Disorders of thyroid function are extremely common – the prevalence of thyrotoxicosis in women is 1–2 per cent, similar to that of spontaneous and iatrogenic hypothyroidism combined. Thyroid disorders are 5–10 times less common in men and can present at any age.

The biochemical diagnosis of thyroid dysfunction has been greatly facilitated by the introduction of sensitive thyroid-stimulating hormone (TSH) and free thyroid hormone assays. However, it must be appreciated that these tests do not identify the cause of the problem, which is important in selecting the appropriate treatment. By far the most common causes of hypothyroidism are autoimmune thyroiditis and thyroid destruction secondary to radioiodine and surgery (see Table 1). Most patients with autoimmune thyroiditis have positive thyroid peroxidase (TPO) antibodies, but these can occur in other disorders, including transient destructive thyroiditis appearing most typically in the postpartum period.

Graves’ disease accounts for 80 per cent of thyrotoxicosis cases and is usually diagnosed clinically by the presence of a diffuse goitre, typical eye signs (see Figure 1), or a personal or family history of associated autoimmune disorders such as pernicious anaemia, vitiligo, type 1 diabetes, Addison’s disease or coeliac disease. TPO antibodies are present in 80 per cent of Graves’ patients. Recent improvements in assay techniques have now made measurement of TSH-receptor antibodies the best specific test for the diagnosis of Graves’ disease, although this test is unnecessary if the patient has clinical signs of eye disease or if it will not alter management, eg if the patient is going to be treated with radioiodine. The main causes of thyrotoxicosis are listed in Table 2. After Graves’ disease, the next most common causes are toxic multinodular goitre (see Figure 2) or a solitary toxic adenoma (see Figure 3).

This review will focus mainly on the management of autoimmune and iatrogenic hypothyroidism and Graves’ disease.
Primary hypothyroidism
- Autoimmune hypothyroidism
- Iatrogenic: treatment of hyperthyroidism or external radiation of the thyroid (eg for lymphoma)
- Drugs: excess iodine, amiodarone, lithium, antithyroid drugs, interferon alfa
- Congenital
- Destructive thyroiditis: silent and postpartum thyroiditis, subacute thyroiditis
- Infiltrative disorders
- Iodine deficiency: common worldwide but absent in UK

Secondary hypothyroidism
- Hypopituitarism
- Hypothalamic disease

Table 1. Principal causes of hypothyroidism

Extensive guidelines for the diagnosis and treatment of both conditions have recently been published.\cite{1,2} The management of ophthalmopathy is beyond the scope of this article, but has been reviewed recently elsewhere.\cite{3} In most cases of primary hypothyroidism, management should be undertaken in primary care. Specialist referral is recommended for all patients with thyrotoxicosis at initial diagnosis and is necessary for the definitive management of those patients needing radioiodine, which is the treatment of choice in most patients with toxic adenoma or multinodular goitre.

Hypothyroidism
In a patient with no remaining thyroid tissue, very high TSH and undetectable free thyroxine (T\textsubscript{4}), the normal replacement dosage of levothyroxine is 1.6µg/kg daily, which is around 100–150µg daily. This dosage can be given from the outset in patients below the age of 60 years with no evidence of heart disease. Patients with lesser degrees of thyroid failure are usually commenced on 50–100µg daily. Currently in the UK, patients with hypothyroidism are entitled to an exemption certificate to allow them to obtain their prescription at no cost.

A frequent mistake is to assess the patient too soon after starting treatment. Dosage changes of 25–50µg levothyroxine daily should be made based on TSH levels measured two to three months after starting treatment. Levothyroxine should be taken at the same time each day, and ideally an hour before breakfast, if the TSH is to be maintained in a narrow, specific range.\cite{4}

Patients should be warned that a full improvement in symptoms may take two to three months, and also told that weight loss, a typical concern, will normally only occur when euthyroidism is restored and coupled with attention to exercise and diet.

