

# Problem Solving in Endocrinology and Metabolism

LEE KENNEDY

and

ANSU BASU

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CLINICAL PUBLISHING

To Rhona, Hannah, Douglas, Alice, Kathleen and Euan for being a great family,  
and especially to Fiona for her support during this and many other projects (LK)

To Indrani and Ishani (AB)

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CLINICAL PUBLISHING

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## CLINICAL PUBLISHING

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# Contents

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Abbreviations vii

## SECTION 01 Thyroid 1

- 1 Graves' disease 1
- 2 Hyperthyroidism – multinodular goitre 6
- 3 Thyroid nodule 11
- 4 Sick euthyroid syndrome 16
- 5 Amiodarone and the thyroid 21
- 6 Subclinical hypothyroidism 27
- 7 Thyroid function in early pregnancy 31
- 8 Post-partum thyroid disturbance 35
- 9 Thyrotoxic crisis 39
- 10 Thyroid eye disease 43

## SECTION 02 Adrenal 49

- 11 Addison's disease 49
- 12 Autoimmune polyglandular syndromes 54
- 13 The incidental adrenal nodule 59
- 14 Cushing's syndrome 63
- 15 Congenital adrenal hyperplasia 68

## SECTION 03 Pituitary 75

- 16 Acromegaly 75
- 17 Prolactinoma 80
- 18 Non-functioning pituitary adenoma 85
- 19 Hypopituitarism: investigation and treatment 90

## SECTION 04 Reproductive 95

- 20 Primary amenorrhoea 95
- 21 Secondary amenorrhoea 99
- 22 Polycystic ovarian syndrome – subfertility 104
- 23 Premature ovarian failure 108
- 24 Hirsutism 113
- 25 Erectile dysfunction 119
- 26 Male hypogonadism 125

**SECTION 05 Growth 131**

- 27** Delayed puberty 131
- 28** Gynaecomastia 136
- 29** Turner's syndrome 142
- 30** Klinefelter's syndrome 147

**SECTION 06 Calcium 153**

- 31** Primary hyperparathyroidism 153
- 32** Hypocalcaemia 158

**SECTION 07 Hypertension 163**

- 33** Hypertension – is it endocrine? 163
- 34** Pheochromocytoma 169
- 35** Conn's syndrome 174

**SECTION 08 Electrolytes 179**

- 36** Hyponatraemia 179
- 37** Hypokalaemia 185
- 38** Hypomagnesaemia 190
- 39** Diabetes insipidus 194
- 40** Spontaneous hypoglycaemia 200

**SECTION 09 Therapeutic 205**

- 41** Corticosteroid and mineralocorticoid replacement 205
- 42** Neutropaenia on carbimazole 210
- 43** Lithium 214
- 44** Calcium and vitamin D 219
- 45** Oestrogen and progesterone 223
- 46** Thyroid hormone replacement 228

**Index 233**

# Abbreviations

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17-OHP	17-hydroxyprogesterone	DI	deiodinase
ACTH	adrenocorticotrophic hormone	DIT	diiodothyronine
ADH	antidiuretic hormone	DITPA	3,5-diiodothyropropionic acid
AECA	anti-endothelial cell antibodies	DOC	deoxycorticosterone
AIDS	acquired immune deficiency syndrome	DST	dexamethasone suppression test
AIT	amiodarone-induced thyrotoxicosis	ECG	electrocardiogram
AITD	autoimmune thyroid disease	ED	erectile dysfunction
ALD	adrenoleukodystrophy	EDTA	ethylenediaminetetraacetic acid
AMI	acute myocardial infarction	EPHESUS	Eplerenone Neurohormonal Efficacy and Survival Study
AMP	adenosine monophosphate	FAI	free androgen index
ANCA	antineutrophil cytoplasmic antibody	FNAC	fine needle aspiration cytology
anti-TPO	antithyroid peroxidase	FSH	follicle-stimulating hormone
APA	aldosterone-producing adenoma	GFR	glomerular filtration rate
APS	autoimmune polyendocrine deficiency syndromes	GH	growth hormone
	autoimmune polyglandular syndromes	GLP	glucagon-like peptide
	adrenergic postprandial syndrome	GMP	guanosine monophosphate
AQP2	aquaporin-2	GnRH	gonadotrophin-releasing hormone
ARR	ratio of plasma aldosterone to plasma renin	GTP	guanosine triphosphate
ATP	adenosine triphosphate	hCG	human chorionic gonadotrophin
AVP	arginine vasopressin	HIV	human immunodeficiency virus
BAH	bilateral adrenal hyperplasia	HLA	human leucocyte antigen
BMD	bone mineral density	HPA	hypothalamic–pituitary–adrenal axis
BMI	body mass index	HRT	hormone replacement therapy
BMR	basal metabolic rate	HU	Hounsfield Unit
CAH	congenital adrenal hyperplasia	ICSI	intracytoplasmic sperm injection
CBZ	carbimazole	IGF	insulin-like growth factor
CC	clomiphene citrate	IPSS	inferior petrosal sinus sampling
CEE	conjugated equine oestrogen	ITU	intensive therapy unit
CI	confidence interval	JNC7	Joint National Committee 7
CRH	corticotrophin-releasing hormone	LH	luteinizing hormone
CT	computed tomography	LOD	laparoscopic ovarian drilling
CTLA-4	cytotoxic T lymphocyte antigen	MDT	multidisciplinary team
DA	dopamine agonist	MEN	multiple endocrine neoplasia
DDAVP	1-desamino-8-d-arginine vasopressin	MIBG	<sup>123</sup> I-metaiodobenzylguanidine
DHEA	dehydro-3-epiandrosterone	MIVAT	minimally invasive video-assisted thyroidectomy
DHEAS	DHEA sulphate		

