T, (D) T, (E) T.