# STARLING REVIEW

# Thyroid hormone in health and disease

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## Abstract

Thyroid disease is common, affecting around 2% of women and 0·2% of men in the UK. Our understanding of the effects of thyroid hormones under physiological circumstances, as well as in pathological conditions, has increased dramatically during the last two centuries and it has become clear that overt thyroid dysfunction is associated with significant morbidity and mortality. Both hypo- and hyperthyroidism and their treatments have been linked with increased risk from cardiovascular disease and the adverse effects of thyrotoxicosis in terms of osteoporosis risk are well established. Although the evidence suggests that successful treatment of overt thyroid dysfunction significantly improves overall survival, the issue of treating mild or subclinical hyper- and hypothyroidism remains controversial. Furthermore, the now well-established effects of thyroid hormones on neurodevelopment have sparked a whole new debate regarding the need to screen pregnant women for thyroid function abnormalities. This review describes the current evidence of the effects of thyroid hormone on the cardiovascular, skeletal and neurological systems, as well as the influence of thyroid diseases and their treatments on the development of malignancy. Furthermore we will describe some recent developments in our understanding of the relationship between thyroid status and health.

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## Introduction

Despite the discovery of a gland in the neck during the Renaissance period, and the knowledge that its enlargement causes neck swelling, it took until 1656 for this gland to be given its modern name 'the thyroid gland' by Thomas Wharton (Wharton 1664). During the 19th century, Coindet, an Edinburgh-trained physician working in Geneva, Switzerland, successfully treated goitres with iodine and in 1891, sheep thyroid extract was used to cure myxoedema (Sawin 2000). It took until 1914 before Kendall and Osterberg isolated the active substance in this extract and named it thyroxine (Kendall 1915, Sawin 2000). During the 19th century, thyrotoxicosis was described for the first time by Robert Graves in women presenting with goitre, rapid heartbeat and exophthalmos, although it was thought that the underlying cause was cardiac in nature (Graves 1835, Sawin 2000). Similarly hypothyroidism as a clinical syndrome was recognised in the 1870s and considered either a neurological or a skin disorder (Gull 1874, Sawin 2000). The dramatic increase in our understanding of thyroid hormone action as well as of the clinical implications of thyroid dysfunction that has occurred during the last two centuries, will be described in this review.

Thyroid hormones are key regulators of metabolism and development and are known to have pleiotropic effects in many different organs. The thyroid gland synthesises and releases triiodothyronine (T3) and thyroxine (T4), which represent the only iodine-containing hormones in vertebrates. T4 is the main product of thyroid secretion and local deiodination in peripheral tissues produces T3, the biologically active thyroid hormone. T3 and T4 are bound to thyroglobulin, providing a matrix for their synthesis and a vehicle for their subsequent storage in the thyroid. More than 99% of the circulating T3 and T4 is protein bound, mainly to T4-binding globulin and to a lesser extent to transthyretin and albumin. Thyroid hormones can rapidly be released from these proteins, this process facilitating their entry into cells. The production of thyroid hormones is controlled by serum thyrotrophin (TSH) synthesised by the anterior pituitary gland in response to TSH–releasing hormone (TRH), which is secreted by the hypothalamus. Unbound or free T3 and T4 (fT3 and fT4 respectively) exert a negative feedback on the synthesis and release of TSH and TRH in order to maintain circulating thyroid hormone levels within the required range.

The actions of thyroid hormones are initiated by their interaction with thyroid hormone receptors (TRs), which belong to a large superfamily of steroid hormone receptors
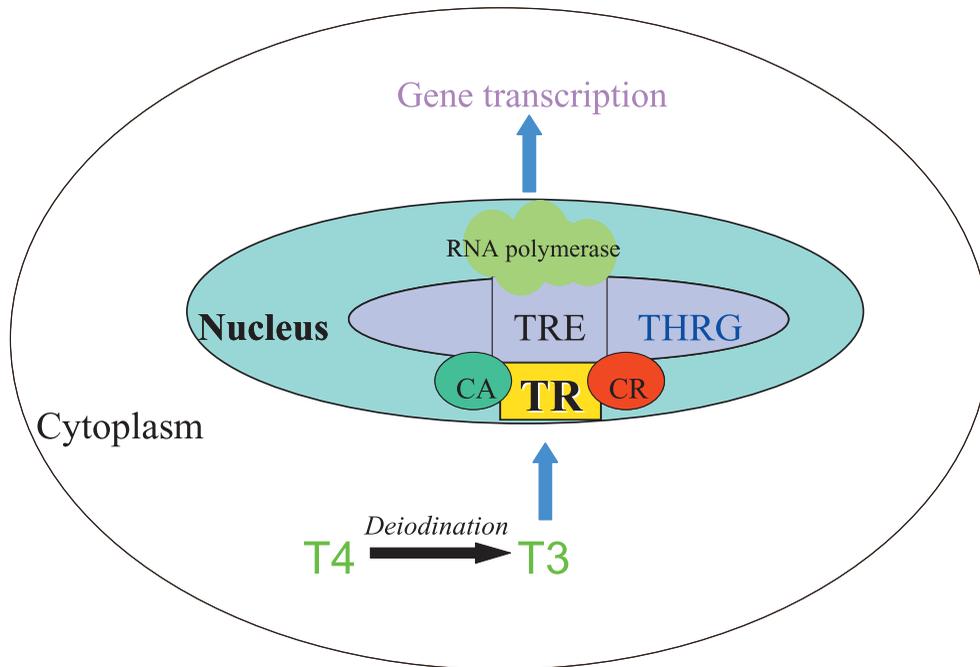
**Figure 1** Transactivation of thyroid hormone responsive genes (THRG) through the binding of T3 to thyroid hormone receptors (TR) followed by T3–TR binding to the thyroid response element (TRE) located in the promoter regions of THRG. Transactivation is regulated by co-activators (CA) and co-repressors (CR) which bring about conformational changes in the DNA structure, altering the thyroid hormone responsive gene accessibility to RNA polymerase, the enzyme responsible for gene transcription.

other members of which include the sex steroid receptors, vitamin D receptors and retinoic acid receptors. Four important TR isoforms (TRα1, TRα2, TRβ1 and TRβ2) have been well characterised in humans while several minor TR isoforms have also been identified more recently (Williams 2000). TRs have a central DNA–binding domain containing two zinc fingers, a carboxy-terminal ligand-binding domain and a transactivation site, as well as an amino-terminal domain with a poorly defined function (Yen 2001). The major functional TRs include TRα1, TRβ1 and TRβ2. They bind the ligand, T3, with similar affinity and binding kinetics, with $K_m$ values of 1–10 nM (Lazar 1993, Yen 2001). T3–TR complexes then bind to thyroid hormone response elements (TREs), which are specific DNA sequences found in the regulatory regions of target genes. During this process, nuclear proteins known as co-repressors and co-activators are recruited or excluded from T3–TR–TRE interactions. This causes a direct conformational change of chromatin through the acetylation or deacetylation of histones locally, which results in the loosening or compaction respect-ively of the chromatin structure, thus regulating the accessibility of the gene to the transcriptional machinery. The functional TRs thus serve to promote or inhibit the transcription of thyroid hormone responsive genes (Munoz & Bernal 1997) (Fig. 1). TR action typically involves homo- and hetero-dimerisation with other TR isoforms and steroid receptors. Whereas TRs can be homodimeric, heterodimerisation with retinoid X-receptors strongly enhances their binding to the TRE (Darling *et al.* 1993). In contrast to the other TRs, the TRα2 protein does not bind T3 and has a postulated modulatory role mediated by competitive binding of the α2 protein to TREs. The expression and regulation of TRs and thyroid responsive genes is variable in different tissues, which allows a multitude of possible ways in which thyroid hormones can exert their effects.

