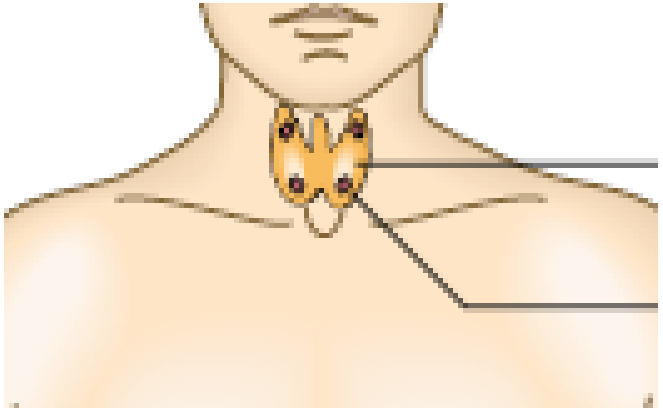
The Thyroid Gland

Dr. Haidar F. Al-Rubaye

Anatomy

The thyroid gland comprises

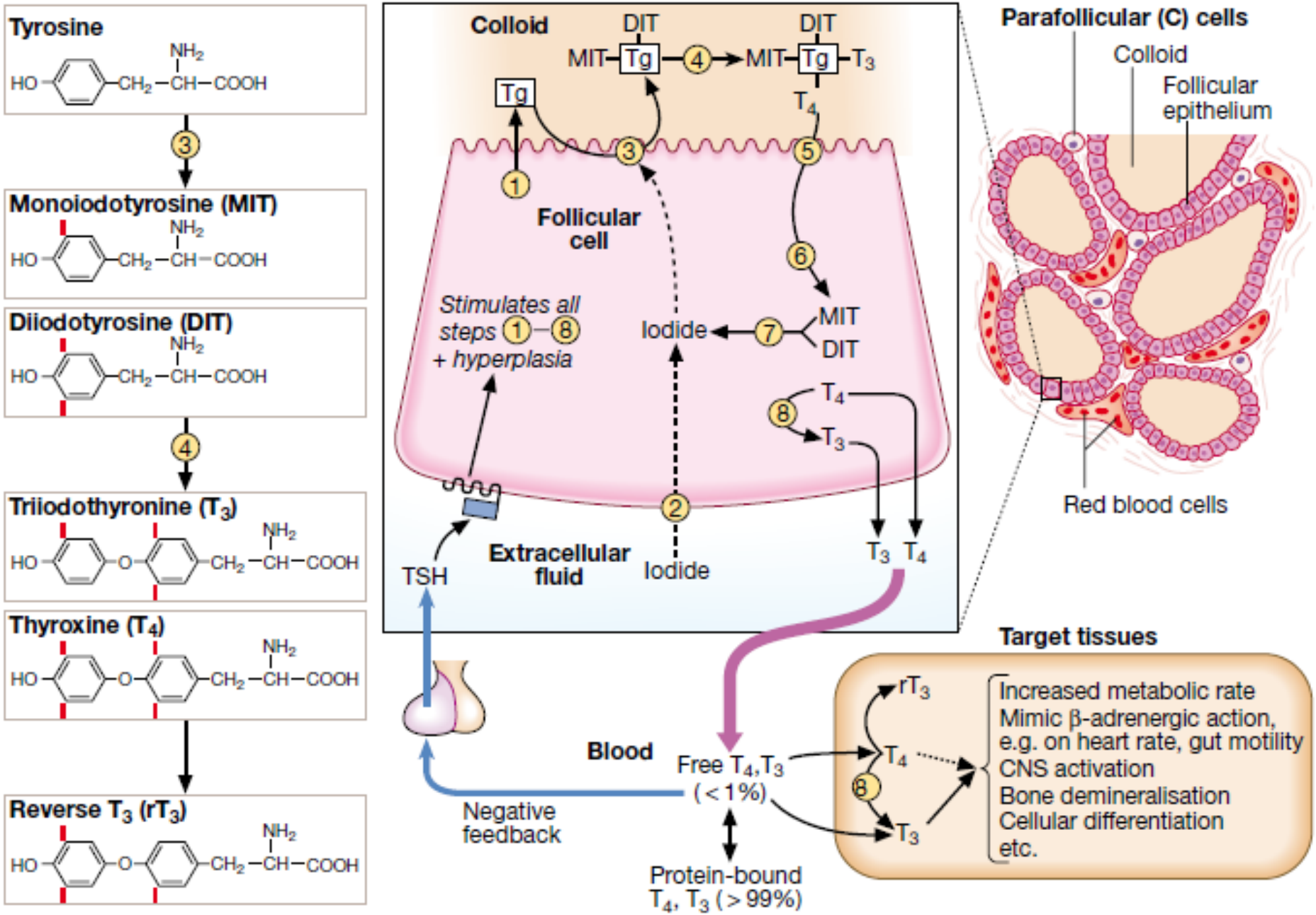
- A **midline isthmus** lying horizontally just below the cricoid cartilage.
- **Two lateral lobes** that extend upward over the lower half of the thyroid cartilage.