MMAS	Massachusetts Male Aging Study	SCA	silent corticotroph adenomas
MMI	methimazole	SCC	side chain cleavage
MNG	multinodular goitre	SERM	selective oestrogen receptor modulator
MORE	Multiple Outcomes of Raloxifene Evaluation	SERPINA	serine protease inhibitor superfamily member A7
MRI	magnetic resonance imaging	SES	sick euthyroid syndrome
NAION	non-arteritic ischaemic optic neuropathy	SHBG	sex hormone-binding globulin
NANC	non-adrenergic non cholinergic [neurones]	SIADH	syndrome of inappropriate ADH secretion
NEFA	non-esterified fatty acid	SMR	standard mortality ratio
NHANES	National Health and Nutrition Examination Study	SPECT	single photon emission computed tomography
NS	non-significant	SST	Short synacthen test
oGTT	oral glucose tolerance test	T <sub>3</sub>	triiodothyronine
OR	odds ratio	T <sub>4</sub>	thyroxine
PADAM	partial androgen deficiency in ageing men	TBG	thyroxine-binding globulin
PCOS	polycystic ovarian syndrome	TBI	traumatic brain injury
PDE-5	phosphodiesterase-5 inhibitor	TBII	TSH receptor antibodies (TSH binding inhibitory immunoglobulins)
PKA	protein kinase A	TED	thyroid eye disease
POF	premature ovarian failure	TNF	tumour necrosis factor
PPAR- $\gamma$	peroxisome proliferator-activated receptor- $\gamma$	TPO	thyroid peroxidase
PPTD	post-partum thyroid disturbance	TRAB	TSH receptor antibody
PSV	peak systolic velocity	TRH	thyrotrophin-releasing hormone
PTH	parathyroid hormone	TSH	thyroid-stimulating hormone
PTHrP	parathyroid-related protein	TTR	transthyretin
PTU	propylthiouracil	UFC	urine free cortisol
RALES	Randomised Aldactone Evaluation Study	VLCA	very low chain fatty acids
RR	relative risk	VMA	vanillylmandelic acid
SAGH	subclinical autonomous glucocorticoid hypersecretion	WHI	Women's Health Initiative
SAME	Syndrome of apparent mineralocorticoid excess		

# Thyroid

- 01 Graves' disease
- 02 Hyperthyroidism – multinodular goitre
- 03 Thyroid nodule
- 04 Sick euthyroid syndrome
- 05 Amiodarone and the thyroid
- 06 Subclinical hypothyroidism
- 07 Thyroid function in early pregnancy
- 08 Post-partum thyroid disturbance
- 09 Thyrotoxic crisis
- 10 Thyroid eye disease

## PROBLEM

### 01 Graves' Disease

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#### Case History



A previously fit 32-year-old woman notices tremor and heat intolerance. She has lost one and a half stones (9.5 kg) in weight over the past 6 months. You note signs of hyperthyroidism and a diffuse goitre. Her mother is treated for hypothyroidism. The patient smokes 20 cigarettes per day. She and her husband want to start a family in the foreseeable future.

**How should she be investigated?**

**Does she require a thyroid scan?**

**What is the preferred first line of treatment?**

**If she has a child, how likely is the child to be affected by Graves' disease?**

## Background



Thyrotoxicosis occurs in 2% of women and 0.2% of men. In younger people, Graves' disease is by far the commonest diagnosis, with peak onset at 20–40 years. Treatment is with drugs, radioactive iodine or surgery. Thionamide drugs are generally the first line of therapy in young women.<sup>1,2</sup> They have been used for over 50 years. They are safe and well tolerated. Up to 10% of patients experience mild side effects including urticaria, skin rash, joint pain, altered taste and nausea. These do not usually necessitate stopping the drug. The most serious side effect is agranulocytosis which occurs in less than 0.4%. Patients should always be warned to report skin rash, sore throat or any other untoward side effect, and this warning should be recorded in their notes. If side effects are reported, full blood count and differential should be requested urgently and consideration should be given to stopping the drug.

There are three thionamide drugs—carbimazole (CBZ), methimazole (MMI), and propylthiouracil (PTU). They are similar in their clinical effect. There have been no substantial head-to-head studies comparing them. CBZ is the most commonly used drug in the UK, whereas MMI is used in the USA and in many European countries. PTU is usually used as second line treatment. It has a shorter duration of action and therefore is best given in divided doses. PTU may have free radical scavenging activity, and it is not the drug of first choice before or after radioactive iodine because it may diminish the effectiveness of the latter. Skin rashes may be commoner with MMI—reported rate in trials was 7% for CBZ compared with 12% for MMI.<sup>2</sup> PTU is the drug of choice in acute severe thyrotoxicosis as it decreases conversion of  $T_4$  to  $T_3$ .

In practice, duration of antithyroid treatment does not appear to be critical. Endocrinologists have all encountered patients who stop taking their drugs after a few months and do not relapse and others who relapse even after prolonged treatment. There is consensus that patients should be treated for at least 6 months, and certainly until serum thyrotropin (TSH) is no longer suppressed and levels of TSH receptor antibodies (TBII) have decreased. Longer treatment may lead to decrease in goitre size, and thus lower risk of relapse. Evidence slightly favours longer than 6 months' treatment; common practice is between 12 and 18 months, and there is no evidence to favour longer treatment.

Most endocrinologists commence patients on high dose and gradually decrease to maintenance dose according to response. Block and replace regimens were based on the hypothesis that antithyroid drugs had immune-modulating and antioxidant properties, and thus may modify the natural history of the disease. Exposure to higher doses of the drug for longer necessitates concurrent thyroid hormone treatment. The two regimens have been compared in 12 studies involving a total of over 1700 patients. The compliance with follow-up varied in these studies. On an intention-to-treat basis, and with follow-up greater than 2 years, relapse rate is just over 50% with either regimen. Higher dose of drug increases risk of side effects. There was no difference in the incidence of agranulocytosis. However, skin rashes were more common in block and replace studies—10% for block and replace vs. 5% for titration (odds ratio [OR] 2.62; 95% confidence interval [CI] 1.20 to 5.75). More people withdrew because of side effects in the block and replace groups.

Treatment with thyroxine following antithyroid drugs was hypothesized to decrease autoantigen exposure and thus lower relapse rate. Three studies have combined thyroxine and low-dose antithyroid drug after initial stabilization with antithyroid drug. No difference in relapse rate was found. In three further studies, antithyroid drug was followed by

a period of thyroxine treatment. In these studies relapse rate was 31% in the thyroxine-treated patients and 29% in those treated with placebo (not significant).

