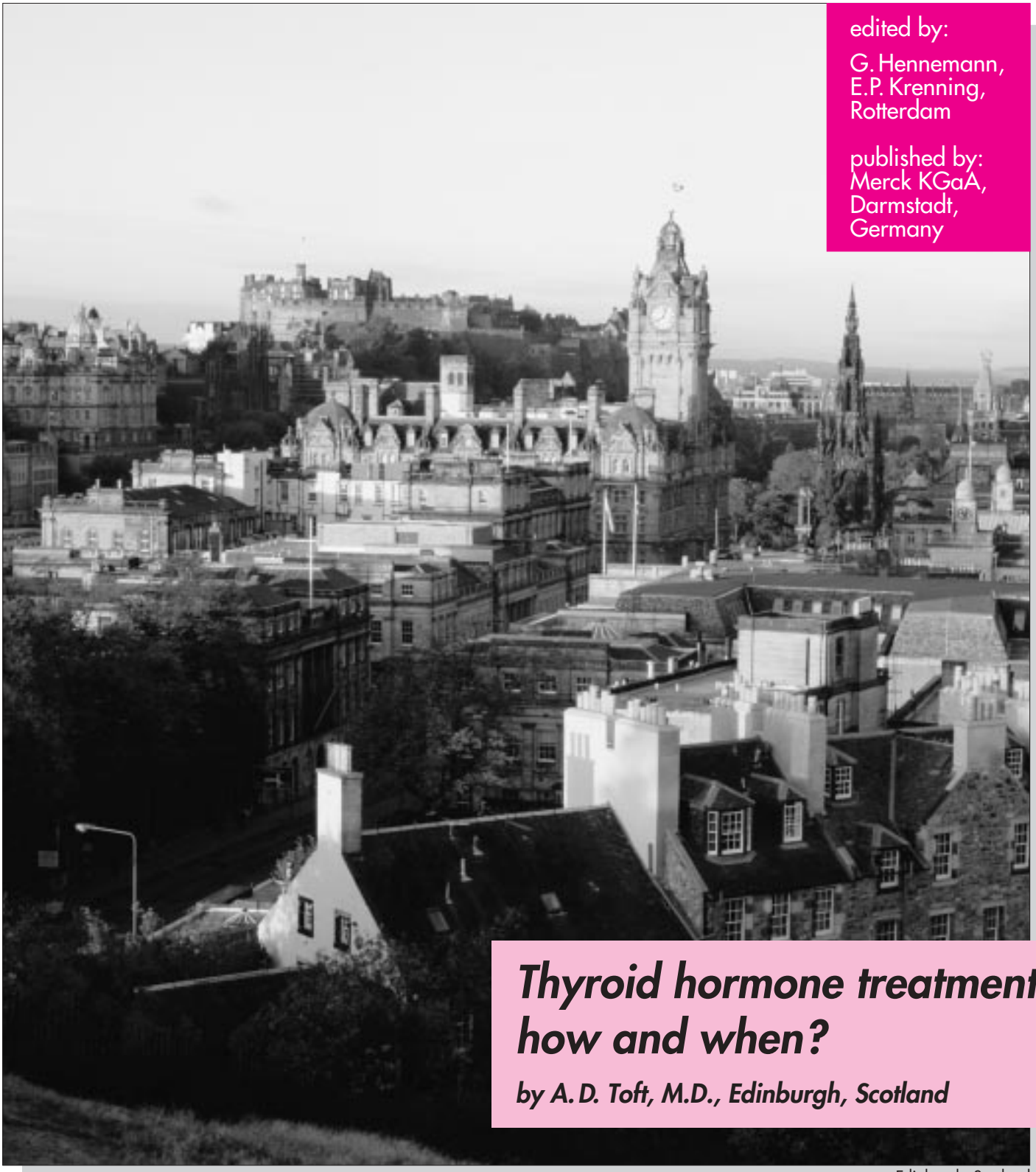
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Thyroid hormone treatment, how and when?

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He is Chairman of the local organising committee of the European Thyroid Association Meeting to be held in Edinburgh in September, 2003.