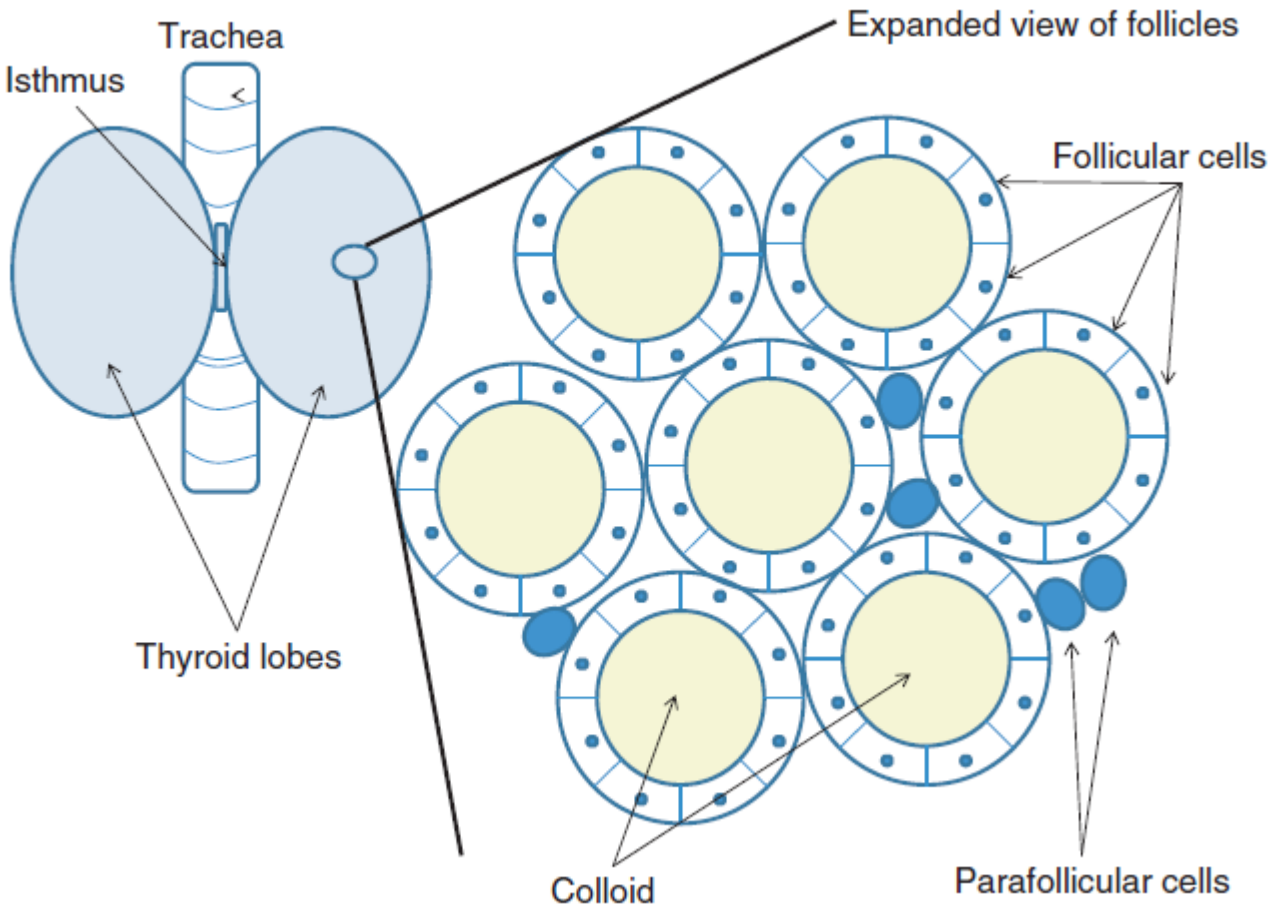
The gland lies deep to the strap muscles of the neck, enclosed in the pretracheal fascia, which anchors it to the trachea, so that the **thyroid moves up on swallowing**.

Histology

- Fibrous septa divide the gland into pseudolobules. Pseudolobules are composed of vesicles called follicles or acini, surrounded by a capillary network.
- The follicle walls are lined by cuboidal epithelium.
- The lumen is filled with a proteinaceous colloid, which contains the unique protein thyroglobulin.
- The peptide sequences of thyroxine (T 4) and tri-iodothyronine (T 3) are synthesized and stored as a component of thyroglobulin.