Thyrotoxicosis may temporarily worsen after  $^{131}\text{I}$  because of a combination of radiation-induced thyroiditis and increased TBII. Severe exacerbation occurs in less than 1%. Antithyroid drugs are frequently used prior to  $^{131}\text{I}$  to achieve more rapid symptom control. There is no real proof that pre-treatment with antithyroid drugs prevents exacerbation of thyrotoxicosis after treatment, but the increase in TBII is less marked, and exacerbations may thus be less severe.<sup>3</sup> Resumption of antithyroid drugs after radioactive iodine achieves symptom control but does not alter the outcome.<sup>4</sup> Antithyroid drugs are generally stopped 4–10 days before therapy and resumed 7 days after.

### Genetics of Graves' disease

Graves' disease results from interaction between genetic and environmental factors. Up to 60% of patients have family history of autoimmune thyroid disease (AITD). About a third of first-degree relatives will develop, or have developed, AITD, and around half will be positive for autoantibodies. Concordance rates are higher for monozygotic twins than for dizygotic twins. Genetic influences are thought to account for up to 80% of the susceptibility to Graves' disease.<sup>5</sup>

The human leucocyte antigen (HLA) complex located at chromosome 6p21 has three classes of antigen:

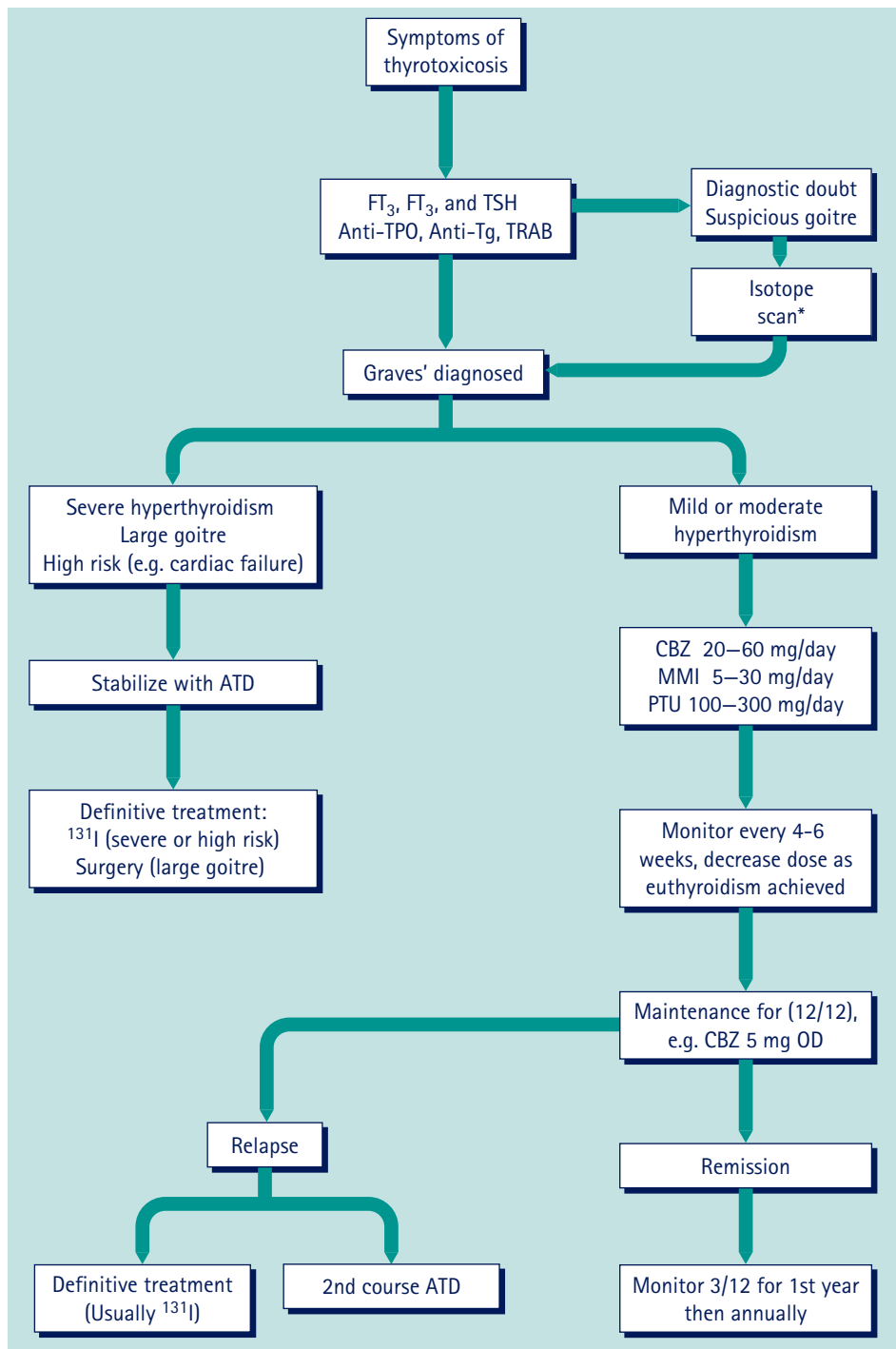
- class I—HLA-A, B and C
- class II—HLA DP, DQ and DR
- class III—complement, tumour necrosis factor (TNF)- $\alpha$ , heat shock protein-70 and other immune regulatory genes.

This is a highly polymorphic region of the genome, conferring susceptibility to a range of diseases. HLA-DR3 is the most useful marker. Among patients with Graves' disease 40–50% are HLA-DR3 positive, compared with 15–30% of the general population. Recent studies have identified associations with other HLA alleles, most notably DQA1\*0501. HLA is probably important in all ethnic groups, but the precise associations in non-Caucasians differ from the above. Cytotoxic T lymphocyte antigen-4 (CTLA-4), located at chromosome 2q33, is a costimulatory molecule involved in interaction between T lymphocytes and antigen-presenting cells. At least four polymorphisms have been identified and confer susceptibility to autoimmune endocrine disease.<sup>6</sup> Together, HLA antigens and CTLA-4 confer around half the susceptibility to Graves'. Other candidate genes include immune regulatory genes, such as the vitamin D receptor, TSH receptor and thyroglobulin.