Overt thyroid dysfunction is common in the general population. The Whickham survey, conducted in the north of England, revealed a prevalence of thyrotoxicosis or hypothyroidism of at least 2% in females and 0·2% in males in the UK (Tunbridge *et al.* 1977). A 20 year follow-up study of the population of Whickham reported a mean incidence of 0·8/1000 per year for hyper-thyroidism and of 4·1/1000 per year for hypothyroidism in women, the incidences in men being negligible and 0·6/1000 per year respectively (Vanderpump *et al.* 1995). Additionally, subclinical thyroid dysfunction, defined as serum TSH levels outside the normal reference range with normal levels of fT4 and fT3, is even more common. Biochemical assessment of thyroid function in a large cohort of 25 863 subjects attending a State–wide health fair

in Colorado revealed a prevalence of elevated TSH of 9·5% and of decreased TSH of 2·2%, with most subjects suffering from subclinical disease defined biochemically (Canaris *et al.* 2000). In agreement with previous studies, the prevalence of both subclinical hyper- and hypothyroidism was found to be greater in women and increased with age. Indeed, an earlier UK survey of 1210 subjects aged over 60 years indicated rates of subclinical hypothyroidism of 11·6% in females and 2·9% in males, with similar values for serum TSH concentrations below the normal range (Parle *et al.* 1991).

Abnormal serum TSH concentrations, especially low serum TSH, may reflect a variety of causes, including therapy with drugs such as glucocorticoids and dopamine, as well as non-thyroidal illnesses (Spencer *et al.* 1990), but a major association is with treatment for thyroid disease itself (Davies *et al.* 1992). Treatment of Graves' hyperthyroidism with antithyroid drugs or radioiodine ($^{131}$I) is frequently associated with prolonged suppression of serum TSH despite restoration of normal circulating thyroid hormone concentrations, while amongst the large population taking thyroid hormone replacement therapy, serum TSH values are abnormal in approximately half (Parle *et al.* 1993, Canaris *et al.* 2000). Furthermore, treatment of hyperthyroidism with either $^{131}$I or surgery is associated with an increased risk of development of either subclinical or overt hypothyroidism (Franklyn *et al.* 1991) and the natural history of nodular goitre is often manifest as eventual development of subclinical or overt hyperthyroidism.

It is well recognised that overt thyroid disease is associated with significant symptoms and signs, while for subclinical thyroid dysfunction the evidence of an association with such symptoms and signs remains less clear (Surks *et al.* 2004). However, there is growing evidence that both mild and overt thyroid dysfunction and their treatments cause clinically significant long-term morbidity and mortality. Before the advent of effective treatments for overt thyrotoxicosis and hypothyroidism, death from cardiovascular disease often resulted. Cardiovascular disease remains the most significant association with thyroid dysfunction and its treatment at this time. The influence of thyroid hormone excess on bone metabolism has led to extensive investigation of osteoporosis risk in those with overt and subclinical thyrotoxicosis. The effects of thyroid hormone on the central nervous system (CNS) are now well recognised and have led to the investigation of thyroid dysfunction in the context of fetal neurodevelopment as well as neuropsychiatric morbidity (especially dementia) in adults. Given the almost ubiquitous influence of thyroid hormones on physiological systems in the human body it is not surprising that thyroid dysfunction has also been associated with significant morbidity unrelated to the heart, skeleton and CNS. Finally, both thyroid dysfunction and its treatment have been implicated in the development of cancers, most attention focusing upon the potential carcinogenic effect of radioiodine therapy in the treatment of hyperthyroidism.

## Current concepts

### Thyroid hormone and the heart

**The effects of thyrotoxicosis on cardiovascular morbidity and mortality** Despite the availability of effective treatments, the major clinically significant effects of thyrotoxicosis remain those on the cardiovascular system, both at presentation and during treatment. Furthermore, there is growing evidence for long-term influences of thyrotoxicosis and its treatment on later cardiovascular morbidity and mortality. Typical cardiovascular symptoms found at presentation of thyrotoxicosis include palpitation, tachycardia, exercise intolerance, exertional dyspnoea and orthopnoea (Klein & Ojamaa 2001). While these are present in the majority of subjects with overt thyroid hormone excess, their clinical importance is overshadowed by the challenges posed by atrial fibrillation (AF), which occurs in 5–15% of patients with thyrotoxicosis and may be the presenting problem (Sandler & Wilson 1959, Forfar *et al.* 1979, Sawin *et al.* 1994, Gilligan *et al.* 1996). Higher prevalence rates are found in older patients and in those with known or suspected underlying organic heart disease (Forfar *et al.* 1979, Nordyke *et al.* 1988). Despite this clear association between thyrotoxicosis and AF, when subjects with new onset of AF have been investigated, overt hyperthyroidism has been reported to be an uncommon cause (<1%) (Krahn *et al.* 1996), so although hyperthyroidism is a risk factor for AF, this association is uncommon in the absence of additional symptoms and signs of thyrotoxicosis.

Effective treatment of thyrotoxicosis is frequently associated with restoration of sinus rhythm. In those with new-onset AF complicating thyrotoxicosis, spontaneous reversion to sinus rhythm may occur in up to 50%, and typically does so within a few months of restoration of euthyroidism (Nakazawa *et al.* 1982). Restoration of normal rhythm is, however, much less likely in those with underlying heart disease or AF of longer duration (Sandler & Wilson 1959, Nakazawa *et al.* 1982, Nordyke *et al.* 1988). In those not returning to normal rhythm spontaneously, pharmacological or electrical cardioversion should be attempted only after the patient has been rendered euthyroid (Nakazawa *et al.* 1982, Klein & Ojamaa 2001).

The potential association between AF and arterial embolisation, especially to the cerebral circulation, is a major factor supporting the argument for effective anticoagulation of those with this complication. Few studies have investigated the rate of peripheral embolism in patients with thyrotoxicosis complicated by AF. One such study investigated 142 subjects with thyrotoxicosis
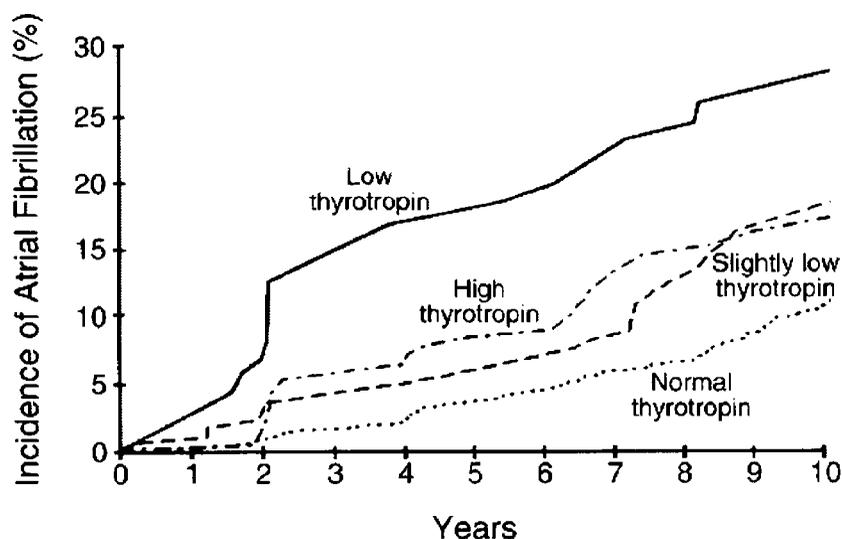
**Figure 2** Cumulative incidence of AF among subjects 60 years of age or older according to serum TSH values at baseline. Low serum TSH values were defined as ≤0·1 mU/l; slightly low values between 0·1 and 0·4 mU/l; normal as 0·4–5·0 mU/l; and high as >5·0 mU/l (Reproduced from Sawin *et al.* 1994, with kind permission from the Massachusetts Medical Society).