Tyrosine
Monoiodotyrosine (MIT)
Diiodotyrosine (DIT)
Triiodothyronine (T_3)
Thyroxine (T_4)
Reverse T_3 (rT_3)
Colloid
DIT
MIT
Tg
T_3
T_4
Follicular cell
Stimulates all steps 1–8 + hyperplasia
Iodide
MIT
DIT
TSH
Extracellular fluid
Iodide
T_3 T_4
Parafollicular (C) cells
Colloid
Follicular epithelium
Red blood cells
Target tissues
rT_3
T_4
T_3
Increased metabolic rate
Mimic β-adrenergic action, e.g. on heart rate, gut motility
CNS activation
Bone demineralisation
Cellular differentiation
etc.
Blood
Free T_4, T_3 (< 1%)
Negative feedback
Protein-bound T_4, T_3 (> 99%)

Anatomy

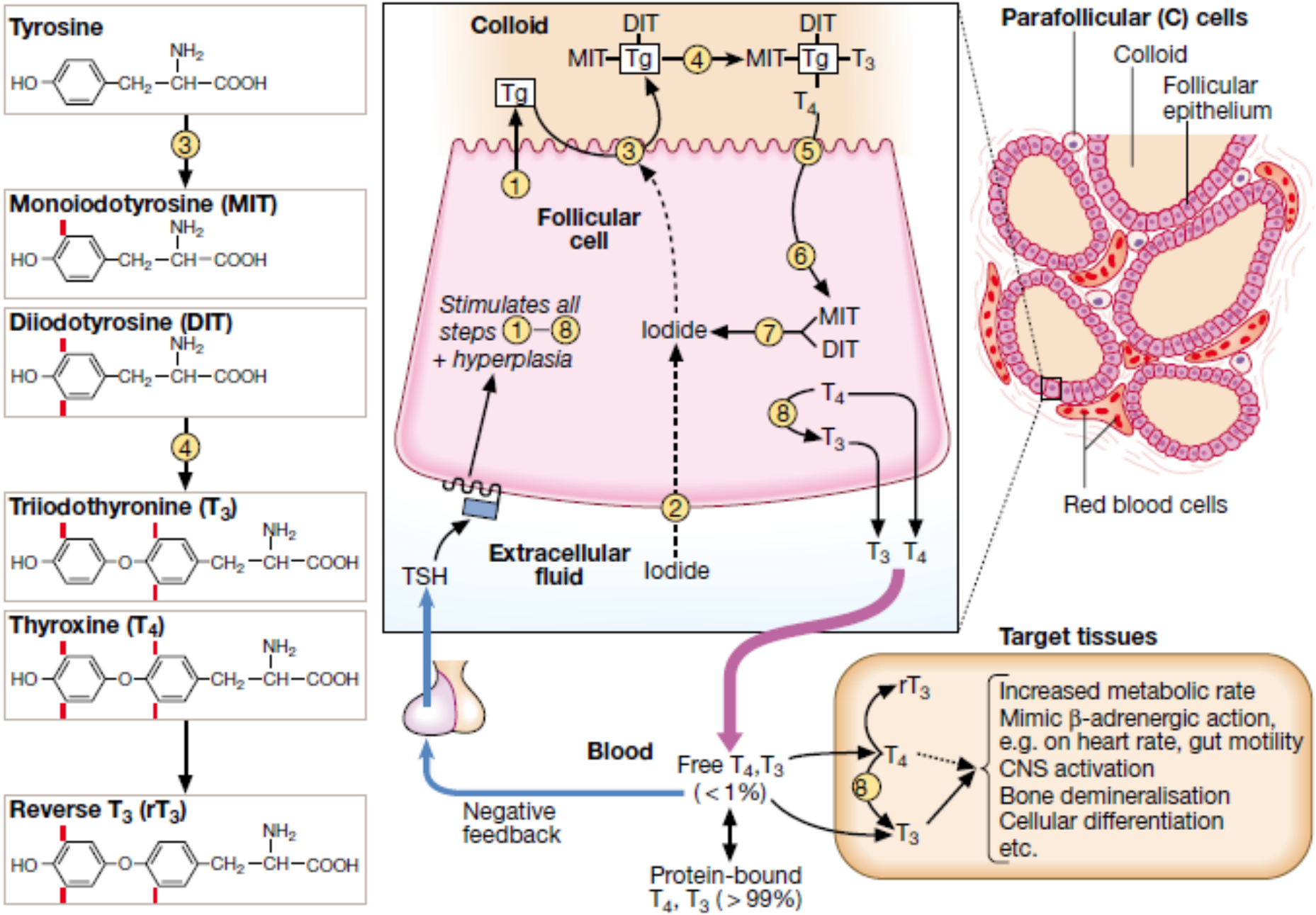

Trachea
Isthmus
Expanded view of follicles
Follicular cells
Thyroid lobes
Colloid
Parafollicular cells

Physiology

- Thyroid hormone contains iodine. Iodine enters the thyroid in the form of inorganic or ionic iodide, which is organized by the thyroid peroxidase enzyme at the cell–colloid interface.
- Subsequent reactions result in the formation of iodothyronines.
- The thyroid is the only source of T4 . The thyroid secretes 20% of circulating T3 ; the remainder is generated in extraglandular tissues by the conversion of T4 to T3 by deiodinases (largely in the liver and kidneys).