## Recent Developments



- 1 Wang *et al.*<sup>7</sup> have shown that the A/G polymorphism at position 40 in exon 1 of CTLA-4 may be a marker for relapse after antithyroid drug therapy. Early identification of patients liable to relapse may allow us to target definitive treatment early.
- 2 The Nurses' Health Study<sup>8</sup> followed 115 109 women aged 25–42 over 12 years. The incident diagnosis of Graves' was 4.6 per 1000. Smoking was a risk factor (hazard ratio



**Fig. 1.1** Use of antithyroid drugs. \*Scan with technetium-99m pertechnetate or iodide. ATD = antithyroid drugs; CBZ = carbimazole; MMI = methimazole; PTU = propylthiouracil; Tg = thyroglobulin; TPO = thyroid peroxidase; TRAB = TSH receptor antibodies.

1.93). Obesity was associated with lower risk of Graves'—hazard ratio for individuals with body mass index (BMI) greater than 30 kg/m<sup>2</sup> was 0.68 (95% CI 0.49 to 0.92).

- 3 Colour Doppler sonography may be useful in diagnosis of thyroid disorders. This is a safe, non-invasive technique to assess blood flow in the thyroid arteries. Results correlate highly with thyroid volume and function. In a preliminary study,<sup>9</sup> thyroid blood flow at baseline was highly correlated with outcome after 14 months of antithyroid drug therapy. Relapse could be predicted with a sensitivity of 71% and specificity of 100%.

## Conclusions



Initial investigations should include thyroid hormone, TSH and thyroid antibodies, including TBII. Full blood count and liver tests should be requested at baseline and at intervals in patients taking antithyroid drugs (Figure 1.1). Thyroid scanning is not routinely warranted unless there is doubt about the diagnosis. Antithyroid drug treatment is usually the first line treatment. Radioactive iodine has been increasingly used in recent years. There is no evidence of teratogenicity. Obviously, it is absolutely contraindicated during pregnancy and most endocrinologists would avoid its use within 6–12 months of conception. The above patient should not be overly concerned about the implications of the disease for her children although, if female, they will inherit a roughly one in three lifetime chance of developing AITD.

## Further Reading



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## PROBLEM

## 02 Hyperthyroidism – Multinodular Goitre

### Case History



A 65-year-old man has noted a swelling in his neck, gradually increasing in size over the past 3 years. Although generally healthy, he has mild angina, which is stable at present. He is being treated with atenolol and isosorbide mononitrate, and uses sublingual nitrate only occasionally. Isotope scan shows 50 g goitre with patchy uptake. His thyrotropin (TSH) is undetectable but his free  $T_4$  is only marginally elevated at 26 pmol/l (normal 12–25 pmol/l).

**Should his hyperthyroidism be treated?**

**He is concerned about radioactive iodine therapy, can we reassure him?**

**Is long-term antithyroid drug treatment advisable?**

**If he opts for surgery, should he have a subtotal or total thyroidectomy?**

### Background



Goitre affects up to 15% of females and 4% of males in developed countries. It is commoner in areas of absolute or relative iodine deficiency. Up to 13% of the world population (i.e. 1.5 billion people) have goitre. Thyroid volume, and prevalence of goitre, increases with age. The differential diagnosis of goitre in elderly people is shown in Table 2.1.

Table 2.1 Goitre in elderly subjects

Diagnosis	Frequency (%)
Non-toxic multinodular	51
Toxic multinodular	24
Solitary nodule	10
Toxic adenoma	5
Graves' disease	4
Hashimoto's thyroiditis	4
Simple goitre	1
Other causes	1

Adapted from Diez.<sup>1</sup>

Autoimmune disease and simple goitre are much more common in younger people, whereas multinodular goitre (non-toxic and toxic) are much more common in elderly people.

Thyroid cancer should always be considered, especially in very young or elderly people with goitre. It accounts for less than 1% of all malignancies in the UK, and malignancy is only present in less than 10% of all excised cold thyroid lesions. The following features increase suspicion of malignancy—age (old or very young), male sex, recent onset and rapid enlargement, irregular shape, fixation to surrounding structures, and enlargement of regional lymph nodes.

Patients with goitre should always be asked about episodes of thyroid dysfunction, family history, and if there has been a history of neck irradiation (which predisposes to thyroid cancer). If hyperthyroid, ask about recent intake of iodine-containing compounds. The commonest obstructive symptoms are tracheal symptoms with dyspnoea and stridor, particularly on exertion; next come oesophageal, mainly dysphagia for solid food; recurrent laryngeal nerve palsy causing hoarseness and venous obstruction causing facial plethora are less common; sympathetic nerve compression with Horner's syndrome is uncommon.