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This is the title of a publication series by Merck KGaA, Darmstadt, Germany. We are publishing papers from renowned international thyroid experts in order to pass on the extensive experience which the authors possess in their field to a wide range of physicians dealing with the diagnosis and therapy of thyroid diseases.

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Thyroid hormone treatment, how and when?

Abstract

Hypothyroidism used to be regarded as a simple condition to treat with adequacy of dosage of thyroid hormones being judged more on patient satisfaction than on biochemical monitoring. As a result of the development of sensitive tests of thyroid function there is now considerable controversy about the correct form and amount of replacement therapy and whether biochemical evidence of overtreatment, as judged by a suppressed serum TSH concentration, is a risk factor for the well-recognised complications of overt hyperthyroidism, namely atrial fibrillation and osteoporosis. On the other hand, a consensus appears to be forming that subclinical hypothyroidism should be viewed as the mildest form of thyroid failure and that it is wise to start thyroid hormone replacement sooner rather than later, particularly in those who are positive for antithyroid peroxidase antibodies.

Ensuring Appropriate Thyroid Hormone Therapy

The "correct" maintenance dose of thyroxine

The development of assays for TSH with a functional sensitivity of 0.1 mU/l or less demonstrated that the dose of thyroxine necessary to restore serum TSH to normal in most patients with primary hypothyroidism was 100–150 μg daily and not the much higher dose of 200 to 400 μg previously employed and recommended in most major textbooks in the 1960s. A significant proportion of patients taking thyroxine have undetectable serum TSH concentrations[1], but are clinically euthyroid and asymptomatic. This has been considered unimportant as it was felt that the TSH-producing thyrotropes of the anterior pituitary were not only uniquely sensitive to minor changes in thyroid hormone concentration within their respective reference ranges[2] but also, unlike other tissues and organs, derived proportionately more T_3 from local monodeiodination of T_4, and less from circulating T_3 [3]. In other words, a "hyperthyroid" thyrotrope did not reflect the metabolic activities of the rest of the body. This view was challenged, however, by a series of reports, showing that if thyroxine were given in doses sufficient to suppress serum TSH without raising serum T_3 and T_4 into the thyrotoxic range, there were changes in the function of other target organs, such as heart, liver, kidney [4,5] and bone [6] that were similar to but much less marked than those present in patients with hyperthyroidism. There is some evidence of tissue adaptation to thyroid hormone excess[7] and the changes may to some extent depend upon the cause of the hyperthyroidism[8]. It was mainly the anxiety that a low serum TSH concentration might eventually lead to reduced bone mineral density that caused the American Thyroid Association (ATA) to state that "the goal of therapy is to restore most patients to the euthyroid state and to normalize T_4 and TSH concentrations" [9]. This policy has

inevitably led the pharmaceutical industry, principally in North America, to produce a bewildering variety of strengths of thyroxine tablets in an attempt to allow the physician to fine-tune the replacement dose. It soon became clear that a significant minority of patients satisfying the criteria of the ATA recommendation did not feel as well as they would wish and only achieved the desired sense of well-being when taking thyroxine in a dose of 50 μg in excess of that necessary to restore serum TSH to normal[10]. Many physicians now take the view that a suppressed serum TSH concentration is acceptable in those taking thyroxine replacement therapy as long as serum T_3 is unequivocally normal, a sentiment supported by a UK consensus statement[11].

Serum TSH concentrations are of no value in assessing the correct dose of thyroxine in patients with central hypothyroidism, and measurements of both serum T_3 and T_4 combined with a biochemical index of thyroid hormone action, such as soluble interleukin 2 receptors, have been suggested[12]. In practice, however, the physician is likely to be influenced more by the well-being of the patient.

Is "a little too much" thyroxine dangerous?