Physiology

- In the blood, T4 and T3 are almost entirely bound to plasma proteins.
- T4 is bound in d order of affinity to T4 -binding globulin (TBG), transthyretin (TTR), and albumin.
- T3 is bound 10–20 times less avidly by TBG and not significantly by TTR.
- Only the free or unbound hormone is available to tissues. The metabolic state correlates more closely with the free than the total hormone concentration in the plasma.
- The relatively weak binding of T 3 accounts for its more rapid onset and offset of action.
- The concentration of free hormones does not necessarily vary directly with that of the total hormones; e.g., while the total T 4 level rises in pregnancy, the free T 4 (FT 4) level remains normal.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Follicular cell
Stimulates all steps 1–8 + hyperplasia
Iodide
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TSH
Extracellular fluid
Iodide
T_3 T_4
Parafollicular (C) cells
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Red blood cells
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etc.
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Negative feedback
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Classification of thyroid disease

	Primary	Secondary
Hormone excess	Graves' disease Multinodular goitre Adenoma Subacute thyroiditis	TSHoma
Hormone deficiency	Hashimoto's thyroiditis Atrophic hypothyroidism	Hypopituitarism
Hormone hypersensitivity		
Hormone resistance	Thyroid hormone resistance syndrome 5'-monodeiodinase deficiency	
Non-functioning tumours	Differentiated carcinoma Medullary carcinoma Lymphoma	

Thyroid Function Tests

TSH

TOTAL T4

TOTAL T3

FREE T4

FREE T3

How to interpret thyroid function test results

TSH	T4	T3	
• Undetected	• Raised	• Raised	**Primary thyrotoxicosis**
• Undetected	• Normal	• Raised	**Primary T3-toxicosis**
• Undetected	• Normal	• Normal	**Subclinical thyrotoxicosis**

TSH	T4	T3	
• Undetected or low	• Raised	• Low, normal or raised	**Sick euthyroidism/ non-thyroidal illness**
• Undetected	• Low	• Low	**Secondary hypothyroidism /Transient thyroiditis in evolution**
• Normal	• Low	• Low	**Secondary hypothyroidism**

TSH	T4	T3	
• Mildly elevated • 5–20 mU/L	• Low	• Low	**Primary hypothyroidism /Secondary hypothyroidism**
• Elevated • > 20 mU/L	• Low	• Low	**Primary hypothyroidism**
• Mildly elevated • 5–20 mU/L	• Normal	• Normal	**Subclinical hypothyroidism**

TSH	T4	T3
• Elevated • 20–500 mU/L	• Normal	• Normal

Artefact

Endogenous IgG antibodies which interfere with TSH assay

TSH	T4	T3
• Elevated	• Raised	• Raised

Non-compliance with T4 replacement (Recent 'loading' dose)
Secondary thyrotoxicosis
Thyroid hormone resistance

Thyrotoxicosis

- Thyrotoxicosis describes a constellation of clinical features arising from elevated circulating levels of thyroid hormone.
- The most common causes are Graves' disease, multinodular goitre and autonomously functioning thyroid nodules (toxic adenoma)
- Thyroiditis is more common in parts of the world where relevant viral infections occur, such as North America

Causes of thyrotoxicosis and their relative frequencies

Cause	Frequency (%)
Graves' disease	76
Multinodular goitre	14
Solitary thyroid adenoma	5
Thyroiditis	
Subacute (de Quervain's)	3
Post-partum	0.5
Iodide-induced	
Drugs (e.g. amiodarone)	1
Radiographic contrast media	-
Iodine prophylaxis programme	-

Causes of thyrotoxicosis and their relative frequencies

Cause	Frequency (%)
Extrathyroidal source of thyroid hormone	
Factitious thyrotoxicosis	0.2
Struma ovarii	-
TSH-induced	
TSH-secreting pituitary adenoma	0.2
Choriocarcinoma and hydatidiform mole	-
Follicular carcinoma ± metastases	0.1