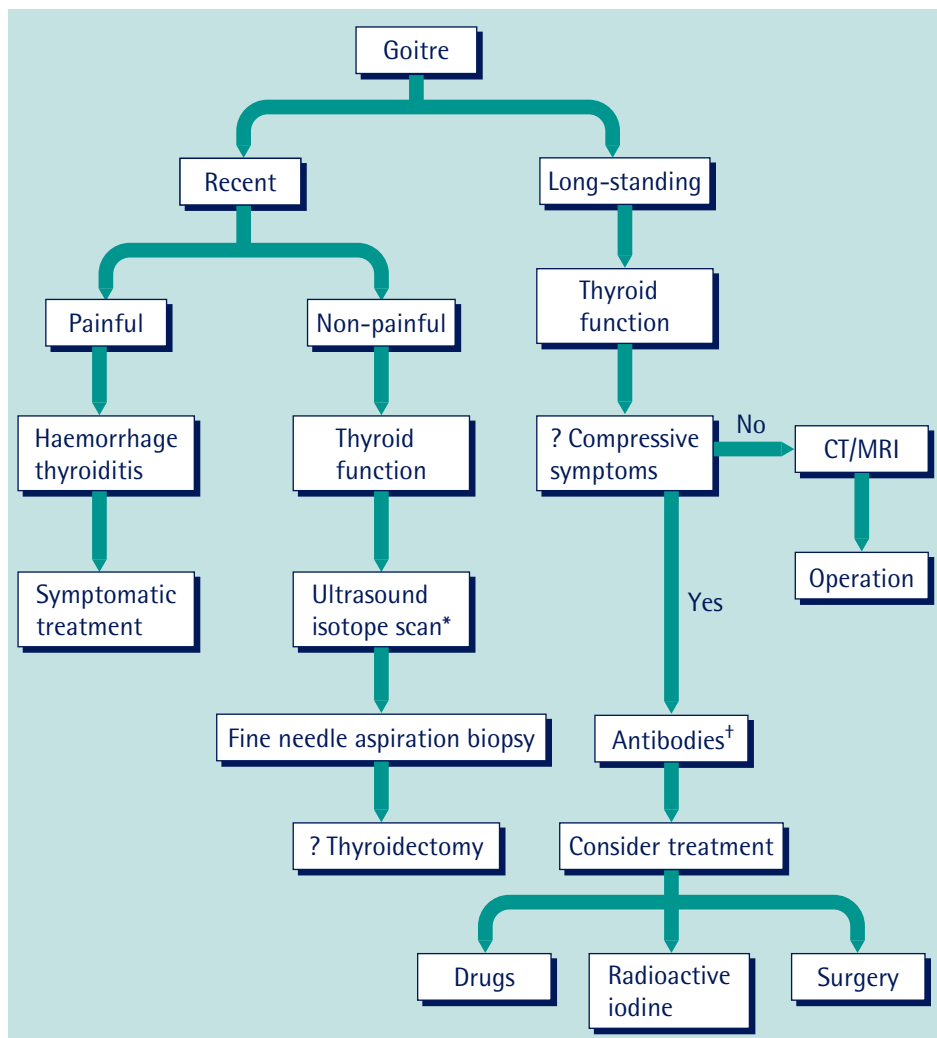
#### Box 2.1 Pemberton's manoeuvre

Raise the arms above the head until they are touching the side of the head. Hold the posture for one minute. Development of facial plethora or inspiratory stridor indicates that the goitre is causing compression.

Fine needle aspiration biopsy, open biopsy, or thyroidectomy should be considered if there is suspicion of malignancy. Where there are compressive symptoms, a suggestion of retrosternal extension or in any large (>100 g) goitre, computed tomography (CT) or magnetic resonance imaging (MRI) should be carried out to delineate the size of the goitre prior to surgery (Figure 2.1). A general guide to estimating thyroid volume is suggested in Table 2.2.

Thyrotoxicosis occurs in 2% of women and in 0.2% of men, and 15% of episodes of clinically apparent thyrotoxicosis occur in people over the age of 60. In elderly people, thyrotoxicosis is most commonly due to multinodular goitre (45–50%), followed by Graves' (20%), iatrogenic (15%) and solitary adenoma (10%). In 5–10% there is no goitre and the aetiology is unclear.

Among the US population, 2.5% have thyrotropin (TSH) of <0.1 mIU/l, including patients treated with thyroxine. There has been considerable debate about the need to treat subclinical hyperthyroidism. Current opinion<sup>2,3</sup> favours treatment, but not for all patients. About 5% of patients progress to clinical thyrotoxicosis each year. Relative risk of developing atrial fibrillation is around 3.0. Overall, 15% of patients with new atrial fibrillation are hyperthyroid. Risk of peripheral embolism has been reported to be as high as 10%. Rate control and anticoagulation are important as indicated. Clinical thyrotoxicosis is a risk factor for osteoporosis. Subclinical thyrotoxicosis increases bone turnover. Some studies have demonstrated beneficial effects of treating subclinical thyrotoxicosis on bone mineral density (BMD). Post-menopausal women with subclinical hyperthyroidism may lose up to 2% BMD per year, with loss being most apparent from



**Fig. 2.1** Investigation of goitre in the elderly patient. \*Isotope scan with technetium 99m pertechnetate or Iodine-123; †Antibodies, antithyroid peroxidase (TPO) and thyrotropin (thyroid-stimulating hormone [TSH]) receptor antibodies.

cortical bone. Observations that quality of life is impaired and risk of cognitive decline is increased need to be confirmed.

Choice of treatment depends on age, underlying diagnosis, and the presence of co-existent illnesses, and patient preference. Recent studies provide some reassurance about long-term drug treatment: Azizi and colleagues<sup>4</sup> showed that long-term methimazole was as safe and effective as radioactive iodine and there was no cost difference. Patients with hyperthyroidism require long-term follow-up whatever treatment they have. Pearce<sup>5</sup> has reviewed adverse events reported from over five million prescriptions of thionamide drugs in the UK between 1981 and 2003. Neutrophil dyscrasia (agranulocytosis or neutropaenia) was rare (0.1–0.5% of cases). It occurred mainly early in treatment (median

Table 2.2 Estimating the size of a goitre

Size (g)	Comparison	Compressive symptoms
<20	Normal thyroid	Not present
	Not visible or palpable	
40	Terminal phalanx of thumbs	Highly unlikely
	Large clove of garlic	
60	Apricot (small)	Unlikely
80	Hen's egg (small)	Possible if extends posteriorly or retrosternally
120	Lemon or orange (small)	Likely
200	Orange (large) or grapefruit	Probable

time 30 days) when the patient was likely to be on a high dose. It may be commoner with propylthiouracil, and is more frequently fatal in elderly people.

Many patients worry about potential risks from radioactive iodine therapy, particularly thyroid carcinoma, leukaemia and genetic damage. The treatment has been used for around 60 years now and long-term studies have confirmed that it is safe. Indeed, there is significantly greater risk from untreated, or undertreated, thyrotoxicosis. Hypothyroidism is much less likely with multinodular goitre compared with diffuse toxic goitre as the radioactive iodine is selectively taken up by the hyperfunctioning nodules. Rare side effects include transient thyrotoxicosis, sialadenitis and radiation thyroiditis—all usually seen with higher doses.

Most specialist centres now favour total rather than partial thyroidectomy for benign disease affecting both lobes of the gland. The major advantage is in avoiding the need for further operation should the gland re-grow or should thyroid cancer be discovered incidentally. Clearly, the patient would require thyroxine replacement following total thyroidectomy. In specialist hands, the rates of temporary vocal cord paralysis (1–2%) and hypoparathyroidism (5–10%) for a total thyroidectomy are comparable with permanent rates of 1% and 2% respectively for subtotal and total thyroidectomy.