There is evidence that endogenous subclinical hyperthyroidism due to early Graves' disease or nodular goitre is associated with reduced bone mineral density,[13–16] atrial fibrillation,[17] increased left ventricular mass and enhanced systolic but impaired diastolic function.[18] Increasingly, the term exogenous subclinical hyperthyroidism is used to describe clinically euthyroid patients taking thyroxine in whom serum TSH is suppressed and there is often an assumption that the exogenous form carries the same risk of morbidity as the endogenous variety. This may be the case in those patients who have developed hypothyroidism following iodine-131 or surgery for Graves' disease or nodular goitre in whom an autonomous remnant may remain[19]. If a standard dose of thyroxine is prescribed to those patients, serum T_3 may lie in the upper part of the reference range as is usually the case in endogenous subclinical hyperthyroidism. However, the majority of patients with a suppressed serum TSH concentration, resulting from thyroxine therapy, have a high normal or elevated serum T_4 and a serum T_3 in the middle of the reference range. Indeed the $T_4 : T_3$ ratio is greater than would be anticipated in endogenous subclinical hyperthyroidism[20]. Patients with exogenous subclinical hyperthyroidism are, therefore, a heterogeneous group which explains why there are as many publications denying an association with reduced bone mineral density as there are those which claim a link. Even if the generic criticisms of the validity of meta-analysis as a method of combining the results of multiple small studies are disregarded, it is difficult to accept the findings of the most often quoted study as not only did it find increased bone loss in postmenopausal women receiving thyroxine suppressive therapy but also inexplicably in premenopausal women taking replacement therapy in whom serum TSH was normal[21].

Various reports have either failed to show an increased rate of fracture in patients with endogenous subclinical hyperthyroidism[1,22] or the risk has disappeared when those with a previous history of hyperthyroidism were excluded[23]. There must be similar reservations about one of the Framingham studies which revealed that a low serum TSH concentration was a risk factor for atrial fibrillation in older persons;[24] the number taking thyroxine was small (41) and, as in the bone mineral density studies, inevitably a heterogenous group.

It would, therefore, be quite wrong to generalize about the wisdom of avoiding a suppressed serum TSH concentration in those receiving thyroxine replacement. A pragmatic approach should be adopted for each patient, depending upon his or her unique circumstances (Table 1).

Table 1 Suggested management of patients taking thyroxine replacement therapy, depending upon pattern of thyroid function test results and clinical symptoms.

TSH	T_4	T_3	Symptoms	Action
normal	normal or raised	normal	none	none
normal	normal or raised	normal	present≈	increase thyroxine by 25–50 µg daily until serum TSH is suppressed but ensure T_3 unequivocally normal
< 0.05 mU/l	normal or raised	normal	none	none
< 0.05 mU/l	normal or raised	normal	yes*	reduce thyroxine by 25–50 µg daily to restore normal TSH
< 0.05 mU/l	normal or raised	high normal or raised	yes* or no	reduce thyroxine by 25–50 µg daily to restore unequivocally normal T_3

≈ Symptoms of possible undertreatment might include tiredness and weight gain.
* Symptoms of possible overtreatment might include unexplained atrial fibrillation and reduced bone mineral density.

Suppression of serum TSH concentrations is part of the management of patients with differentiated thyroid carcinoma and may be valuable in achieving maximum goitre shrinkage in patients with Hashimoto's thyroiditis and significant thyroid enlargement. Although unlikely, any evidence of overtreatment should prompt a reduction in dose of thyroxine of 25–50 µg daily in order to achieve a serum TSH concentration which is low, but detectable, as there is no evidence that this lesser degree of suppression is deleterious in the long-term.

Starting dose of thyroxine

There is no evidence base for determining how thyroxine therapy should be initiated, but it is customary to prescribe 50 µg daily, increasing to 100 µg daily after 3–4 weeks. Measurement of serum T_4 and TSH at two months after starting will dictate any further adjustment of dosage. In the elderly, and particularly in those with symptomatic ischaemic heart disease, a starting dose of 25 µg daily is advisable with increments of 25 µg every 3–4 weeks, recognising that full replacement dosage may not be achieved without coronary artery bypass grafting or angioplasty. In those in whom hypothyroidism has developed rapidly and has been detected early, such as following total thyroidectomy for thyroid carcinoma, a full replacement dose of 100–150 µg daily may be given from the outset.