20.7 Clinical features of thyroid dysfunction

Thyrotoxicosis		Hypothyroidism	
Symptoms	**Signs**	**Symptoms**	**Signs**
Common			
Weight loss despite normal or increased appetite	Weight loss	Weight gain	Weight gain
Heat intolerance	Tremor	Cold intolerance	
Palpitations	Palmar erythema	Fatigue, somnolence	
Dyspnoea	Sinus tachycardia	Dry skin	
Irritability, emotional lability	Lid retraction, lid lag	Dry hair	
Fatigue		Menorrhagia	
Sweating			
Tremor			
Less common			
Osteoporosis (fracture, loss of height)	Goitre with bruit[1]	Constipation	Hoarse voice
Diarrhoea, steatorrhoea	Atrial fibrillation[2]	Hoarseness	Facial features:
Angina	Systolic hypertension/	Carpal tunnel syndrome	Purplish lips
Ankle swelling	increased pulse pressure	Alopecia	Malar flush
Anxiety, psychosis	Cardiac failure[2]	Aches and pains	Periorbital oedema/myxoedema
Muscle weakness	Hyper-reflexia	Muscle stiffness	Loss of lateral eyebrows
Periodic paralysis (predominantly in Chinese)	Ill-sustained clonus	Deafness	Anaemia
Pruritus	Proximal myopathy	Depression	Carotenaemia
Alopecia	Bulbar myopathy[2]	Infertility	Erythema ab igne (Granny's tartan)
Amenorrhoea/oligomenorrhoea			Bradycardia
Infertility, spontaneous abortion			Hypertension
Loss of libido, impotence			Delayed relaxation of tendon reflexes
Excessive lacrimation			Dermal myxoedema
Rare			
Vomiting	Lymphadenopathy	Psychosis (myxoedema	Ileus
Apathy	Spider naevi	madness)	Ascites
Anorexia	Onycholysis	Galactorrhoea	Pericardial and pleural effusions
Exacerbation of asthma	Pigmentation	Impotence	Cerebellar ataxia
	Gynaecomastia		Myotonia

[1]In Graves' disease only.
[2]Features found particularly in elderly patients.

Clinical features of thyrotoxicosis & hypothyroidims- common symptoms

Thyrotoxicosis-symptoms

- Weight loss
- Heat intolerance
- Palpitations
- Dyspnoea
- Irritability, emotional lability
- Fatigue
- Sweating
- Tremor

Hypothyroidism-symptoms

- Weight gain
- Cold intolerance
- Fatigue, somnolence
- Dry skin
- Dry hair
- Menorrhagia

Clinical features of thyrotoxicosis & hypothyroidims-common signs

Thyrotoxicosis-signs

- Weight loss
- Tremor
- Palmar erythema
- Sinus tachycardia
- Lid retraction, lid lag