## Recent Developments



- 1 Uptake of radioactive iodine into multinodular goitres is often fairly low, meaning that many patients need repeated doses. Albino *et al.*<sup>6</sup> administered 0.1 mg of recombinant human TSH (rhTSH) 1 and 2 days prior to <sup>131</sup>I. Iodine uptake increased from 12% to 54%. The treatment was highly successful, and thyroid volume decreased within a few months. There was an appreciable incidence of transient thyrotoxicosis and painful thyroiditis with the treatment, and 65% of patients became hypothyroid.
- 2 Significant advances have been made in thyroid surgery, including use of thyroid artery embolization prior to surgery for large goitres, ablation of thyroid nodules using ethanol and thus avoiding the need for operation, and autotransplantation of cryopreserved thyroid tissue in patients developing postoperative hypothyroidism. Experience

is increasing with minimally invasive video-assisted thyroidectomy (MIVAT).<sup>7</sup> Although not suitable for large and invasive goitres, this technique has the advantages of not requiring general anaesthesia and short hospital stay, and low complication rate.

- 3** In a follow-up study of nearly 16 000 person years, Franklyn *et al.*<sup>8</sup> showed that patients treated with <sup>131</sup>I had a slight excess mortality (standard mortality ratio [SMR] 1.14, confidence interval 1.04 to 1.24) compared with the background UK population. This was due to cardiovascular disease and was not apparent in patients rendered hypothyroid. These data confirm the safety of radioactive iodine and emphasize the need for effective treatment, even if hypothyroidism develops.

## Conclusions



The above patient has three significant problems: goitre, subclinical hyperthyroidism and angina. Recent evidence leaves little doubt that the hyperthyroidism should be treated. Radioactive iodine would be the treatment of first choice in most centres. This is safe and effective, and will help to shrink the goitre, or at least stop it growing further. Available evidence suggests that long-term treatment with thionamide drugs is a safe alternative. The patient will need ongoing follow-up for his thyroid disease whatever option he chooses. He may be more likely to be followed up by an endocrinologist if he remains on drug treatment. Surgery is relatively contraindicated because of his angina. In specialist centres, total or near-total thyroidectomy would be preferred to avoid the possibility of a second operation.

## Further Reading



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## PROBLEM

## 03 Thyroid Nodule

### Case History



JC is a 48-year-old man who has developed a swelling in the right side of his neck over the past 3 months. It is not painful, and he has no compressive symptoms. His health is generally good. You note a 2 cm diameter swelling in relation to the right lobe of the thyroid. He is clinically euthyroid and thyroid function is normal.

**What is your differential diagnosis?**

**How would you investigate the swelling further?**

**He would like to know what the chances are that the lump is malignant.**

**He is afraid of surgery and asks if it is safe to follow him up medically.**

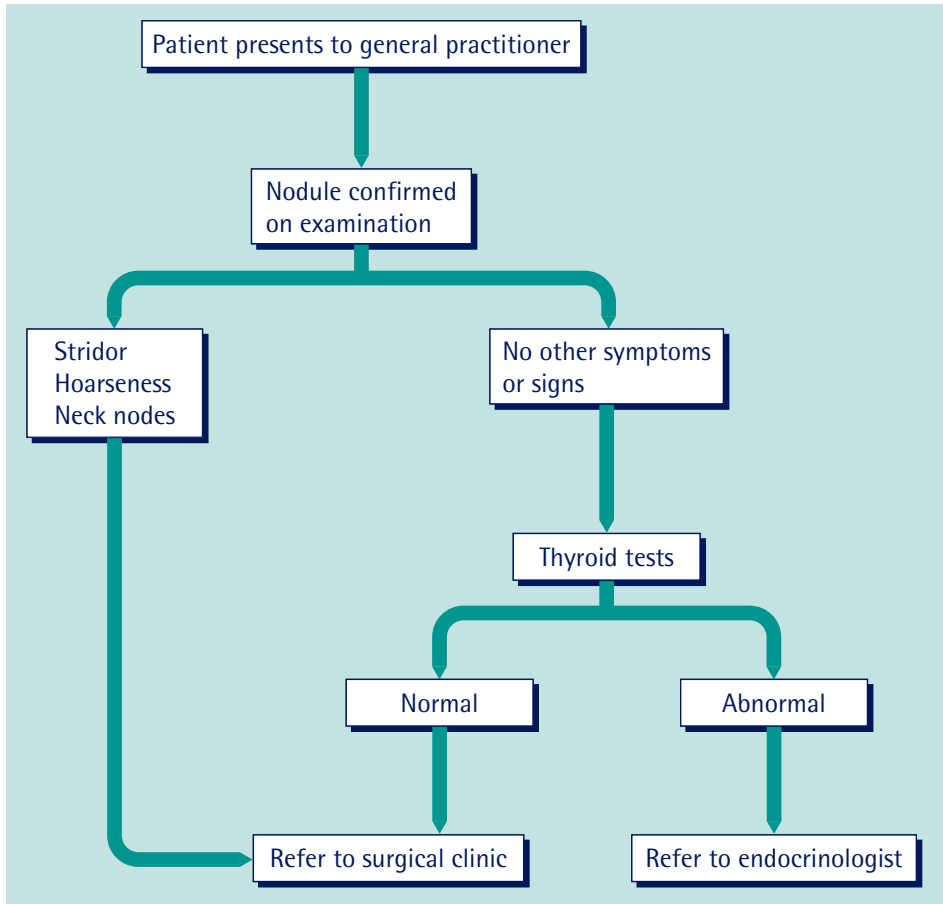
### Background



Thyroid nodules are extremely common. Around 5% of the US population has a thyroid nodule, and most of these are greater than 2 cm in their maximum diameter.<sup>1</sup> The vast majority (>95%) are benign. With ultrasound detection, the prevalence of thyroid nodules is even higher—up to 50% in women over the age of 60 years, a finding borne out by autopsy studies. Prevalence of thyroid nodules is also considerably higher in areas of relative iodine deficiency. Lesions less than 1 cm in diameter are called ‘micronodules’.