Variation in dosage of thyroxine

Once thyroxine therapy is established it is good practice to review patients annually and measure serum TSH not only to ensure compliance but also to determine whether an adjustment of dose is required. The most common reason for a raised serum TSH in a patient taking 150 µg or more of thyroxine daily is poor compliance; and the apparent paradox of raised serum TSH and raised T_4 is most likely due to overzealous tablet taking for the few days earlier by a patient who had previously been taking thyroxine sporadically. There is, however, an increasing list of circumstances in which the dosage of thyroxine may need to be adjusted, usually upwards (Table 2). The most recent observation is that women taking oestrogen either for contraception or for hormone replacement therapy may require an increase in the dose of thyroxine, although this is not as common an occurrence as during pregnancy[25].

Table 2 Situations in which an adjustment of the dose of thyroxine may be necessary.

Increased dose required	
Use of other medication	
Phenobarbitone, Phenytoin, Carbamazepine, Rifampicin, *Sertraline, *Chloroquine	increased thyroxine clearance
Cholestyramine, Sucralfate, Aluminium hydroxide, Ferrous sulphate, Dietary fibre supplements	interference with intestinal absorption
Pregnancy, *Oestrogen therapy*	increased concentration of serum thyroxine-binding globulin
After surgical or iodine-131 ablation of Graves' disease	reduced thyroidal secretion with time
Malabsorption e.g. coeliac disease	
Decreased dose required	
Aging	decreased thyroxine clearance
Graves' disease developing in patient with long-standing primary hypothyroidism	switch from production of blocking to stimulating TSH-receptor antibodies

* mechanism not fully established.

Thyroxine alone or in combination with triiodothyronine?

For the first half of the 20th century the only treatment available for hypothyroidism was animal thyroid extract which, although usually effective, was of variable potency and the rapid serum peak of its triiodothyronine component gave rise to troublesome palpitations in some patients 1 to 2 hours after ingestion. It was largely abandoned in the 1960s when readily standardised synthetic thyroxine became widely available[26] and, as triiodothyronine was derived only from peripheral monodeiodination of the ingested thyroxine, peak concentrations were avoided. Some patients, however, swore by the increased efficacy of thyroid extract and would go to considerable lengths to obtain supplies, but they were considered eccentric as indeed were the practitioners who supplied them.

Recently there has been a renewal of interest in treating hypothyroidism with both thyroxine and triiodothyronine based on the results of studies in animals and in patients. In rats which had been thyroidectomized, and therefore made hypothyroid, it was only possible to restore normal tissue levels of T_3 and T_4 and normal serum concentrations of T_3, T_4 and TSH by administering a combination of both hormones. It required supraphysiological doses of thyroxine given alone to achieve normal tissue concentrations of T_3 [27,28]. In patients a combination of thyroxine and triiodothyronine approximating the ratio normally secreted by the thyroid gland resulted in significant improvements in mood and neuropsychological function, as compared with a higher dose of thyroxine alone – and, of most interest, this improvement occurred without suppression of serum TSH[29]. Further evidence that monotherapy with thyroxine may be inadequate derives from a study of weight gain following treatment of hyperthyroidism. Those patients who developed hypothyroidism and were given thyroxine in a dose which restored serum TSH to normal gained significantly more weight than those who remained euthyroid with normal serum TSH as a result of endogenous secretion of T_3 and T_4.[30] If such findings are replicated it will be important for synthetic combinations of thyroxine and triiodothyronine to be available in a ratio of 10:1, with the latter in slow release form to avoid cardiac adverse effects. The average daily replacement therapy is likely to be thyroxine 100 μg and triiodothyronine 10 μg. Although most patients are satisfactorily controlled with thyroxine alone, an appropriate combined preparation would perhaps improve well-being in those dissatisfied with replacement rather than suppressive doses of monotherapy while at the same time removing the possible risks associated with exogenous subclinical hyperthyroidism.