Hypothyroidism-signs

- Weight Gain

Clinical features of thyrotoxicosis & hypothyroidims- common signs

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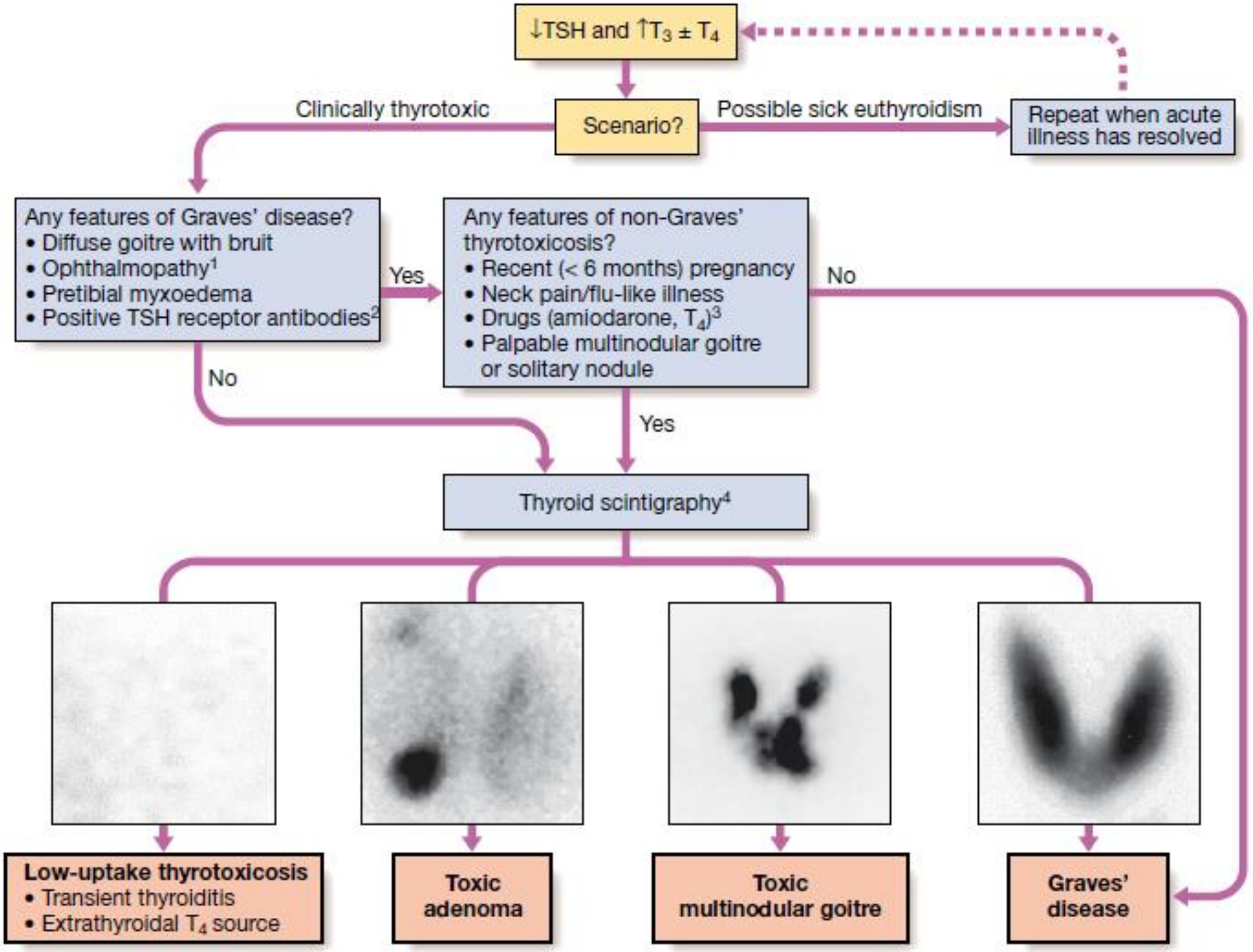
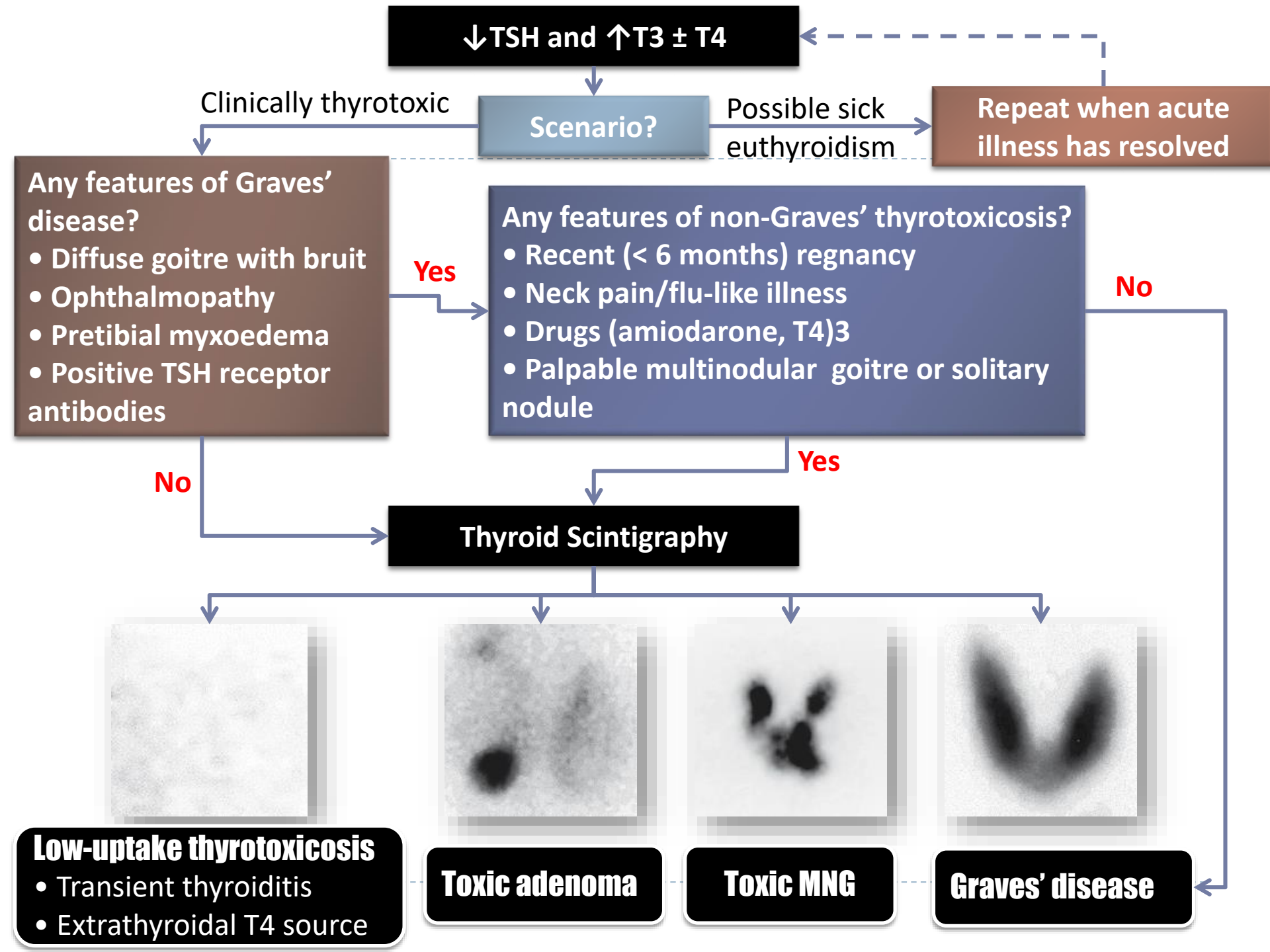
Amenorrhoea/oligomenorrhoea			Bradycardia
Infertility, spontaneous abortion			Hypertension
Loss of libido, impotence			Delayed relaxation of tendon reflexes
Excessive lacrimation			Dermal myxoedema

- The most common symptoms are weight loss with a normal or increased appetite, heat intolerance, palpitations, tremor and irritability.
- Tachycardia, palmar erythema and lid lag are common signs.
- Not all patients have a palpable goitre, but experienced clinicians can discriminate the diffuse soft goitre of Graves' disease from the irregular enlargement of a multinodular goitre.

