CURRENT ASPECTS OF THYROID DISEASE

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INTRODUCTION

During the past two decades or so, advances in immunology and molecular biology have contributed to a substantial increase in our understanding of many aspects of the pathophysiology of thyroid disease.[1] This review will indicate some of these advances prior to illustrating their significance in clinical practice. Emphasis is placed on recent developments and it is not intended to provide full clinical descriptions.

THYROID HORMONE ACTION

Since the discovery that the thyroid hormone receptor is derived from the erb c oncogene, it has been realised that there are two receptor types, alpha and beta, whose genes are located on chromosomes 3 and 17 respectively.[2] There is now known to be differential tissue distribution of the active TRs alpha 1 and beta 1 and 2. For example, TR beta 2 is mainly confined to the pituitary gland. Thyroid hormone action at the cell level occurs when the ligand (T3) binds to the T3 receptor in the nucleus, thereby activating a complex chain of events that results in protein synthesis.

THYROID IMMUNOLOGY

The demonstration of thyroid autoimmunity in 1956 by Roitt and colleagues, as well as others, paved the way for an appreciation of both the humoral and the cellular aspects of thyroid autoimmunity.[3] The major thyroid autoantigens have been identified and their genes characterised (Table 1).

The effects of humoral immunity on the pathogenesis of autoimmune thyroid disease are well established, but changes in the cellular immune system also occur. The characterisation of so-called Th1 and Th2 immune responses,[4] in addition to further elucidation of T-cell interaction with antigen, has aided discussion of (but not solved) the details of the immune dysfunction in these conditions. Since the description of the HLA system and the association of certain haplotypes with autoimmune endocrine disease, including Graves' disease and Hashimoto's thyroiditis, it was anticipated that the immunogenetics of these diseases would shed definitive light on their pathogenesis. This hope has only been partially achieved, and the relative risk of the HLA haplotype has been low; other factors must be sought. Developments in the understanding of the interaction between the T lymphocyte and the presentation of antigen (e.g. co-stimulatory signals) have enabled further immunological insight.[5] However, the role of environmental factors should not be overlooked. The ambient iodine concentration may affect the incidence of autoimmune thyroid disease, and iodine has documented immune effects in the thyroid gland both *in vitro* and *in vivo*.[6] Studies of thyroid disease in twins also indicate that environmental as well as genetic factors are important in the aetiology of many thyroid diseases.[7]

GRAVES' DISEASE

Thyroid stimulation caused by IgG TSH-stimulating antibodies is the cardinal feature in this condition. The antibody binds to the very large extracellular domain of the thyroid stimulating hormone (TSH) receptor, resulting in conformational change and subsequent intracellular cyclic AMP stimulation.[8] Stress appears to be an initiating factor,[9] although why the disease is six to seven times more common in women is not clear.

The treatment of Graves' hyperthyroidism has not altered in principle during the past 50 years despite intensive research. Furthermore, the goal of predicting which individual patient will relapse after receiving a course of antithyroid drugs has not been achieved. In addition to the presence or absence of TSH receptor antibodies, knowledge of other factors is clearly necessary to clarify

TABLE 1
Features of the major thyroid autoantigens.

	TSHR	**NIS**	**TPO**	**Tg**
Chromosome	14	19	2	8
MW kda	85	65–77	105–110	660
Protein	G protein	Transmembrane transporter	Haemoprotein enzyme	Iodinated glycoprotein
Function	Receptor for TSH	Iodide uptake	Iodination and coupling of Tyrosine	Storage of T4 + T3

TSHR Thyroid stimulating hormone receptor
NIS Sodium iodide symporter
TPO Thyroid peroxidase
Tg Thyroglobulin

the problem. Differences in preference for either radioiodine therapy or drug therapy have been observed in the US, Europe and Japan,[10] due at least in part to economic reasons as well as availability of facilities. In the US, radioiodine is the favoured first choice for treatment, whereas antithyroid drugs are the first choice in Europe and Japan. Surgical treatment is a minority choice in all areas.