Mild thyroid failure
In patients with mild thyroid failure, progression of thyroid destruction may occur over months or years, and therefore initial follow-up at three- to six-month intervals is worthwhile until the tempo of the hypothyroidism is established; thereafter annual follow-up should suffice. Once on a full replacement dosage, TSH levels should be checked every year.

Older patients and heart disease
For patients older than 50 years or those with heart disease, the usual starting dose of levothyroxine is 25µg once daily, adjusted in steps of 25µg every four weeks according to response, angina symptoms and TSH levels. Occasional patients with severe angina, which cannot be further improved by treatment, may be unable to tolerate the full replacement dose as the hypothyroid state acts as an effective antianginal in its own right. Daily levothyroxine requirements may decrease by 25–50µg in older patients.

TSH suppression
Some patients do not feel completely well despite restoration of normal TSH levels. There is indirect evidence that TSH levels in untreated individuals in the upper half of the reference range are associated with a slightly increased risk of future hypothyroidism,\cite{5} indicating that such TSH levels might already represent a degree of thyroid impairment, and therefore it seems sensible to titrate levothyroxine dosage to bring TSH levels into the lower half of the reference range (below 2mIU/L) in patients requiring treatment who feel unwell.

TSH suppression, ie TSH levels below the lower limit of the reference range, is associated with an increased risk of atrial fibrillation and lower bone mineral density.\cite{2} The latter occurs particularly in postmenopausal women who have already had an episode of thyrotoxicosis and now have iatrogenic hypothyroidism. Therefore, dosages that suppress the TSH below the lowest part of the reference range should be avoided, except when deliberate TSH suppression is desired, for instance in the treatment of thyroid cancer.

It has been suggested that a combination of levothyroxine and liothyronine may improve well-being when compared to levo-
thyroxine treatment alone. However, liothyronine as presently formulated is unsatisfactory for replacement as the half-life is short, leading to widely fluctuating thyroid hormone levels. The evidence to date suggests there is no overall benefit from the addition of current preparations of liothyronine and combined treatment is not recommended routinely for hypothyroid patients. Referral to an endocrinologist should be considered for patients who wish to discuss combination treatment further.

Another fairly frequent management problem is the patient who has erratic TSH levels despite a constant dose of levothyroxine, or who appears to require ever-increasing doses. The usual cause is poor adherence, and levothyroxine requirements in excess of 200µg daily suggest that tablets are being missed, although it is important first to rule out malabsorption (especially coeliac disease and conditions in which there is impaired acid secretion, including Helicobacter pylori infection and autoimmune gastritis), out-of-date tablets and the effect of certain drugs on levothyroxine absorption or kinetics (see Table 3).

A tactful discussion usually reveals a problem with adherence. This can be improved by telling patients that the long half-life of levothyroxine (seven days) makes it safe to take any tablets that have been missed during a week.

Pregnancy

Hypothyroidism should be diagnosed and treated prior to pregnancy, as an elevated maternal TSH in the first trimester of pregnancy is associated with a minor degree of intellectual impairment in the baby. Fertility is also impaired and the risk of miscarriage is increased.

A preconception TSH-level check is therefore ideal in women already taking levothyroxine to ensure that replacement is adequate. As a minimum, TSH and free $T_4$ levels should be measured once pregnancy is confirmed and at the beginning of the second and third trimesters.

Levothyroxine requirements increase by around 50 per cent in pregnancy and ideally this increase should be anticipated, with the patient being encouraged to increase thyroxine by 25–50µg per day as soon as they are pregnant and a thyroid function test being done four to six weeks later. A simple way to achieve this is by asking patients to take two extra doses of levothyroxine per week once pregnancy is confirmed. The aim should be to maintain free $T_4$ levels in the upper part of the reference range. The normal levothyroxine dose is resumed after delivery, and there are no implications for breastfeeding.