Investigation of thyrotoxicosis

- The first-line investigations are serum T3, T4 and TSH.
  - If abnormal values are found, the tests should be repeated and the abnormality confirmed in view of the likely need for prolonged medical treatment or destructive therapy.
  - In most patients serum T3 and T4 are both elevated but T4 is in the upper part of the normal range and T3 raised (T3 toxicosis) in about 5%.
  - Serum TSH is undetectable in primary thyrotoxicosis but values can be raised in the very rare syndrome of secondary thyrotoxicosis caused by a TSH-producing pituitary adenoma.


↓TSH and ↑T_3 ± T_4
Scenario?
Clinically thyrotoxic
Possible sick euthyroidism
Repeat when acute illness has resolved
Any features of Graves' disease?
• Diffuse goitre with bruit
• Ophthalmopathy[1]
• Pretibial myxoedema
• Positive TSH receptor antibodies[2]
Yes
No
Any features of non-Graves' thyrotoxicosis?
• Recent (< 6 months) pregnancy
• Neck pain/flu-like illness
• Drugs (amiodarone, T_4)[3]
• Palpable multinodular goitre or solitary nodule
No
Yes
Thyroid scintigraphy[4]
Low-uptake thyrotoxicosis
• Transient thyroiditis
• Extrathyroidal T_4 source
Toxic adenoma
Toxic multinodular goitre
Graves' disease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• Drugs (amiodarone, T4)3
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Yes
No
Thyroid Scintigraphy
Low-uptake thyrotoxicosis
• Transient thyroiditis
• Extrathyroidal T4 source
Toxic adenoma
Toxic MNG
Graves' disease

Investigation of thyrotoxicosis

- When biochemical thyrotoxicosis has been confirmed, further investigations should be undertaken to determine the underlying cause, including measurement of **TSH receptor antibodies** (TRAb, elevated in Graves' disease, and **isotope scanning**.

Prevalence of thyroid autoantibodies (%)

	Antibodies to:		
	Thyroid peroxidase	Thyroglobulin	TSH receptor
Normal population	8–27	5–20	0
Graves' disease	50–80	50–70	80–95
Autoimmune Hypothyroidism	90–100	80–90	10–20
Multinodular goitre	~30–40	0	0
Transient thyroiditis	~30–40	0	0

1 Thyroid peroxidase (TPO) antibodies are the principal component of what was previously measured as thyroid 'microsomal' antibodies.

2 TSH receptor antibodies (TRAb) can be agonists (stimulatory, causing Graves' thyrotoxicosis) or antagonists ('blocking', causing hypothyroidism).

Non-specific laboratory abnormalities in thyroid dysfunction*

Thyrotoxicosis

- **Serum enzymes**
  - Raised alanine aminotransferase, γ-glutamyl transferase (GGT), and alkaline phosphatase from liver and bone
- **Raised bilirubin**
- **Mild hypercalcaemia**
- **Glycosuria:** Associated diabetes mellitus, 'Lag storage' glycosuria

Hypothyroidism

- **Serum enzymes**: Raised creatine kinase, aspartate aminotransferase, lactate dehydrogenase (LDH)
- **Hypercholesterolaemia**
- **Anaemia**: Normochromic normocytic or macrocytic
- **Hyponatraemia**

*These abnormalities are not useful in differential diagnosis, so the tests should be avoided and any further investigation undertaken only if abnormalities persist when the patient is euthyroid.