SUBCLINICAL HYPERTHYROIDISM

This refers to the situation where the serum TSH concentration is suppressed but the thyroid hormone concentrations (either free or total) are within the normal reference range. This situation is often discovered by chance following presentation with non-specific symptomatology, and the question to be asked then is whether or not treatment should be offered. In favour of treatment is the demonstration from long-term data from the Framingham study that persons otherwise normal, but with this thyroid profile, develop atrial fibrillation significantly more frequently than carefully matched euthyroid control subjects.[11] However, no randomised trials comparing treatment vs no treatment have been carried out in patients with sub clinical hyperthyroidism. At present, a reasonable strategy is to consider each patient individually, taking into consideration factors such as age, general medical condition, cardiac status and possible effects on bone density, before coming to a treatment decision.

THYROID-ASSOCIATED OPHTHALMOPATHY

Thyroid-associated ophthalmopathy is present in many but not all patients with Graves' disease. The aetiology is not known but the demonstration of the TSH receptor in orbital fat[12] and various antibodies to extraocular[13] muscle components suggest involvement of both these tissues in this immunologically-mediated disease. Cigarette smoking is also a significant risk factor.[14] It is agreed by many (though not all) that radioiodine therapy may exacerbate the condition, and that this is ameliorated by a six to eight week course of prednisolone at the time of therapy. Recent improvement in assessment of eye disease by CT and MRI orbital scanning, in addition to careful ophthalmic examination, have made it possible to assess the effects of steroids (pulsed dose or maintenance) with or without azathioprine, radiotherapy and/or operative intervention to achieve surgical decompression on outcome. Nevertheless, only a few well-conducted randomised trials have been carried out in this field, and much further work is required.

The psychological effect of even mild ophthalmopathy should not be overlooked and there is a need for more oculoplastic procedures to be performed when the disease has become quiescent. Correction of strabismus, lid retraction, lid lag and excess periorbital fat deposition will contribute to significant improvement in appearance.

OTHER CAUSES OF HYPERTHYROIDISM

Activating somatic mutations of the thyrotropin receptor gene have been identified in some autonomously functioning thyroid adenomas which cause hyperthyroidism; germ line mutations are seen in some cases of familial hyperthyroidism.[17] The latter are characterised by a diffuse goitre but negative thyroid stimulating anitbodies. Patients with toxic multinodular goitre often have been known to have euthyroid goitre for many years, but the development of nodular autonomy is often associated with an increase in the ambient iodine concentration resulting in hyperthyroidism. Other factors leading to autonomy are less well defined but growth characteristics including oncogenic stimulation are relevant. Some of the nodules in these patients are monoclonal and the cell line may have activating mutations of the TSH receptor gene. It is important to recognise these mutations as genetic counselling may then be given as well as a decision reached on the need for a complete removal of the thyroid gland.

THERAPY OF HYPOTHYROIDISM

Hypothyroidism is most often due to Hashimoto's autoimmune thyroditis, post-radioiodine therapy or following bilateral subtotal thyroidectomy. Other causes such as amiodarone- or lithium-induced hypothyroidism also occur. Therapy with thyroxine should have as goals patient wellbeing coupled with normal circulating thyroid hormone concentrations. Often only the former is achieved at the expense of a suppressed TSH, an elevated thyroxine level with a normal tri-iodothyronine concentration. In my opinion, sole reliance on the TSH measurement to indicate adequacy of replacement therapy often results in under-replacement from a clinical point of view. Clearly the caveats relating to bone density and cardiac arrhythmias must be carefully considered in this situation. The reasons for the difficulty in correlating clinical status with hormone concentration are probably related to the fact that thyroid hormone receptors exist in different isoforms and there is also differential tissue distribution of these receptors. Although the TSH level represents an accurate indication of pituitary thyroid status, there are no other indices of a similar level of precision reflecting thyroid status in other tissues.

Patients with circulating thyroid hormone concentrations in the normal reference range should not be treated with thyroid hormone following presentation with non-specific symptomatology which might be thought to be thyroid-related. Mention should be made of a recent study in which a combination of T4 and T3 was given as replacement therapy with beneficial effects on some psychological aspects.[18] The patient population was not homogenous and further work is required before this combination therapy can be judged to be of value.