Subclinical hypothyroidism

Because of increased awareness and improved thyroid function tests, patients are often identified at an early stage of thyroid failure, when the TSH is elevated but free $T_4$ levels are normal. Although called subclinical hypothyroidism, implying that this state is asymptomatic, up to 25 per cent of such patients may have symptoms suggestive of hypothyroidism, including cognitive impairment, although such symptoms are nonspecific. Thyroid function tests should be repeated after three months if the TSH is $<10$mIU/L, and if the TSH is still elevated, a trial of levothyroxine may be warranted to determine whether such symptoms improve, although guidelines suggest that there may be little or no benefit from this approach. Annual thyroid function testing is required in patients with subclinical hypothyroidism who do not start levothyroxine. Individuals with elevated TSH level and positive TPO antibodies (see Figure 4) are at par-

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**Table 3. Possible drug interactions with levothyroxine**

- Reduced absorption (give levothyroxine several hours after drug)
  - Colestyramine, colestipol
  - Sucralfate
  - Ferrous sulfate
  - Aluminium hydroxide
  - Charcoal
  - Proton-pump inhibitors

- Increased metabolism
  - Rifampicin
  - Phenytoin, carbamazepine

- Interactions
  - Enhances anticoagulant effect of warfarin, acenocoumarol and phenindione
  - Avoid lofepramine
  - Enhances metabolism of propranolol

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Figure 2. Toxic multinodular goitre (radionuclide scan)

Figure 3. Toxic adenoma (radionuclide scan)
particularly high risk of developing overt hypothyroidism (roughly 5 per cent per year, compared with 2 per cent per year if the TSH alone is abnormal).9 Levothyroxine should be given long term to those with a TSH >10mIU/L and it is recommended that any degree of subclinical hypothyroidism in pregnancy should also be treated with levothyroxine.

Many patients complain of symptoms suggestive of hypothyroidism but have normal TSH and free T4 levels. There has been an unconventional view, particularly held by some private practitioners, that such patients warrant a trial of levothyroxine or desiccated thyroid extract (eg Armour; this product is not licensed in the UK and is not recommended for the treatment of established hypothyroidism). However, there is no scientific basis for the suggestion that this group of patients has a state of subtle thyroid dysfunction, and trials of levothyroxine, when suitably controlled, show no benefit.10 A normal TSH rules out primary hypothyroidism, and if there are features suggestive of hypothyroidism, a normal free T4 level will rule out the much rarer type of secondary (pituitary-dependent) hypothyroidism. If both tests are normal, the patient is euthyroid and an alternative cause for the symptoms should be sought.

**Thyrotoxicosis**

The main causes of thyrotoxicosis are shown in Table 2; making an accurate diagnosis is central to the choice of treatment. Destructive thyroiditis causing transient thyrotoxicosis usually settles spontaneously within four to six weeks. Antithyroid drugs are ineffective as the thyrotoxicosis is caused by stored hormone release rather than the increased synthesis of hormone, which occurs in true hyperthyroidism. A beta-blocker, such as propranolol 20–80mg three times daily, may be useful in controlling symptoms; atenolol 50mg daily is an alternative but is less effective as it is more cardioselective.

If the patient has severe subacute (or viral) thyroiditis, prednisolone – starting at a dosage of 40mg daily – may be indicated, which should be tapered off over two to four weeks depending on the symptomatic response. Many patients have only mild thyroid tenderness that responds well to a NSAID. Antithyroid drugs inhibit thyroid hormone synthesis and also reduce the level of autoantibodies that cause Graves’ disease: as a result, they can achieve a cure in 40–50 per cent of patients with Graves’ disease. These drugs will control the symptoms of thyrotoxicosis in other forms of hyperthyroidism but recurrence will ensue as soon as the drug is discontinued. Patients usually prefer radiiodine to surgery as primary treatment for a toxic adenoma or toxic multinodular goitre. The rest of this review will concentrate on Graves’ disease.