Indications for Thyroid Hormone Treatment other than over Thyroid Failure

Subclinical hypothyroidism

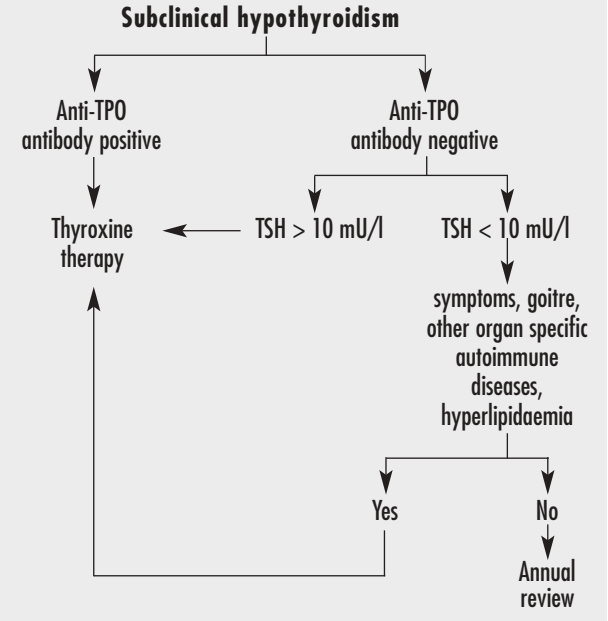
There is a consensus forming that subclinical hypothyroidism (raised serum TSH but normal thyroid hormone concentrations) represents the mildest form of thyroid failure, and as such should usually be treated with thyroxine. Those favouring therapy are most influenced by the knowledge that between 25–50% of such patients feel better when taking thyroxine,[31] and by the inexorable progression to overt thyroid failure of approximately 5% each year in those who possess antithyroid peroxidase antibodies; a risk which increases with higher serum TSH concentrations[32].

As hyperlipidaemia is common in overt hypothyroidism it was anticipated that treatment of subclinical hypothyroidism with thyroxine would improve the lipid profile. However, most patients with subclinical hypothyroidism do not have increased serum total cholesterol and triglyceride concentrations and no substantial reduction occurs after restoration of serum TSH to normal. A recent meta-analysis of the effectiveness of therapy of subclinical hypothyroidism on serum lipids showed a median decrease in serum total cholesterol and LDL-cholesterol of only 5%,[33] and smaller studies have suggested that thyroxine has no effect on lipid concentrations unless serum TSH is greater than 10 mU/l. Although associations have been recognised between autoimmune thyroid disease[34] and subclinical hypothyroidism[35] and myocardial infarction, the link does not seem to be through hyperlipidaemia.

A raised serum TSH concentration does not necessarily imply hypothyroidism and, if there is no obvious reason for the elevation such as previous treatment of hyperthyroidism with surgery or iodine-131, or the presence of other organ specific autoimmune diseases (pernicious anaemia, insulin-dependent diabetes mellitus, Addison's disease, vitiligo) it is sensible to repeat the measurement in 3–6 months. Furthermore, serum TSH concentrations are not normally distributed within the population and there is a significant tail of values between the upper limit of the reference range of 3.5–5.0 mU/l and 8–10 mU/l which is not associated with evidence of thyroid disease, particularly in men.

Figure 1 summarises the current views of the management of subclinical hypothyroidism.[36]

Figure 1 An algorithm for the management of subclinical hypothyroidism, amended from Cooper.[36] TPO: thyroid peroxidase.



Temporary hypothyroidism

Most patients with primary hypothyroidism require lifelong treatment with thyroxine. There are, however, well-recognised situations in which the thyroid failure is transient. For example, during the recovery phase of subacute or painless thyroiditis (including postpartum thyroiditis) patients may have asymptomatic or mild hypothyroidism for a few weeks which does not usually justify treatment. Hypothyroidism caused by chronic autoimmune thyroiditis may

remit spontaneously, particularly if excessive iodine intake has been implicated, as in treatment with the antidysrhythmic drug, amiodarone. It is often not appreciated that hypothyroidism may be transient if it occurs within 6 months of subtotal thyroidectomy or iodine-131 for hyperthyroidism. If thyroxine therapy is required at an early stage a suboptimal dose of 75 μg daily should be prescribed. Measurement of serum T_4 and TSH at 6 months will indicate whether continued treatment with a higher dose is required (raised serum TSH) or whether the thyroxine can be discontinued (low or normal TSH) and thyroid function reassessed 4–6 weeks later.