CONGENITAL HYPOTHYROIDISM

This occurs in one per 4,000 and has been routinely screened for in neonates in the Western world for the past 25 years. As thyroid hormone plays a critical role in fetal and neonatal brain maturation, it is essential to start thyroxine therapy as early as possible after diagnosis. Usually this is achieved by two weeks of age. Recent advances in genetic analysis have resulted in the appreciation of a diverse number of causes of congenital hypothyroidism (Table 2).

THYROID HORMONE RESISTANCE SYNDROME (RTH)

This is an uncommon but important disorder as it illustrates the mechanism of thyroid hormone action; some patients with the condition may have been treated unnecessarily for apparent thyroid dysfunction which does not exist. The syndrome is characterised by reduced responsiveness of target issues to circulating thyroid hormones. In practice

TABLE 2
Aetiology of congenital hypothyroidism.

Permanent	
	Thyroid dysgenesis
	Thyroid agenesis
	TSH – defective synthesis (central hypothyroidism)
	– hypo-responsiveness
	– hyper-responsiveness
	Stimulating G protein deficiency
	Iodide transport defect
	Iodide organification defect
	Thyroglobulin synthesis defect
	Iodotyrosine deiodinase deficiency
	Other gene defects
Transient	
	Maternal antithyroid drug ingestion
	Excess maternal iodide ingestion (e.g. amniofetography)
	TSH receptor blocking antibodies
	Extreme prematurity
	Transient hyperthyrotrophinaemia

this is demonstrated by an inappropriate secretion of TSH in the presence of high thyroxine and T3 concentrations. These biochemical findings may also be seen in other disorders, such as a TSH secreting tumour, acute psychiatric disorders and some drugs (e.g. amiodarone). Most patients with generalised resistance to thyroid hormone are euthyroid when all the peripheral indices of thyroid function are measured. Pituitary resistance is selective and the patient may develop hyperthyroidism which may be life threatening. The clinical and neuropsychological features are the subject of several reviews.[19] Extensive research has also been carried out into the molecular pathology of this syndrome. The condition is due to a mutation in the TR beta gene, and is familial and dominantly inherited. The effect of the various mutations (more than 70 have been described) is to reduce or otherwise interfere with the binding of T3 to its receptor and thereby inhibit its action at the cell level. This in turn will result in high TSH levels, goitre and, usually, maintenance of normal or high hormone concentrations. Careful monitoring of peripheral effects of thyroid hormone, particularly cardiac function, should be done. Measurement of growth and neurological function are important when managing RTH in childhood.

PREGNANCY, THYROID FUNCTION AND DISEASE

Pregnancy has an appreciable effect on thyroid economy.[20] An increased excretion of iodine in the urine during pregnancy accounts for the increase in thyroid volume even in areas of moderate dietary iodine intake.[21] Iodine deficiency during pregnancy is associated with maternal goitre and reduced maternal T4 level which is seen in areas of endemic cretinism. The increase in thyroid volume is substantially greater in iodine-deficient areas. This gestational goitrogenesis is preventable by iodine supplementation, not only in areas of severe iodine deficiency (24 hour urinary iodine less than 50 μg), but in countries such as Belgium and Denmark, where trials have shown clear beneficial effects on maternal thyroid size.[22] The aim of these studies is to increase the iodine supply to pregnant and lactating women to at least 200 μg/day.[23]

Thyroid hormone transport proteins increase during pregnancy, particularly TBG, which increases due to enhanced hepatic synthesis and a reduced degradation rate due to oligosaccharide modification. A transient rise in FT4 occurs in the first trimester due to the relatively high circulating human chorionic gonadotrophin (hCG) concentration and a decrease of FT4 and FT3 in the second and third trimester, albeit within the normal reference range. In iodine-deficient areas (including marginal iodine deficiency seen in many Continental European countries) the pregnant woman may become significantly hypothyroxinaemic with preferential T3 secretion.