(Bar–Sela *et al.* 1981). Twelve of 30 patients in AF had an embolic event (40%) compared with none in sinus rhythm (112 patients); the mean age of the patients in AF was significantly higher than those in sinus rhythm (56 vs 39 years). A further retrospective study investigating 610 patients with thyrotoxicosis, indicated that age – rather than the presence of AF – was the main risk factor for embolisation, a finding which may be explained by the relatively small number of patients in AF (Petersen & Hansen 1988). Twelve (13%) of those in AF had an embolic event compared with 15 of the 519 patients (2·9%) in sinus rhythm. During the first year, the cerebrovascular event frequency (in those with AF and sinus rhythm considered together) was nonetheless higher than that expected in the general population of the same age. Taken together, the existing data suggest that the rate of embolism in thyrotoxic AF exceeds that for non-thyrotoxic AF not associated with rheumatic heart disease. Furthermore, the majority of clinically evident emboli in thyrotoxic AF involve the CNS and occur most commonly early in the course of the disease (Presti & Hart 1989). Whether it is appropriate to extrapolate findings highlighting the clear association of AF and peripheral emboli in large cohorts without thyrotoxicosis (Gilligan *et al.* 1996) to those with thyrotoxicosis, and therefore to support the role of anticoagulation, remains to be determined.

In addition to overt thyrotoxicosis, AF has been shown to be associated with subclinical hyperthyroidism. An important study of 2007 subjects aged over 60 years and comprising part of the Framingham population, described a nearly tripling of the likelihood of AF during a 10 year follow-up period in patients with a low serum TSH (Sawin *et al.* 1994). These subjects did not have AF at the start of the study and were classified according to their serum TSH concentration (Fig. 2). A total of 192 patients (10%) developed AF and the cumulative incidence of AF at 10 years was highest among subjects with a low TSH (28% compared with 11% among those with a normal TSH (*P*=0·005)). The incidences of AF in those with a slightly low TSH and a high TSH concentration were not significantly different from those with a normal TSH concentration (16 and 15% respectively). After adjustment for other known risk factors (smoking, diabetes, hypertension, left ventricular hypertrophy, myocardial infarction, congestive cardiac failure and cardiac murmur) the relative risk (RR) for developing AF in those with a low TSH was 3·1 (95% confidence interval (CI) 1·7–5·5) compared with those with a normal TSH (*P*<0·001). Those with a slightly low TSH concentration had an RR of 1·6 (*P*=0·05 compared with normal values). The study population was heterogeneous in that it included subjects taking thyroid hormone therapy and those with thyrotoxicosis; however, excluding subjects taking thyroid hormone replacement or those with overt hyperthyroidism at the start of the study had little effect on the significance of the increased RR found in the low TSH concentration group.

A further retrospective study of 23 638 subjects evaluated the risk of AF in subclinical hyperthyroidism (Auer *et al.* 2001). The cohort comprised a heterogeneous group in whom TSH was measured for a variety of reasons including screening, suspected thyroid disease and

**Table 1** Observed and expected numbers of deaths and standardised mortality ratios for causes of death in patients with hyperthyroidism treated with $^{131}$I (adapted from Franklyn *et al.* 1998)

| Cause of death | No. of deaths | | SMR (95% CI) | P value |
| --- | --- | --- | --- | --- |
| | Observed | Expected | | |
| All causes | 3611 | 3186 | 1·13(1·1–1·2) | <0·001 |
| Cardiovascular disease | 1258 | 1018 | 1·2(1·2–1·3) | <0·001 |
| Rheumatic heart disease | 67 | 21 | 3·2(2·5–4·2) | <0·001 |
| Hypertensive heart disease | 59 | 28 | 2·1(1·6–2·7) | <0·001 |
| Ischaemic heart disease | 867 | 812 | 1·1(1·0–1·1) | 0·03 |
| Cerebrovascular disease | 605 | 446 | 1·4(1·2–1·5) | <0·001 |

concomitant disease, in either a hospital in-patient or out-patient setting. AF was found in 2% of those with normal serum TSH, 13·8% of those with overt hyperthyroidism and 78 of 613 (12·7%) subjects with subclinical hyperthyroidism (defined as TSH<0·4 mU/l and normal serum fT4 and fT3). This association of AF with low serum TSH represented a more than 5-fold higher prevalence compared with those with normal TSH concentration (RR 5·2, 95% CI 2·1–8·7, P<0·01).

In addition to the association between AF and embolic complications in thyrotoxicosis described above, several studies have examined the relationship between thyrotoxicosis and mortality from vascular disease. A follow-up study of 1762 patients with thyrotoxicosis treated in the US between 1946 and 1964 (80% treated with $^{131}$I) revealed, during a mean period of follow-up of 17·2 years, a significant increase in mortality from all causes (standardised mortality ratio (SMR) 1·3, 95% CI 1·2–1·4), together with a specific increase in mortality from diseases of the circulatory system (SMR 1·4, 95% CI 1·3–1·6) (Goldman *et al.* 1988). A larger study of 10 552 Swedish patients treated with radioiodine and followed for an average of 15 years revealed a similar increase in mortality from cardiovascular diseases (SMR 1·65, 95% CI 1·59–1·71) (Hall *et al.* 1993). We also identified and investigated a cohort of 7209 subjects with hyperthyroidism treated with $^{131}$I between 1950 and 1989 (Franklyn *et al.* 1998). The vital status of the cohort was determined in 1996, and cause of death ascertained in those who had died. The underlying cause of death was compared with age-specific mortality data for England and Wales and SMR used as a measure of RR. During a period of follow-up of 105 028 person-years of risk, 3611 subjects died, the expected number of deaths being 3186 (P<0·001). Significant increases in risk of death were observed for all categories of heart disease and for cerebrovascular disease (Table 1). Excess mortality due to cardiovascular and cerebrovascular causes was most common in the first year after radioiodine, and declined thereafter. Increased mortality was observed in all age groups; cardiovascular mortality was most

marked in those aged over 50 years at treatment because of increased event frequency with increasing age. Excess mortality in this cohort (and the Swedish cohort described above) (Hall *et al.* 1993) may have reflected an adverse influence of hyperthyroidism itself, a specific adverse effect of radioiodine, or influences of subsequent hypothyroidism and its treatment with T4. In the UK study, the relationship between mortality and time from treatment (i.e. the observation that the greatest excess in mortality was observed during the first year when thyroid dysfunction is at its worst), as well as the relationship between mortality and dose of $^{131}$I (an indirect marker of the severity of hyperthyroidism), suggests that it is hyperthyroidism itself which was the major factor determining adverse outcome. This is probably mediated through influences of cardiac rate, rhythm and function, as well as exacerbation of any underlying valvular, hypertensive or ischaemic heart disease.