**Antithyroid drugs**

The properties of the antithyroid drugs in use – the thiouamides carbimazole and propylthiouracil – are shown in Table 4. Carbimazole is the favoured drug in the UK, propylthiouracil being used when a patient develops minor side-effects with carbimazole. The inhibitory effect of propylthiouracil on T4 to tri-iodothyronine (T3) conversion is only of practical benefit in severe thyrotoxicosis (thyrotoxic crisis or ‘storm’) and is offset by the need for more frequent dosing and the small tablet size (50mg) necessitating the use of sometimes 9–12 tablets a day.

Propylthiouracil is more protein bound than methimazole, the active metabolite of carbimazole, and therefore less likely to cross the placenta or to enter breastmilk. However, these benefits are modest and meticulous control of thyroid function is still needed with any thyroid drug used in pregnancy or during lactation.

**Administration** Antithyroid drugs can be given in two ways: titration or block-replace regimens. In the first, the patient is given carbimazole 20mg two or three times daily, and the dose is lowered every three to six weeks, based on free T4 measurement.

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**Figure 4. Suggested management of subclinical hypothyroidism**

[Diagram showing the suggested management of subclinical hypothyroidism]
Both regimens have their advocates. I prefer the block-replace daily for carbimazole. The dosage of antithyroid drug remains constant, usually 40mg, the same starting dosage of carbimazole or propylthiouracil is given in the block-replace regimen, but thereafter levothyroxine is added to maintain euthyroidism. Levothyroxine 100µg daily is usually needed around four weeks after starting the antithyroid drug when free T4 levels are near normal range. The dose of levothyroxine is adjusted based on free T4 levels, but the dosage of antithyroid drug remains constant, usually 40mg daily for carbimazole.

Both regimens have their advocates. I prefer the block-replace regimen because the titration regimen must be continued for 18–24 months to achieve a remission rate of 40–50 per cent, whereas the same rate is achieved using the block-replace regimen for six months. Unless there is frequent monitoring of thyroid hormones with the titration regimen, fluctuation of thyroid hormone levels is likely, but this is much less of a problem with the block-replace regimen.

The side-effects of antithyroid drugs (see Table 5) are, to some extent, dose related, but there is little practical difference between the two regimens. This is due to the shorter treatment duration of the block-replace regimen, which counteracts the higher average daily dose. Furthermore, side-effects are most common in the first three months of treatment, when high doses of drug are used in both regimens.

Drug-induced rash may respond to an antihistamine or a corticosteroid, to achieve a maintenance dosage of 5–10mg daily; 5mg carbimazole is equivalent to 50mg propylthiouracil.

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Drug-induced rash may respond to an antihistamine or a switch from one antithyroid drug to another; the latter is also indicated in the case of arthralgia. Patients should receive a written warning regarding symptoms suggestive of agranulocytosis (defined as a granulocyte count of less than 0.5×10⁹/L), with instructions to stop treatment and seek an immediate full blood count if they develop. The drug should be resumed as soon as the absence of agranulocytosis is confirmed; emergency hospital admission is needed if agranulocytosis develops and no antithyroid drug should be given thereafter. Lesser degrees of leukopenia are more common, and indeed may be a feature of Graves’ disease itself. It is recommended that the drug is stopped if the granulocyte count is less than 1.0×10⁹/L whereas continuation with close monitoring is possible if the count is between 1.0 and 1.5×10⁹/L.¹¹

Propylthiouracil should be avoided in children as they are particularly susceptible to severe hepatotoxicity and death as a complication of taking this drug.¹²

**Outcome after antithyroid drugs**

Around two-thirds of relapses of Graves’ disease occur in the year after treatment is stopped, and relapse 10 or more years after antithyroid drug treatment is unusual. Relapse occurs most frequently in those with large goitres and severe hyperthyroidism. Contrary to conventional opinion, younger patients are also less likely to enter remission than patients older than 50 years.¹³ A high dietary iodine intake (from seaweed or kelp tablets, for instance), smoking and a history of allergy also reduce the chances of remission. Other tests to predict outcome, including measurement of TSH-receptor antibodies, are insufficiently specific and sensitive to be of value in the management of individual cases.