Apparently normal pregnant women who are known to be marginally hypothyroid during gestation (i.e. with a raised TSH concentration) have children whose intellectual development is significantly inferior to control women who have been shown to be euthyroid during pregnancy.[24] These studies have been performed in iodine-sufficient areas but have yielded similar results to those seen in iodine-deficient regions. The health impact of these data is substantial as the prevalence of a raised TSH in gestation is around 2·5%, and 15% of children born to these mothers will have an IQ less than 85, compared to just 5% of children born to mothers with normal thyroid function during pregnancy.

A further aspect of gestational thyroid status is that about 10% of women will have circulating thyroid antibodies (usually antithyroid peroxidase) which are a marker for the subsequent development of postpartum thyroid dysfunction (see below). These data raise important questions in relation to the advisability of routine screening of thyroid function in early pregnancy, for example at the booking clinic.

Hyperthyroidism in pregnancy occurs in up to 0·2% of women. The commonest cause is Graves' disease (85–90%), but other causes, such as toxic multinodular goitre, toxic adenoma and subacute thyroiditis, may occur. Rarer causes include struma ovarii, hyperemesis gravidarum and hydatidiform mole.

The clinical presentation of hyperthyroidism may not be as obvious as symptoms of tachycardia, sweating, dyspnoea and nervousness, which are all seen in normal pregnancy, as are cardiac systolic flow murmurs. Maternal complications include miscarriage, abruptio placentae and pre-term delivery. Congestive heart failure and thyroid 'storm' may also occur, and the risk of pre-eclampsia is significantly higher in women with poorly controlled hyperthyroidism.[25] Neonatal hyperthyroidism, prematurity and intrauterine growth retardation may also be observed. Hyperthyroidism should undoubtedly be treated during pregnancy to lessen this complication rate.

Gestational amelioration of Graves' disease is often associated with a reduction in titre of TSHR Ab and a change from stimulatory to blocking antibody activity.[26] A variety of TSHR Ab directed against the TSH receptor may occur in pregnant patients with Graves' disease: Zakarija *et al.*,[27] for example, reported the presence of two species of stimulating antibody in a patient who gave birth to three children with transient neonatal hyperthyroidism. Thyroid stimulating hormone blocking antibodies have been shown to cause maternal hypothyroidism which

developed during gestation.[28] In addition, TSAb can cross the placenta and be shown by cordocentesis to be present in the fetus.[29]

MANAGEMENT OF GRAVES' HYPERTHYROIDISM IN PREGNANCY (SEE TABLE 3)

Carbimazole is still widely used although there is now a good case for preferably using propylthiouracil (PTU) as this drug does not seem to be associated with the (admittedly rare) occurrence of *aplasia cutis* in the newborn. Propylthiouracil should be given in a dose of 100–150 mg three times daily until the patient becomes euthyroid, at which time the dose should be reduced to the lowest amount possible to maintain the euthyroid state with serum T4 at the upper end of normal.[25] It should be continued up to, and through, labour, if necessary. In terms of rapidity of action and fetal hypothyroidism inducing potential, little reason exists to choose PTU over carbimazole. The so-called 'block and replace' regimen in which thyroxine is given with antithyroid drug should be used with caution because the dose of antithyroid drug might be too high and cause fetal goitre and hypothyroidism. Hashizume *et al.*[30] reported that T4 administration to pregnant women with Graves' hyperthyroidism during pregnancy and after delivery, together with methimazole, was effective in reducing the incidence of postpartum recurrence of hyperthyroidism (*vide infra*), but these results have not been confirmed.

HYPOTHYROIDISM AND PREGNANCY

The prevalence of hypothyroidism in pregnancy as demonstrated by the finding of an elevated TSH is 2·5%.[31] A woman with a high TSH should be given thyroxine therapy for her own benefit as well as for that of the fetus. An increased thyroxine dose requirement occurs in those women already receiving the hormone before pregnancy.[32] Usually an increase of 50 mg is sufficient, but thyroid function should be monitored as some women will need more than this.