It is known, too, that mild or subclinical thyroid hormone excess can influence cardiac function, with documented effects on heart rate, cardiac morphology defined by echocardiography and incidence of supraventricular dysrhythmias (Biondi *et al.* 1994, 2000). An important question is whether these markers of cardiac status are associated with changes in clinically significant end-points in patients with low serum TSH. One Scottish study reported hospital admission rates due to ischaemic heart disease amongst subjects taking long-term T4 therapy. They compared findings in those with suppressed serum TSH (<0·05 mU/l) (representing about half of the cohort) with those in whom TSH was detectable but not elevated (Leese *et al.* 1992). Patients within the study population who were aged under 65 years on T4 therapy had an increased risk of hospital admission due to ischaemic heart disease compared with the general population (females 2·7 vs 0·7%; males 6·4 vs 1·7%, P<0·01). The risk was no different between those with normal and suppressed serum TSH, arguing against a specific adverse influence of subclinical hyperthyroidism secondary to ingestion of T4 ('exogenous' subclinical hyperthyroidism).

In order to define vascular risk in subjects with 'endogenous' subclinical hyperthyroidism (i.e. those not taking thyroid hormones), we recently investigated vascular mortality in a community-based cohort of subjects with low serum TSH and followed over a 10 year period (Parle *et al.* 1991, 2001). The cohort comprised 1191 subjects aged 60 years and over who were not receiving T4 therapy or antithyroid medication. A serum TSH concentration was measured at baseline in 1988–1989. Causes of death were determined for those who died after the follow-up period and were compared with age-, sex- and year-specific data for England and Wales. Mortality from all causes was found to be significantly increased at 2, 3, 4 and 5 years after initial measurement in those with a low serum TSH concentration ($\leq 0.5$ mU/l, $n=71$) compared with the expected mortality for the control population of England and Wales. The SMR at year 2 was 2·1 (95% CI 1·0–4·5), at year 3 was 2·2 (95% CI 1·2–4·0), at year 4 was 1·9 (95% CI 1·0–3·4) and at year 5 was 2·0 (95% CI 1·2–3·3). This increase in all-cause mortality was almost completely accounted for by significant increases in mortality due to circulatory diseases. A comparison of those with low serum TSH and the remainder of the cohort also confirmed significant increases in vascular mortality. The underlying cause of TSH reduction in this UK cohort was not investigated but probably reflected true endogenous (mild) hyperthyroidism (rather than other influences such as drug therapies or non-thyroidal illnesses) because there was an inverse relationship between mean serum concentrations of free thyroid hormones and serum TSH amongst the cohort, and many had clinical features of thyroid disease such as goitre. Furthermore, common causes of death, other than vascular causes, were not associated with low serum TSH in this cohort, which would be expected if serum TSH were a non-specific reflection of other illnesses. The size of this cohort was insufficient to allow definition of mortality in those with fully suppressed, rather than low but detectable serum TSH, the former probably being the most relevant group in terms of long-term risk. Nonetheless, these data, together with the AF incidence data evident in the elderly Framingham population (Sawin *et al.* 1994), have lent support to the view that antithyroid treatment should be considered in those with persistent suppression of TSH and evidence for underlying thyroid disease (thyroid nodular disease or Graves' disease), especially if associated with AF or known cardiac disease (Fatourechi 2001, Surks *et al.* 2004). Crucial evidence for a beneficial effect of such treatment, i.e. reduction in AF incidence or vascular mortality in those with subclinical hyperthyroidism, awaits the results of randomised controlled clinical trials.

**The effects of hypothyroidism on cardiovascular morbidity and mortality** The haemodynamic changes typical of hypothyroidism are opposite to those of thyrotoxicosis, but they are generally accompanied by fewer symptoms and signs (Klein & Ojamaa 2001). Overt hypothyroidism has been reported to be specifically associated with cardiovascular disease, although evidence for a true association is largely confined to older literature reporting findings from relatively small numbers of patients (Vanhaelst *et al.* 1967, Steinberg 1968). Given the hypercholesterolaemia and diastolic hypertension found in overt thyroid failure, such an association is, however, plausible.

It is well recognised that caution must be exercised in introducing T4 replacement therapy in those with hypothyroidism and ischaemic heart disease because of the risk of worsening angina or induction of myocardial infarction. However, these complications are rare and study of a large series of patients treated for hypothyroidism and evaluated for new or worsening angina, indicated an improvement in the symptoms of ischaemic heart disease in many subjects (Keating *et al.* 1961). One study has described an increased short-term mortality following coronary artery bypass grafting in those receiving T4 replacement therapy when compared with those without (5·9 vs 2·6%, $P=0.02$). In this study T4 dose and serum T4 concentration were inversely related to mortality amongst those taking T4 therapy (Zindrou *et al.* 2002), suggesting that insufficient T4 therapy may have played a role in the described adverse outcome.

Given the likely association of untreated overt hypothyroidism with cardiovascular disease, much attention has focused on the possible link between subclinical hypothyroidism and cardiovascular disease. Again, it has been hypothesised that such a link could be mediated via an adverse effect of mild thyroid deficiency on the lipid profile, although the nature and degree of this adverse influence remain controversial and are probably relatively minor (Caraccio *et al.* 2002). There is also some evidence, from a study comparing 57 women with subclinical hypothyroidism and 34 euthyroid controls, of an association between raised TSH and diastolic hypertension (Luboshitzky *et al.* 2002). Despite these potential mechanisms for increased cardiovascular risk, cross-sectional data from 3678 subjects enrolled in the Cardiovascular Health Study revealed no differences in prevalences of angina, myocardial infraction, transient ischaemic attack, stroke or peripheral artery disease, when comparing those with subclinical hypothyroidism and controls with normal TSH (Cappola & Ladenson 2003). In accord with this, an important 20 year follow-up study of the population of Whickham in the UK (Vanderpump *et al.* 1996) reported negative outcomes in terms of morbidity and mortality from ischaemic heart disease in 97% of the original cohort (2779 subjects) who were available for follow-up. Analysis of deaths from all causes, and specifically from ischaemic heart disease, revealed no association with autoimmune thyroid disease. No specific associations with hypothyroidism, presence of antithyroid antibodies or raised serum TSH levels at the time of first survey, were evident in this

large cohort study. These findings are in agreement with our own 10 year follow-up study of a cohort of 1191 in the community aged over 60 years, which examined all-cause and vascular mortality according to serum TSH at screening (Parle *et al.* 2001). While an association between low serum TSH and increased all-cause and vascular mortality was evident, as described above, no adverse effect on mortality 10 years later was seen for those within the cohort with raised serum TSH at screening.