Expert assessment is essential to detect cancerous lesions, and to decrease likelihood of the patient having unnecessary surgery.<sup>2</sup> Widespread use of fine needle biopsy has decreased the proportion of patients requiring surgery while increasing the proportion of excised glands that have significant pathology. A proposed schema for investigation and management of thyroid nodules is shown in Figure 3.1. Initial assessment should include history and careful examination (look for irregularity of the nodule, size, fixation to surrounding tissues, regional lymph node enlargement and hoarseness), thyroid function tests, autoantibodies (antithyroid peroxidase (anti-TPO) and anti-thyroglobulin), fine needle aspiration cytology (FNAC) with or without ultrasound guidance, and inspection of the vocal cords if surgery is likely. Additional investigations include ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI), plasma calcitonin measurement, flow-volume loop if there are respiratory symptoms, chest X-ray, and isotope scan of the thyroid. Thyroglobulin is useful for postoperative surveillance of patients with thyroid tumours but its measurement at presentation is not of diagnostic benefit.

FNAC is the cornerstone of investigation in the endocrine clinic.<sup>3</sup> However, it does not always yield diagnostic information. Around 10% are non-diagnostic, 75% are benign, and 5% show papillary, anaplastic or medullary cell carcinomas. The remaining 10% are follicular



**Fig. 3.1** Evaluation of a thyroid nodule. Adapted from Utiger<sup>1</sup>—patients with suspicious lesions should be referred to a combined or surgical clinic within 2 weeks of presentation.

lesions of which 20% are carcinomas. In these, carcinoma can only be distinguished from adenoma on the basis of invasion of the capsule, blood vessels or lymphatics. This distinction cannot be made on FNAC, and these lesions are therefore usually referred for surgery. Different diagnostic categories of FNAC are now recognized and routinely used (Table 3.1).

Differential diagnosis for the above patient is set out in Figure 3.2. Papillary carcinoma is the most common malignancy of endocrine glands. Its incidence is increasing throughout the world, particularly in young women. Some of this apparent increase may be due to increased detection of early and occult lesions. Incidence of papillary cancer is 2.3 per 100 000 women per year and 0.9 per 100 000 men. Each year in England and Wales, 900 new cases are diagnosed and 250 deaths from the condition. With optimal management, the overall outlook is very good with up to 90% of those diagnosed in middle life surviving 10 years. The adequacy of surgical management, postoperative thyroid ablation with radioactive iodine, and careful monitoring for recurrences are all important determinants of prognosis.

Table 3.1 Diagnostic categories from fine needle aspiration cytology

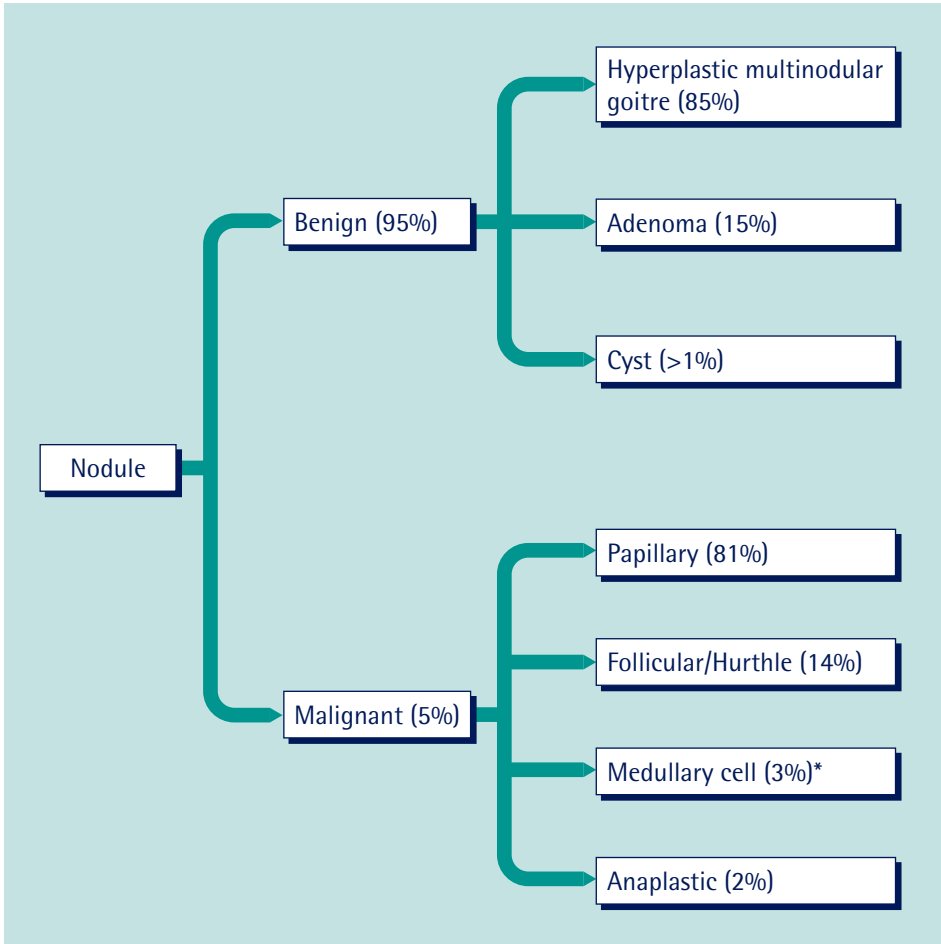
Category	Description
Thy 1	<i>Non-diagnostic</i> Action: Repeat (? with ultrasound guidance)
Thy 2	<i>Non-neoplastic</i> Action: Repeat at 3–6 months*
Thy 3	<i>All follicular lesions</i> Action: Discuss with MDT, thyroid lobectomy <sup>†</sup>
Thy 4	<i>Abnormal, suspicious of malignancy</i> Action: Discuss with MDT, thyroid lobectomy <sup>†</sup>
Thy 5	<i>Diagnostic of malignancy</i> Action: Management by surgeon and oncologist

\*Two non-neoplastic biopsies are required to exclude malignancy. <sup>†</sup>With completion thyroidectomy depending on intra-operative and histological findings. MDT = multidisciplinary team.