POSTPARTUM THYROID DISEASE (PTD)

Postpartum thyroiditis (PPT)

Following the first modern clinical description of PPT by Roberton in 1948,[33] the condition was rediscovered in Canada[34] and Japan[35] in the 1970s and has been reviewed.[36] Of the ten per cent of pregnant women who have positive anti-TPO antibodies during gestation, 50% will develop postpartum thyroid dysfunction characterised by transient hyperthyroidism occurring about 13 weeks, transient hypothyroidism at around 19 weeks or both sequentially. Twenty to thirty per cent of hypothyroid women progress to permanent hypothyroidism within one year postpartum. Those women who develop transient thyroid dysfunction have a 50% chance of permanent thyroid dysfunction after seven years and should therefore be followed long-term. In addition, women who are anti-TPO Ab positive have an increased incidence of mild to moderate postpartum depressive symptoms compared to antibody-negative women.

Postpartum thyroiditis is a destructive thyroiditis similar to sub-acute thyroiditis but is almost invariably painless; it is associated with a low thyroidal radioiodine uptake, increased serum thyroglobulin and urinary iodine. The condition is related to the 'immune rebound' seen after pregnancy and is analogous to the postpartum relapse of rheumatoid arthritis and systemic lupus erythematosus. Treatment of the hyperthyroid phase is usually not necessary, but the hypothyroid period is often profoundly symptomatic and thyroxine should be given.

POSTPARTUM GRAVES' DISEASE

Women with an immunogenetic predisposition to develop Graves' disease often will do this in the postpartum period because of the immune changes previously described. The differentiation of this form of hyperthyroidism from that due to thyroiditis may be made by determining the iodine uptake or the presence of TSH receptor antibodies.

THYROID CANCER

Thyroid cancer accounts for only about one per cent of tumours in humans but the study of the pathogenesis has yielded a large amount of information about molecular mechanisms of causation.[37] As alluded to above, a mutation of the TSH receptor gene can give rise to an activating mutation which results in a benign hyperfunctioning adenoma. Activating point mutations have also been found in the alpha sub-unit of the Gs protein gene which is involved in producing an increase in cyclic AMP in the cell in response to TSH stimulation.

The study of the role of oncogenes in thyroid cancer has shown a high frequency of RAS gene mutations in

TABLE 3
Management of Graves' disease in pregnancy.

Confirm diagnosis
Start propylthiouracil
Render patient euthyroid – continue with low dose ATD up to and during labour
Monitor thyroid function regularly throughout gestation (four to six weekly) adjust ATD if necessary
Check TSAb
Discuss treatment with patient effect on patient effect on fetus breast feeding
Inform obstetrician and paediatrician
Review postpartum – check for exacerbation

benign and malignant tumours. It is clear that this oncogene acts to cause follicular cell proliferation leading to papillary as well as follicular cancer. The RET proto-oncogene (which encodes a tyrosine kinase receptor) is activated and rearranged in papillary carcinoma and known as RET/PTC (papillary thyroid cancer). Interestingly, germ line mutations of the RET gene are associated with the different syndromes of medullary thyroid cancer (familial, MEN IIA, MEN IIB, sporadic medullary cancer). Other oncogene abnormalities in the TRK, MET and p53 genes are described in differentiated thyroid cancer. Recent molecular analysis of childhood thyroid cancers resulting from the catastrophic release of radioactive nuclides at Chernobyl in 1986 has shown a high frequency of oncogene mutations, particularly in RET/PTC and RAS.

In general, the management of thyroid cancer is a radical resection of the tumour followed by radioiodine ablation therapy of any residual functioning thyroid tissue. The patient then receives suppressive doses of thyroxine. The introduction of the recently developed recombinant thyroid stimulating hormone preparation[38] has led to a significant improvement in quality of life for patients at the time when thyroid scanning is necessary for follow-up assessment. Refinements in the assay methodology of serum thyroglobulin, the marker of the presence of functioning thyroid tissue, have also improved the assessment of tumour recurrence.[39]

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