Data from small case-control and cross-sectional studies have indicated a link between subclinical hypothyroidism and coronary artery disease (Tieche *et al.* 1981, Dean & Fowler 1985). A large Dutch study has reported the association between subclinical hypothyroidism and aortic calcification as well as myocardial infarction amongst a cohort of 1149 women living in Rotterdam (Hak *et al.* 2000). Subclinical hypothyroidism (defined as serum TSH>4 mU/l) was present in 10·8% of participants and was associated with a greater age-adjusted prevalence of aortic atherosclerosis (odds ratio 1·7, 95% CI 1·1–2·6) and myocardial infarction (odds ratio 2·3, 95% CI 1·3–4·0). These associations were slightly stronger in women with both subclinical hypothyroidism and positive thyroid antibodies but the presence of antibodies to thyroid peroxidase (TPO) was not itself independently associated with these end-points. There was no association with incident myocardial infarctions. The authors of this study estimated a high population attributable risk for subclinical hypothyroidism and atherosclerosis. That attributable risk must, however, be viewed cautiously since the estimation is derived from one study alone and should not therefore be considered comparable with risk attributed to other extensively investigated factors such as smoking and diabetes mellitus.

*The effects of thyroid hormones on the skeleton*

Thyroid hormones are known to exert direct effects upon bone formation and resorption, thyroid hormone excess resulting in net loss of bone and hence reduction in bone mineral density (BMD) (Ross 1994). It is well recognised that overt hyperthyroidism results in reduction in BMD and that treatment of the disease results in an increase in BMD. However, even with effective antithyroid therapy a complete restoration of BMD to pre-morbid levels does not always occur (Ross 1994). In a cross-sectional study comparing women treated for hyperthyroidism with radioiodine with age-matched controls, we found that femoral neck and lumbar spine BMD was significantly reduced in the post-menopausal group, although BMD was similar in patients and controls in the pre-menopausal group (Franklyn *et al.* 1994). These findings suggest that post-menopausal oestrogen-deficient women are the ones at particular risk of potential adverse effects of hyperthyroidism upon bone metabolism. As is the case with most of these studies, the clinically important question

remains whether the reductions in BMD associated with overt hyperthyroidism translate into increased risk of osteoporotic fracture.

A large prospective study followed 9516 white women aged over 65 for an average of 4·1 years for incident fractures of the femur and revealed a 1·8-fold increased RR amongst those with previous hyperthyroidism (95% CI 1·2–2·6) (Cummings *et al.* 1995). In accord with these findings, data from our own mortality study described above (Franklyn *et al.* 1998) provided evidence for an increase in mortality from fracture of the femur in subjects with hyperthyroidism treated with radioiodine (SMR 2·9, CI 2·0–3·9), in accord with the specific incidence data reported for fracture of the femur. A further case-control study, reported an increased fracture incidence rate ratio (1·26–2·29) around the time of diagnosis amongst 11 776 subjects with hyperthyroidism, with return to control incidence after diagnosis (Vestergaard & Mosekilde 2002). These findings are in contrast to another large prospective study of over 9000 post-menopausal women, which failed to show an association of thyrotoxicosis with fractures of the ankle and foot (Seeley *et al.* 1996). The effect of thyroid hormone excess may thus be different depending on the type of fracture investigated.

Like overt hyperthyroidism, subclinical hyperthyroidism (especially that associated with T4 therapy) has been implicated in the development of osteoporosis. Early studies reported significantly reduced bone mass in patients on prolonged T4 treatment (Ross *et al.* 1987, Paul *et al.* 1988), resulting in concern about the potential risk of premature development of osteoporosis in patients receiving T4 therapy (Franklyn & Sheppard 1990). However, several well-conducted studies subsequently failed to demonstrate any detrimental effect on bone mass in T4-treated patients, even in those taking T4 in doses sufficient to suppress serum TSH (Franklyn *et al.* 1992, Hanna *et al.* 1998). Two meta-analyses of published literature have addressed this controversy and have suggested that thyroid hormone treatment, both in specific groups with suppressed serum TSH and in those with normal serum TSH, is associated with a minor but statistically significant reduction in BMD (Faber & Galloe 1994, Uzzan *et al.* 1996), although analysis of the findings is complicated by heterogeneity of patient groups investigated, particularly in terms of past history of hyperthyroidism. It should be noted that such studies of BMD have not addressed the question of whether T4 therapy is a risk factor for clinically relevant end-points such as fracture incidence and mortality.

A study of 1100 patients on T4 replacement in Scotland found no significant differences in fracture rates in patients on T4 when compared with the general population (Leese *et al.* 1992). The prospective study of over 9516 post-menopausal women described above (Cummings *et al.* 1995) reported an increased RR for incident fracture of the femur in those taking thyroid hormone (RR 1·6, 95%

CI 1·1–2·3), but this was no longer significant when adjusted for a previous history of hyperthyroidism (which was present in 36% of those prescribed T4). A prospective cohort study of 686 women older than 65 years followed for a mean of 3·7 years, revealed that hyperthyroidism conferred a 2-fold increase in risk of hip fracture, but the use of thyroid hormone itself was not associated with increased risk of hip fracture (Bauer *et al.* 2001). One further population study of 4473 subjects with auto-immune hypothyroidism has suggested an increased incidence of fracture both before and after diagnosis (Vestergaard & Mosekilde 2002), although the finding of an apparent association before diagnosis (i.e. before commencement of T4 therapy) argues against an influence of thyroid hormone excess in producing these findings.

To specifically address the effect of T4 therapy on occurrence of fracture of the femur we have used the UK General Practice Research database (which records drug prescribing information) in a population-based case-control study of those prescribed T4 (Sheppard *et al.* 2002). Amongst a cohort of 23 183 subjects prescribed thyroid hormones, the occurrence of fracture of the femur was not significantly higher compared with a group of 92 732 matched controls. Compared with controls, T4 takers had higher reported rates of medical diagnoses and drug therapies, potentially confounding fracture risk. Prescription of T4 was not an independent predictor of femur fracture amongst females (adjusted odds ratio (AOR) 1·03, 95% CI 0·92–1·16), but interestingly it was an independent predictor amongst males (AOR 1·69, 95% CI 1·12–2·56). The prevalence of T4 prescription is much lower in males than females (reflecting the prevalence of autoimmune thyroid disease); however, this gender group has been poorly investigated in terms of effect of thyroid status on bone, and may be at particular risk.

Overall, the data regarding clinically apparent osteoporosis and thyroid status support an adverse effect of overt hyperthyroidism upon fracture risk, an effect that may be sustained despite successful antithyroid therapy. The importance of subclinical hyperthyroidism in terms of osteoporosis risk requires further investigation, especially risk related to 'endogenous' subclinical hyperthyroidism such as that found in patients with nodular goitre. As yet, there is little evidence that T4 therapy alone, even in doses sufficient to suppress serum TSH, is associated with increased risk of fracture, although caution must be exercised in high risk groups, especially postmenopausal women (and possibly men).