Goitre suppression

Thyroxine in a dose sufficient to suppress serum TSH may be necessary to achieve maximum goitre shrinkage in patients with Hashimoto's thyroiditis.[37] Although thyroxine is often prescribed in an attempt to decrease the size of the thyroid in patients with diffuse or nodular goitre and to prevent regrowth after surgery, there are conflicting views on its effectiveness, reflecting the complexity of the causes of the disorder. However, what is established is that the natural history of multinodular goitre is the slow progression to hyperthyroidism over a period of approximately 20 years as autonomously functioning nodules increase in size and number. It follows, therefore, that in any patient with a nodular goitre and a low serum TSH concentration, thyroxine therapy is inadvisable since it may induce hyperthyroidism. In what is usually an elderly population this may have serious consequences such as the development of atrial fibrillation complicated by systemic embolism.

Combination therapy with antithyroid drugs

Although most patients with Graves' disease are readily controlled with an antithyroid drug alone, there are circumstances when a "block and replace" regime with thyroxine combined with carbimazole (methimazole) or propylthiouracil is appropriate. In some patients thyroid function, while taking an antithyroid drug diligently, fluctuates between hyper- and hypothyroidism due to variation in the concentrations or ratios of stimulating and blocking TSH-receptor antibodies. Good control can only be achieved in this circumstance using combination therapy. In addition, in patients with significant ophthalmopathy it is essential to maintain as good control of thyroid function as possible and this is often most readily achieved by a "block and replace" regime, which may have the added advantage of the immunosuppressive action of sustained high dose antithyroid drug therapy. Despite earlier claims, combination therapy does not lead to an increased remission rate in patients with Graves' disease either given for a period of 18 months or more, or when the regime is applied unconventionally such that thyroxine alone is continued after the antithyroid drug is stopped.[38,39]

Non-thyroidal illness

The biochemical changes of low serum TSH and T_3 associated with illness or starvation are often considered teleologically as an adaptive response to spare calories and protein. However, it is not clear whether severe illness can, in some circumstances, cause the potentially detrimental entity of "tissue hypothyroidism".[40] Although the present consensus is that thyroid hormone treatment is not indicated in patients with significant non-thyroidal illness, this has become a controversial issue. For example, there are studies which have shown improvements in cardiac output and systemic vascular resistance in patients with chronic cardiac failure following treatment with intravenous T_3,[41] but there is, as yet, no evidence that intervention improves survival.

Triiodothyronine in doses as high as 60 μg daily, which would produce symptoms of hyperthyroidism in normal individuals, have been employed in psychiatric practice in the treatment of depressed patients who respond unsatisfactorily to standard therapies, and to hasten the

response to antidepressants, but the results are inconclusive.[42]