Patients should be assessed about 6 and 12 weeks after treatment is stopped and then every three months to the end of a year. Thereafter, annual follow-up is sufficient; around 15 per cent of patients successfully treated with antithyroid drugs develop spontaneous hypothyroidism 10–15 years later due to the associated autoimmune thyroiditis.

Symptoms of Graves’ disease usually resolve slowly once treatment begins and patients with severe symptoms secondary to sympathetic overactivity, e.g. palpitations, sweating or tremor, may benefit from a beta-blocker for the first few weeks of treatment.

For patients who are intolerant of thioamide drugs, there is little medical alternative. Potassium perchlorate or lithium can reduce thyroid hormone synthesis but have serious side-effects and should only be used on the advice of an endocrinologist. Potassium perchlorate, however, is sometimes very useful for hyperthyroidism caused by excessive iodine intake (the Jod-Basedow phenomenon), including one type of amiodarone.

<table>
<thead>
<tr>
<th>Properties of antithyroid drugs</th>
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</thead>
<tbody>
<tr>
<td><strong>Serum half-life</strong></td>
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<tr>
<td>6–8 hours</td>
</tr>
<tr>
<td><strong>Intrathyroidal turnover</strong></td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
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<tr>
<td><strong>Influence of disease</strong></td>
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<tr>
<td><strong>Renal Hepatic</strong></td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
</tr>
<tr>
<td><strong>Inhibitor of T4 to T3 deiodination</strong></td>
</tr>
</tbody>
</table>

¹rapidly metabolised to methimazole

Table 4. Properties of antithyroid drugs

<table>
<thead>
<tr>
<th>Minor side-effects (2–5% of patients)</th>
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</thead>
<tbody>
<tr>
<td>pruritus</td>
</tr>
<tr>
<td>urticarial or maculopapular rash</td>
</tr>
<tr>
<td>arthralgia</td>
</tr>
<tr>
<td>fever</td>
</tr>
<tr>
<td>gastrointestinal upset</td>
</tr>
<tr>
<td>altered taste</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Major side-effects (less than 0.2% of patients)</th>
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</thead>
<tbody>
<tr>
<td>agranulocytosis</td>
</tr>
<tr>
<td>aplastic anaemia</td>
</tr>
<tr>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>hepatitis (propylthiouracil)</td>
</tr>
<tr>
<td>cholestatic jaundice (carbimazole)</td>
</tr>
<tr>
<td>SLE-like syndrome</td>
</tr>
</tbody>
</table>

Table 5. Side-effects of antithyroid drugs
induced thyrotoxicosis, as antithyroid drugs are relatively ineffective in this setting.

Atrial fibrillation secondary to hyperthyroidism reverts to sinus rhythm in around half of patients when rendered euthyroid. The threshold to initiate anticoagulation therapy is a CHA2DS2-VASc score ≥1, but self-limiting atrial fibrillation during the early phase of hyperthyroidism may not impose an additional risk of ischaemic stroke, so long-term anticoagulants are not usually needed.

Choice of medical versus other treatments
At diagnosis, a careful discussion with the patient is necessary to detail the likely outcome after antithyroid drugs and to offer the patient the choice of alternative treatment with radioiodine or surgery. Most patients with Graves’ disease elect to try a course of antithyroid drugs initially as there is a low rate of subsequent hypothyroidism. Radioiodine and, less commonly, surgery are then used for relapses. UK guidelines for the use of radioiodine in benign thyroid disorders have been published.

Some UK centres, however, recommend radioiodine as initial treatment in all patients, in line with the majority of North American practice, in the belief that definitive treatment is a worthwhile goal from the outset. This approach may be particularly useful for the older patient with cardiovascular disease.

About 90 per cent of Graves’ patients are successfully treated with a single dose of radioiodine, and most of the rest are rendered euthyroid by a second dose given at least six months after the first. One drawback with radioiodine is hyperthyroidism, which occurs in 40–60 per cent of patients within a year and in 5–10 per cent per year thereafter; another is the need for precautions to reduce the radiation exposure of children and pregnant women the patient may encounter. Attempts to calculate an optimal individual dosage of radioiodine that avoids hypothyroidism while maximising the chances of a cure have proved futile, and instead doses of 400–600MBq are recommended for uncomplicated Graves’ disease.