## Thyroid hormones and the neurological system

**Effects of thyroid hormones on the developing fetal brain** Classically, maternal thyroid hormones have not been thought to play a major role in development of the fetal CNS. However, over the past decade epidemiological evidence (Haddow *et al.* 1999, Pop *et al.* 1999, 2003) suggests that even relatively mild maternal hypothyroxinaemia, particularly in early pregnancy, may adversely affect the long-term neurodevelopment of the offspring. These findings have sparked an international debate about the need to screen women prenatally for subclinical hypothyroidism. The leading cause of maternal hypothyroidism worldwide remains iodine deficiency and the prevalence in endemic areas varies widely. In iodine-replete areas, subclinical hypothyroidism is largely of autoimmune aetiology and prevalence rates in early pregnancy have been reported to be in the region of 2·5% in the US (Klein *et al.* 1991). However, a study performed in the north-east of England, which is considered a non-iodine-deficient area, has estimated using urinary iodide excretion rate measurements that 3·5% of pregnant women are iodine-deficient and a further 40% borderline deficient (Kibirige *et al.* 2004).

In a series of three follow-up studies on the offspring of pregnant women in The Netherlands, Pop and colleagues examined the effects of low thyroid hormone levels in pregnancy on child neurodevelopment. In the first study (Pop *et al.* 1995), aimed at investigating the relationship between maternal depression and thyroid disease, blood samples were obtained at 32 weeks of gestation and fT4 as well as TPO antibodies were determined. Not only did the children of depressed women attain significantly lower General Cognitive Index (a correlate of IQ) scores on the McCarthy test at aged 5, logistic regression analysis also revealed that the strongest predictor of IQ was maternal TPO antibody level, not maternal depression. Pop speculated that this correlation reflected an 'epiphenomenon', which may be due to thyroid insufficiency earlier in gestation rather than the direct effect of the antibodies on the fetal brain (Pop *et al.* 1995).

In a second study, this group measured fT4 and TPO antibody levels in another cohort of pregnant women at both 12 and 32 weeks of gestation and found that maternal fT4 concentrations at 12 weeks of gestation was indeed the strongest predictor of infant mental development (Pop *et al.* 1999). The third study compared women with low fT4 levels (at or below the 10th centile) at 12 weeks of gestation with women who had normal fT4 levels at this stage of pregnancy. Women who were not diagnosed with hypothyroxinaemia, and were therefore not treated during pregnancy, were further subdivided according to their fT4 levels at two subsequent time-points in pregnancy. They found that infants of women with initially low fT4 levels that were sustained throughout pregnancy were most likely to show delayed development. In contrast, women with initially low levels who recovered through the course of pregnancy had children at less risk of later impairment. The offspring of women with marginally normal fT4 levels initially that declined later in pregnancy were moderately at risk of impairment (Pop *et al.* 1999, 2003).

Further evidence of the effects of maternal hypothyroidism on fetal development comes from a

well-publicised 1999 study from the US, by Haddow *et al.* (1999). It describes the neurodevelopmental status of the children of 62 women with serum TSH concentrations above the 98th percentile at 16 weeks of gestation compared with 124 matched controls. None of the children screened positive for neonatal hypothyroidism. In most cases, the maternal hypothyroidism was unknown during pregnancy because the women were asymptomatic and hypothyroidism was only recognised after tests were conducted on stored serum samples many years later. Compared with controls, the children of hypothyroid mothers had significantly reduced intelligence levels (on average 4 points lower on the Wechsler Intelligence Scale for Children) and performed less well on all 15 of the neuropsychological tests performed at assessment between the ages of 7 and 9 years.

The children of a subgroup of 14 women who received T4 treatment during pregnancy (albeit inadequate doses since their TSH levels were elevated at 16 weeks), had more normal IQ scores but several specific deficits such as poor attention were more marked than in the untreated group. The children of the remaining 48 biochemically hypothyroid women who were not treated during the pregnancy performed worse, with an average 7 point lower IQ score compared with controls; 19% of these scored 85 or less, which is clinically significant in terms of special educational and social needs. Interestingly, the serum total T4 and fT4 concentrations in the treated and the non-treated hypothyroid women were similar during pregnancy. This study has been considered pivotal since it suggests that subclinical hypothyroidism in women can have long-term consequences upon the neuropsychological development in their offspring, and that T4 supplementation can improve the outcome, even when supplementation is inadequate.

All of these studies demonstrate the sensitivity of the fetal CNS to changes in thyroid status. They also demonstrate that not only the severity of maternal hypothyroidism, but also the timing of it are important. Normal maternal thyroid hormone concentrations thus appear critical, particularly in the first trimester, to attain normal neurodevelopment. Appreciable amounts of thyroid hormones are only detectable in the human fetal circulation from 14–16 weeks of gestation, which is believed to represent the time of onset of endogenous thyroid hormone release (Thorpe-Beeston *et al.* 1991, Fisher 1997) even though the fetal thyroid gland begins accumulating iodide from 10–12 weeks of gestation (Shepard 1967, Fisher *et al.* 1976). The fetus is, therefore, entirely reliant on the maternal supply of thyroid hormones for normal development in the first and early part of the second trimester. Hence, a rise in iodine intake or T4 supplementation from the first trimester is necessary in pregnant women with potential iodine deficiency and/or pre-existing hypothyroidism. A recent prospective study of hypothyroid women who were planning pregnancy

indicated a mean 47% increase in T4 requirements during the first half of pregnancy. The need for an increase occurred from as early as 5 weeks of gestation and continued until delivery (Alexander *et al.* 2004). The authors of that study proposed that all women with hypothyroidism should receive a 30% increase in T4 treatment as soon as pregnancy is confirmed, with a subsequent adjustment of T4 replacement dosage depending on the serum TSH levels.

We do, however, need to exercise caution as the human fetal brain may be intolerant of maternal hyperthyroxinaemia, as well as hypothyroxinaemia. A recent study on uncontrolled maternal Graves' disease during pregnancy has found an adverse impact on the development fetal pituitary function resulting in central congenital hypothyroidism (Kempers *et al.* 2003), although this scenario may be less common than mild neurodevelopmental delay caused by maternal hypothyroidism.

Despite what appears to be a sizeable proportion of the pregnant population being affected by subclinical hypothyroidism, the issue of screening remains controversial. A Symposium on Thyroid Health in Pregnant Women held in April 2004 brought together leading physicians and scientists in this field; the consensus opinion reached was that there is currently insufficient scientific evidence to recommend universal thyroid function screening of all women before or during pregnancy; however, there should be a low threshold for screening those at risk, for example those with a personal or family history of thyroid dysfunction, a personal history of other autoimmune conditions such as diabetes mellitus, or obstetric complications known to be associated with hypothyroidism (i.e. recurrent miscarriage and preterm labour) (Sullivan 2004). A similar consensus view was reached by the expert panel which carried out the systematic review of studies on subclinical thyroid dysfunction and provided guidelines for its management (Surks *et al.* 2004).

**Neuropsychiatric morbidity from thyroid dysfunction and its treatment** There is no doubt that overt thyroid dysfunction is associated with significant symptoms and an adverse effect on quality of life. As neuropsychological tools have become more sensitive, it has become apparent that even mild TH insufficiency in humans can produce measurable deficits in very specific neuropsychological functions, and that the specific consequences of TH deficiency depends on the precise developmental timing of the deficiency (Zoeller & Rovet 2004). Few studies have, however, addressed the prevalence of symptoms and other 'non-specific' markers of morbidity in those with subclinical thyroid dysfunction. While some studies have suggested an association between various symptoms and mild or subclinical thyroid dysfunction, overall the evidence for a link is relatively weak (Surks *et al.* 2004).