"Hypothyroidism" despite normal tests of thyroid function

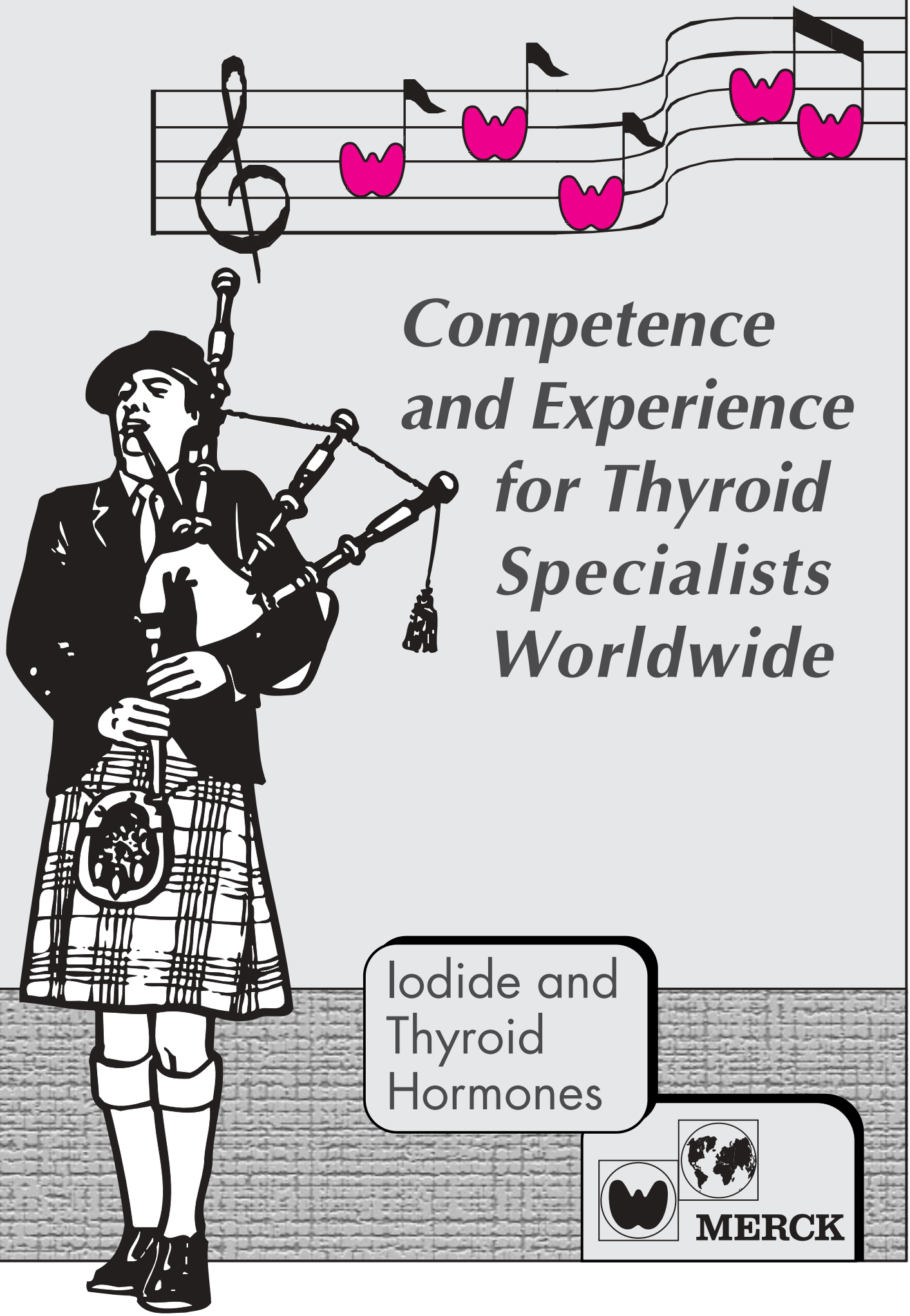
There is a vociferous lobby of patients, supported by some doctors with an eccentric view of thyroid physiology, that hypothyroidism can exist in the presence of normal tests of thyroid function. Known in North America as Wilson's syndrome, affected patients complain of a variety of non-specific symptoms, such as fatigue, weight gain and low mood and make extravagant claims for the efficacy of thyroid hormone therapy. Their belief is that the reference ranges for serum T_4 and TSH are so wide that what are considered normal values may not be normal for them. Their stance does not take into account the fact that the pituitary thyrotroph is very sensitive to minor changes in thyroid hormone concentrations within the normal range[2] and, for example, a reduction in free T_4 from 20 to 14 pmol/l would be associated with a significant increase in serum TSH. For Wilson's syndrome to exist would require a re-setting of the hypothalamic-pituitary-thyroid axis which has never been described. Furthermore, the only double-blind placebo-controlled trial of patients with symptoms which could be attributed to thyroid failure but with normal tests of thyroid function, not surprisingly, failed to show any benefit from thyroxine therapy.[43]

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