Pregnancy and breastfeeding are absolute contraindications to radioiodine, and ophthalmopathy may appear or worsen after radioiodine, especially in smokers. Caution is needed in the latter group and prophylactic prednisolone for 6–12 weeks after radioiodine should be considered.

Surgery remains a useful option, provided there is appropriate surgical expertise. Most surgeons aim to leave as small a remnant as possible (near-total thyroidectomy) to reduce the chance of recurrence. This is especially true for patients whose Graves’ disease has relapsed and who have an unlayable fear of radioiodine, who cannot avoid close contact with their children after radioiodine, or who want rapid removal of a goitre for cosmetic reasons. It is also indicated if there is a coincidental thyroid nodule whose nature is uncertain after fine-needle aspiration biopsy.

Graves’ disease in pregnancy
Meticulous control of Graves’ disease in pregnancy is necessary to maintain normal fetal thyroid hormone levels and, ideally, women contemplating pregnancy should be euthyroid before conception. In this regard, there are no sustained teratogenic risks from previous radioiodine treatment, provided more than six months have elapsed since treatment (this rule applies to men and women). If a woman does become pregnant and has active Graves’ disease, the block-replace regimen is contraindicated as the disproportionate transfer of antithyroid drug may cause fetal hypothyroidism.

Carbimazole treatment in pregnancy has been associated with fetal aplasia cutis and choanal atresia. As propylthiouracil is not associated with these abnormalities, this drug is preferable during the first trimester in women who are or who wish to become pregnant, and whose thyroid dysfunction requires antithyroid drug treatment.

Free $T_4$ levels need close monitoring during pregnancy, and the lowest dose of antithyroid drug that maintains maternal free $T_4$ levels in the upper part of the reference range should be given.

The autoimmune process tends to ameliorate in the later stages of pregnancy, necessitating a reduction in dosage, and the antithyroid drug can usually be stopped at the beginning of the third trimester. Such spontaneous remission lasts into the postpartum period, but relapse is common three to six months after delivery and should be anticipated, with arrangements for regular thyroid function tests at this time.

Graves’ disease in neonates and children
Up to 1 per cent of pregnancies in women with Graves’ disease are associated with the development of fetal and neonatal thyrotoxicosis, due to the transplacental passage of TSH receptor-stimulating antibodies. This complication can be predicted by identifying a high maternal level of these antibodies during the last trimester, and by fetal tachycardia and failure to thrive.
The fetus can be treated by giving the mother antithyroid drugs, but this obviously requires close monitoring. The neonate usually requires an antithyroid drug for one to three months until the maternal antibodies disappear.

Breastfeeding is safe with antithyroid drugs, but the lowest dosage should be given and thyroid function should be checked in the baby if the mother is receiving carbimazole 20mg or more daily.

Graves’ disease is rare in children and uncommon in adolescents. Theoretical concerns over the safety of radioiodine have in the past made many endocrinologists cautious about using radioiodine in these groups, and in general such patients are usually treated with long-term antithyroid drugs to allow undisrupted schooling. Surgery or radioiodine can then be planned when the patient is older to fit in with circumstances, although there is a case that radioiodine should be considered more often as first-line treatment in selected children with Graves’ disease.18

Conclusion
Disorders of thyroid function are common. Hypothyroidism is readily treated with levothyroxine in dosages that normalise TSH levels. Patients with thyrotoxicosis, however, require an accurate diagnosis to determine the optimum therapy; for Graves’ disease, the best treatment initially is usually a course of antithyroid drugs. Relapse occurs in around 40–50 per cent of patients and can be treated definitively with radioiodine or surgery.

References

Declaration of interests
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Professor Weetman is emeritus professor of medicine at the University of Sheffield