Very few studies have investigated more finite endpoints such as the presence of significant psychiatric

disease. A possible association between dementia and subclinical hyperthyroidism has been described. A study of a subgroup of the Rotterdam cohort in whom thyroid function had been examined ($n$=1843) suggested that reduced serum TSH (<0·4 mU/l) at baseline was associated with an approximately 3-fold increased risk for incident diagnoses of dementia (RR 3·5, 95% CI 1·2–10·0) or Alzheimer's disease (RR 3·5, 95% CI 1·1–11·5) over a 2 year period of follow-up, after adjustment for age and sex and other potential confounders such as AF (Kalmijn *et al.* 2000). Supporting evidence for a direct effect of subclinical thyroid dysfunction on dementia risk in this study was the finding that incident dementia was especially common in those with positive antithyroid antibodies and was inversely related to serum T4 levels. Interestingly, this cohort study did not provide evidence for a link between dementia and subclinical hypothyroidism despite a similar prevalence in the cohort to subclinical hyperthyroidism.

### Effects of thyroid hormones on other organ systems

In addition to their effects on the heart, bone and nervous system, thyroid hormones also exert effects on many other organs systems including the lungs, skin, gut, kidney and liver. The respiratory system and the thyroid gland are interrelated since the thyroid gland is in close proximity to the trachea and the functions of both systems are coupled to cellular oxidative metabolism. In addition, the alterations in systemic haemodynamics associated with thyroid dysfunction critically affect blood pressure and renal function. Furthermore, both hypo- and hyperthyroidism are associated with symptoms and signs of gastrointestinal dysfunction suggesting that thyroid hormone deficiency or excess disrupt the normal homeostatic mechanisms of the gut. Thyrotoxicosis has been associated with a number of abnormalities in liver function tests and Hashimoto's thyroiditis has been linked to autoimmune liver disease. Finally a multitude of skin abnormalities may accompany thyroid dysfunction regardless of its aetiology although conditions such as Graves' disease may be associated with distinctive cutaneous signs.

### Cancer risk and thyroid dysfunction and its treatment

Because of the known effects of thyroid hormone on mitogenesis and apoptosis, several studies have addressed the question of whether thyroid diseases are themselves associated with increased risk of malignant disorders. A retrospective follow-up study of 7338 women who attended the Massachusetts General Hospital thyroid clinic and who were followed on average for more than 15 years suggested small but significant increases in total cancer deaths in women with nodular goitre, thyroid adenoma and hyperthyroidism and in those with Hashimoto's thyroiditis (Goldman *et al.* 1990). An increase in cancer

deaths was, however, also observed in those within the cohort without evidence for thyroid disease when compared with the general population, so the results must be viewed with caution. The risk of cancer has also been reported in a cohort of 57 326 subjects discharged from a Danish hospital with a diagnosis of hyperthyroidism, hypothyroidism or goitre (Mellemgaard *et al.* 1998). Overall cancer incidence was not significantly increased in this large cohort, but thyroid cancer risk (as well as cancers at some other sites) was found to be increased in all three groups of thyroid disease patients. These findings suggest a non-specific association between thyroid disease and the risk of malignancy, especially thyroid cancer. In turn, these data may reflect true disease associations or links between malignancy risk and autoimmune disease (as the major underlying cause of thyroid dysfunction in the developed world). Furthermore, in patients with thyroid dysfunction, an apparent association with cancer risk may reflect treatment administered.

In particular, several reports have linked a variety of thyroid disorders to breast cancer. A study comparing 150 breast cancer patients and 100 control individuals demonstrated increased prevalences of autoimmune and non-autoimmune thyroid diseases (38 vs 17%, $P$=0·001 and 26 vs 9% respectively) (Turken *et al.* 2003). Furthermore, the fact that human mammary carcinomas express NIS, the protein responsible for iodide uptake in thyroidal and non-thyroidal tissues, has been proposed as a potential novel strategy to treat breast cancer with [131]I (Boelaert & Franklyn 2003).

Radioiodine is increasingly regarded as the treatment of choice in most cases of hyperthyroidism, including those with Graves' hyperthyroidism which has relapsed after drug therapy and in those with toxic nodular hyperthyroidism. Nonetheless, concerns amongst both patients and doctors remain regarding the long-term safety of radioiodine therapy, especially in terms of cancer risk (Baxter *et al.* 1993). These concerns have been heightened by reports of a marked increase in incidence in thyroid cancer amongst children exposed to ^{131}I after the Chernobyl reactor accident (Moysich *et al.* 2002) and a possible association between thyroid cancer and ^{131}I exposure from Nevada atmospheric nuclear bomb tests (Gilbert *et al.* 1998).

Although several studies of cancer risk in patients treated with ^{131}I for hyperthyroidism have been reported, results have been conflicting. A study of a large cohort of Swedish subjects examining the incidence of leukaemia in those exposed to ^{131}I, either during diagnostic scanning or during treatment of hyperthyroidism or thyroid cancer, found no significant excess risk of leukaemia (Hall *et al.* 1992*b*). More recent studies have similarly found no evidence of association of malignancy with exposure to radioiodine for diagnostic scanning purposes (Dickman *et al.* 2003). The large Swedish cohort treated with ^{131}I for hyperthyroidism has also been investigated for risk of solid

tumours (Holm *et al.* 1991). Overall cancer incidence was increased (standardised incidence ratio (SIR) 1·06, 95% CI 1·01–1·11) and analysis of a sub-group of 10 year survivors revealed significantly increased risks for cancers of the stomach, kidney and brain. Furthermore, the risk of stomach cancer has been reported to increase with time and with increasing dose of radioactivity administered (Holm *et al.* 1991, Hall *et al.* 1992*a*). Other studies, comparing cancer risk in those treated for hyperthyroidism with radioiodine and those treated surgically, failed to reveal any difference in cancer incidence or mortality at these or other specific sites (Hoffman *et al.* 1982).

Since the thyroid is the major site of radiation exposure following radioiodine treatment, attention has focused on the risk of malignancy in this organ. The small size of most published studies of those treated for hyperthyroidism and the relatively low incidence of thyroid cancer mean that an increase in thyroid cancer incidence after radioiodine therapy has not been convincingly described. However, analysis of 35 593 patients with hyperthyroidism, 65% of whom received radioiodine, and seen in 26 centres throughout the US and UK from 1946 to 1964 did reveal an increase in thyroid cancer mortality (Ron *et al.* 1998). Increased cancer risk was not confined to those treated with $^{131}$I, being observed in addition in those treated exclusively with antithyroid drugs.

We also examined both cancer incidence and mortality in a cohort of 7417 subjects treated with $^{131}$I for hyperthyroidism (Franklyn *et al.* 1999). During 72 073 person-years of follow-up, 634 cancer diagnoses were made compared with an expected number of 761 (SIR 0·83, 95% CI 0·77–0·90). The RR of cancer mortality was also reduced in the cohort (observed cancer deaths 448, expected 499; SMR 0·90, 95% CI 0·82–0·98). The reduction in cancer risk reflected significant decreases in incidence of cancers of the pancreas, bronchus and trachea, bladder and lymphatic and haematopoietic systems. Mortality from cancers at each of these sites was also reduced. It is notable, however, that there were significant increases in incidence and mortality for cancers of the small bowel (SIR 4·81, 95% CI 2·16–10·72; SMR 7·03, 95% CI 3·16–15·66) and thyroid (SIR 3·25, 95% CI 1·69–6·25; SMR 2·78, 95% CI 1·16–6·67), although absolute risk of development or death from these cancers was small. The findings from this study as well as the large study of Ron *et al.* (1998) are reassuring in terms of overall safety of $^{131}$I treatment and cancer risk. The evidence does suggest an increased RR of thyroid cancer in hyperthyroid patients treated with radioiodine, although the absolute risk remains small, and indeed is likely to reflect, at least in part, association with underlying thyroid disease rather than $^{131}$I exposure per se.