The following recommendations should be considered:

- Patients with suspected or proven thyroid cancer should be managed by an endocrine surgeon or by a surgeon with appropriate experience in endocrine surgery.
- Proven cancer should be managed in a centre with appropriate cytology, pathology, endocrinology, nuclear medicine, genetics and oncology.
- Differentiated thyroid cancer (papillary and follicular) should be managed by total lobectomy as a minimum procedure. Total or ‘completion’ thyroidectomy may be needed depending on intra-operative and pathological findings.
- Radioactive iodine ablation should be considered in patients who have undergone total thyroidectomy. This will improve detection of recurrence and is associated with improved survival.
- Patients with differentiated cancer should be treated with titrated doses of thyroxine to achieve complete thyrotropin (TSH) suppression (<0.1 mIU/l). TSH and thyroglobulin should be monitored at regular intervals. Increased thyroglobulin suggests recurrent tumour.
- Management and regular review should be undertaken by a multidisciplinary team.
- Rare forms of thyroid cancer including medullary carcinoma, anaplastic lesions, and lymphoma should be managed in a specialist centre.

Thyroid cancer is best managed by a specialist team. Prognosis of localized disease is excellent (Table 3.2). Following total thyroidectomy and radioactive iodine ablation, the patient is started on suppressive doses of thyroxine. Follow-up iodine scanning is carried out at 4–6 months and thereafter annually. Thyroxine is stopped 6 weeks prior to each scan and the patient is started on triiodothyronine (20 µg three times daily). This is stopped 2 weeks prior to radioactive iodine ablation. Increased TSH is necessary to ensure that a high proportion of radioactive iodine is taken up. Use of recombinant human TSH (rhTSH)



**Fig. 3.2** Differential diagnosis of a 2 cm thyroid nodule. \*75% of medullary cell cancers are sporadic, 25% are familial—mostly associated with multiple endocrine neoplasia type 2 (MEN2). Hurthle (oxyphilic) cells are large follicular cells with abundant pink-staining material. The tumours can be benign and are often slow growing. Prognosis and treatment is similar to other follicular lesions.

**Table 3.2** Prognosis from papillary thyroid cancer

Stage	Description	Mortality (%)*
I	<45 years, tumour <1 cm, no metastases T1 N0 M0	1.7
II	>45 years, any size metastases Any T, any N, M1	15.8
III	>45 years, local invasion T4, N0, M0 or any T, N1, M0	30.0
IV	>45 years with metastases Any T, any N, M1	60.9

\*Mortality is 10-year cancer specific mortality.

shortens the period during which the patient is hypothyroid. Thyroglobulin is most useful as a marker for recurrence when TSH is not suppressed and should thus be checked at the time of follow-up scan—if the thyroid has been successfully ablated, thyroglobulin should be negative. TSH suppression is also useful in some cases of benign thyroid disease—TSH is a growth factor for both benign and malignant thyroid cells.

## Recent Developments



- 1 Papillary cancers are often present in multiple foci within the thyroid. This may arise from metastatic primary tumour or independent development of multiple tumours. Shattuck *et al.*<sup>4</sup> have recently investigated the clonal origin of multifocal papillary cancers in women by studying polymorphisms of the androgen receptor gene on the X chromosome. They confirmed that multifocal papillary cancers, in many cases, may develop as independent primary tumours.
- 2 Nodules greater than 2 cm in diameter generally trigger intervention. The natural history of smaller lesions and occult thyroid carcinomas is largely unknown. Indeed, many of them are never diagnosed. Papillary cancers have a higher chance of being multifocal and of local spread, whereas papillary and follicular lesions are equally likely to spread distantly. A recent study from Germany has suggested that intervention before tumours grow to 2 cm is highly beneficial for prognosis.<sup>5</sup>
- 3 FNAC has been invaluable in risk stratification of lesions. There is considerable interest in minimally invasive surgery for low-risk thyroid lesions. Ultrasound-guided laser photocoagulation is useful for treatment of benign lesions<sup>6</sup> and has good cosmetic results with low risk of side effects.

## Conclusions



The above patient is over 45 years of age and has a swelling of recent onset which is greater than 2 cm in diameter. Investigations with a view to considering surgery are definitely indicated. However, it is most likely that this is a benign nodule—either a dominant hyperplastic nodule in a multinodular goitre or, thinking of his age, a benign adenoma. Thyroid function tests, autoantibody measurements, ultrasound and isotope scanning should all be considered but the major investigation is FNAC. If the lesion is low risk, it is safe to defer surgery and carry out further biopsy at 3–6 months, as treatment of papillary and follicular cancers with surgery, radioactive iodine ablation and suppressive thyroxine therapy is highly effective. Early treatment of all high-risk lesions is recommended.

## Further Reading



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## PROBLEM

# 04 Sick Euthyroid Syndrome

## Case History



A 56-year-old man presents with an acute myocardial infarction. Examination reveals mild cardiac failure. He has been feeling quite tired and experiencing chest pains with only minimal exertion. His thyroid tests reveal a low free  $T_4$  at 10 pmol/l (normal 12–25 pmol/l) and thyrotropin (thyroid-stimulating hormone [TSH]) at the lower end of the reference range (0.6 mIU/l, normal 0.15–3.5 mIU/l).

**Could his thyroid test results have a bearing on his reported state of health?**

**How would you investigate this further?**

**Does he require thyroid replacement therapy?**

## Background



Modern thyroid tests with free hormone measurements and high-sensitivity thyrotropin (TSH) assays have made it easier to diagnose thyroid dysfunction. Sick euthyroid syndrome refers to the physiological changes that occur in patients with non-thyroidal illness in the absence of thyroid disease. Clinicians are often advised not to check thyroid tests during a severe intercurrent illness as thyroid disease. However, we now recognize that the changes that occur in thyroid function in patients with sepsis, myocardial infarction, cardiac failure, and other critical illnesses are of prognostic importance. The physiological basis for these changes is now becoming understood. Thyroid hormone measurements in these circumstances can be helpful and the possibility that interventions to correct the thyroid changes in these circumstances may improve prognosis has been entertained.