While studies have so far examined the risk of cancer following treatment of hyperthyroidism with radioiodine, it should be noted that this therapy is increasingly used in the treatment of benign goitre (Hegedus *et al.* 2003).

Extrapolation of data from those with hyperthyroidism to those with goitre may be appropriate; however, further studies of the latter patient group should be undertaken. Radiation treatment is also used in those with thyroid disease in the context of orbital radiotherapy for Graves' ophthalmopathy. One study has addressed subsequent cancer risk in a small cohort of 250 patients and found no evidence for radiation induced cancers (Schaefer *et al.* 2002).

## Future perspectives

### Identification of a new thyroid hormone transporter

Although it was originally believed that thyroid hormones enter the cells by passive diffusion it is now clear that cellular uptake is effected by carrier-mediated processes. Several inorganic anion transporters and L-type amino-acid transporters have been shown to facilitate plasma membrane transport of thyroid hormone (Hennemann *et al.* 2001).

The recent characterisation of monocarboxylate transporter 8 (MCT8), the most specific and powerful T3 transporter found to date (Friesema *et al.* 2003), has emphasised a significant role for membrane transporters in the regulation of local T3 action. The MCT8 gene on the X chromosome encodes a 613 amino acid protein with 12 predicted transmembrane domains. Different novel mutations in the MCT8 gene have been described in association with a new syndrome of X-linked mental retardation found so far in male infants from more than six different families worldwide (Dumitrescu *et al.* 2004, Friesema *et al.* 2004). Interestingly, these boys demonstrate global neurological defects and elevated circulating T3 levels without any of the skeletal and bowel manifestations associated with hypothyroidism, which suggests a specific role for MCT8 in CNS development. MCT8 protein has been detected in adult rat brain and a neuronal localisation in developing rat CNS has been postulated (Friesema *et al.* 2004). However, the precise anatomical and temporal expression of MCT8 during brain development has yet to be described in rodents or humans.

### Tests of thyroid dysfunction and non-thyroidal illness

There is considerable evidence that abnormalities of circulating thyroid hormones and TSH characteristic of the 'euthyroid sick syndrome' are associated with adverse outcome in terms of morbidity and mortality related to other illnesses. This association undoubtedly reflects the influence of 'non-thyroidal' illnesses of increasing severity on thyroid hormone metabolism and TSH secretion. For example, low serum T3 has been reported to be an independent predictor of poor survival among critically ill patients (Maldonado *et al.* 1992) and low serum T4 and T3

are associated with poor outcome in subjects undergoing bone marrow transplantation (Vexiau *et al.* 1993, Schulte *et al.* 1998). Furthermore, in elderly subjects, reduced circulating thyroid hormones are associated with worse nutritional state and worse post-operative outcome in those undergoing emergency surgery (Girvent *et al.* 1998). In a retrospective case note review of nursing home residents, low serum TSH (found in 40 subjects and typically associated with normal T4 and low serum T3) was associated with increased mortality during a short period of follow-up (Drinka *et al.* 1996). Since the finding of a low serum TSH was shown to be transient in approximately half, it was likely that in many subjects in this study this reflected the influence of an illness state rather than thyroid hormone excess.

These associations between the changes in thyroid function tests associated with non-thyroidal illness and morbidity and mortality have led to speculation that correction of these biochemical abnormalities may improve prognosis. Several studies have now addressed this possibility. Two such studies have examined the role of thyroid hormone supplementation in children undergoing cardiac surgery. One study randomised 14 infants aged less than 1 year and undergoing surgery for ventricular septal defect or tetralogy of Fallot to receive placebo or T3 infusion (0·4 µg/kg) immediately before cardiopulmonary bypass and again with myocardial reperfusion. As expected, the control group demonstrated a prompt reduction in circulating T3 at the time of surgery and this was effectively reversed in the T3-treated group. T3 treatment was associated with an increase in heart rate and product of peak systolic pressure and rate, suggesting enhancement of cardiac reserve (Portman *et al.* 2000). A larger trial involving 40 children again undergoing surgery for congenital heart disease randomised subjects to T3 infusion (2 µg/kg on day 1 after surgery, then 1 µg/kg up to 12 days post-operatively). In the placebo group, concentrations of TSH, T4, fT4 and T3 fell after surgery and reverse T3 rose. Serum T3 was significantly higher in the T3-treated group while other measurements were unaffected. In addition, the mean change in cardiac index was higher in the T3-treated subjects (20·4 vs 10·0%) and systolic cardiac function improved most in those with longer cardiopulmonary bypass operations. Adverse events were not observed and T3 treatment was associated with reduction in the need for post-operative intensive care (Bettendorf *et al.* 2000).

One study of adults has provided some evidence for a beneficial effect of thyroid hormone supplementation in adults (Klemperer *et al.* 1995). This study of 142 subjects undergoing coronary artery bypass surgery and randomised to receive T3 (0·8 µg/kg bolus at time of aortic cross-clamp removal and then as an infusion (0·113 µg/kg per h for 6 h)). The mean post-operative cardiac index was higher, and the systemic vascular resistance lower, in the T3 group compared with the placebo group, although

there was no difference in the incidence of arrhythmias, in the need for vasodilator or inotropic drugs, or in peri-operative morbidity or mortality. Thus, unlike in children, the infusion of T3 in adults undergoing cardiac surgery, while resulting in a change in haemodynamic parameters, did not affect clinically significant end-points. A routine role for T3 supplementation in subjects undergoing cardiopulmonary bypass, as well as those in other situations (e.g. emergency surgery, critically ill subjects) associated with reduction in circulating T3, remains to be established in further randomised controlled trials.

### The use of tissue-selective thyroid hormone analogues

Many of the actions of thyroid hormones are tissue-specific and are primarily mediated by a panel of TR isoforms that are expressed in different ratios in different tissues. Because of these tissue-specific hormone signalling pathways, the development of synthetic thyroid hormone analogues with tissue-selective hormone actions appears highly desirable (Scanlan *et al.* 2001). In 1963, the first of these thyroid hormone analogues was described (Blank *et al.* 1963) and medicinal chemistry efforts since have demonstrated that selective thyromimetics can be produced through a variety of approaches. Specifically, liver-selective, cardiac-sparing thyromimetics have been investigated as potential cholesterol-lowering drugs and their use for the prevention and reversal of atherosclerosis has been advocated (Taylor *et al.* 1997, Chiellini *et al.* 1998). Animal studies have shown promising results (Taylor *et al.* 1997) and selective TRβ activation in rats and monkeys has been shown to provide a potentially useful treatment for obesity and cholesterol reduction (Grover *et al.* 2004). However, the widespread use of these compounds for the treatment of metabolic disorders appears a long way off.

### Acknowledgements

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