Management

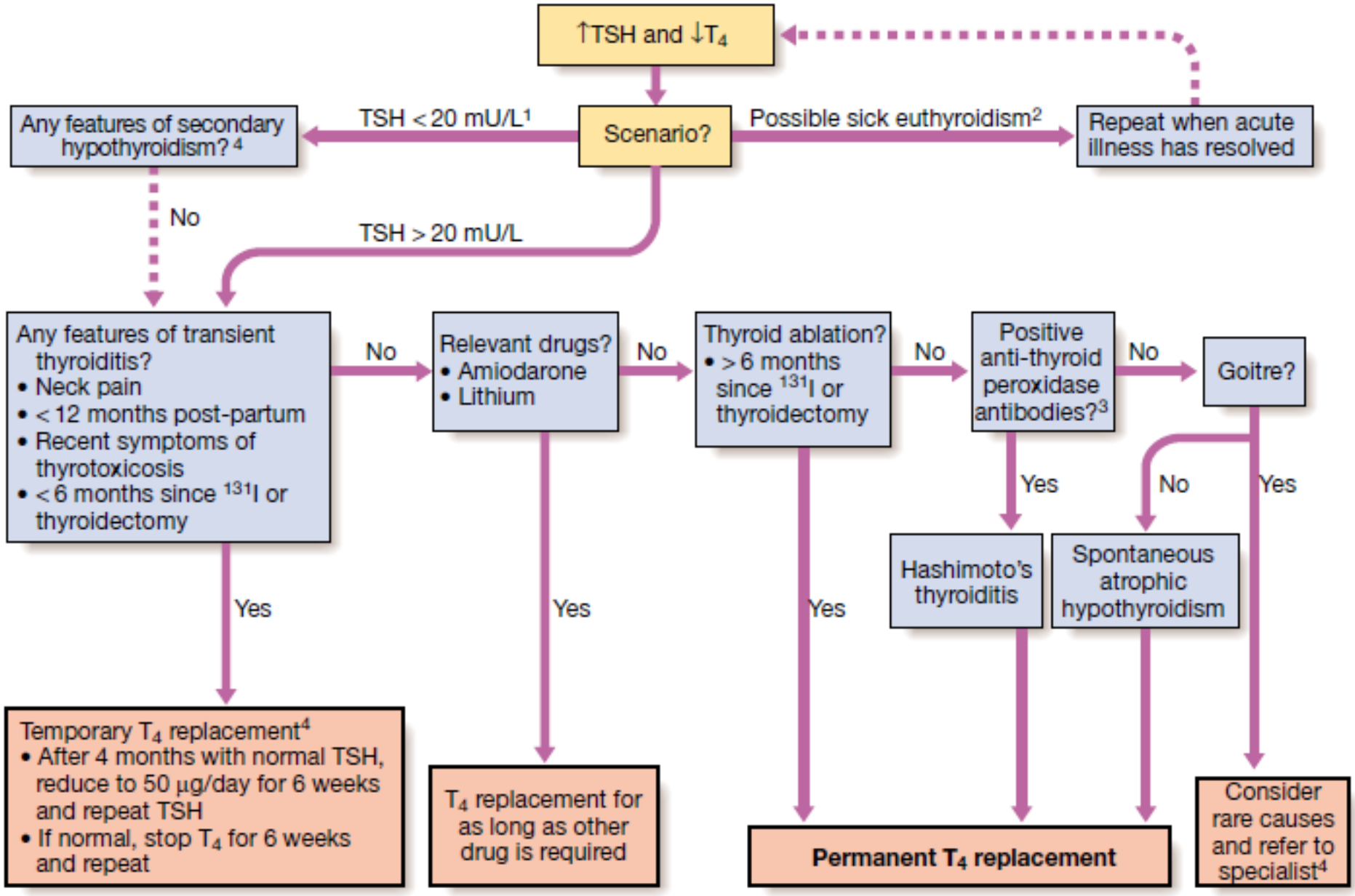
- Definitive treatment of thyrotoxicosis depends on the underlying cause and may include antithyroid drugs, radioactive iodine or surgery.
- A non-selective β- adrenoceptor antagonist (β-blocker), such as propranolol (160 mg daily) or nadolol (40–80 mg daily), will alleviate but not abolish symptoms in most patients within 24–48 hours.
- Beta-blockers should not be used for long term treatment of thyrotoxicosis, but are extremely useful in the short term, whilst patients are awaiting hospital consultation or following ^{131}I therapy.

Hypothyroidism

- Hypothyroidism is a common condition with various causes but autoimmune disease (Hashimoto's thyroiditis) and thyroid failure following ^{131}I or surgical treatment of thyrotoxicosis account for over 90% of cases, except in areas where iodine deficiency is endemic.
- Women are affected approximately six times more frequently than men.

Causes	Anti-TPO antibodies[1]	Goitre[2]
Autoimmune		
Hashimoto's thyroiditis	++	±
Spontaneous atrophic hypothyroidism	–	–
Graves' disease with TSH receptor-blocking antibodies	+	±
Iatrogenic		
Radioactive iodine ablation	+	±
Thyroidectomy	+	–
Drugs		
Carbimazole, methimazole, propylthiouracil	+	±
Amiodarone	+	±
Lithium	–	±
Transient thyroiditis		
Subacute (de Quervain's) thyroiditis	+	±
Post-partum thyroiditis	+	±

Causes	Anti-TPO antibodies[1]	Goitre[2]
Iodine deficiency, e.g. in mountainous regions	–	++
Congenital		
Dyshormonogenesis	–	++
Thyroid aplasia	–	–
Infiltrative		
Amyloidosis, Riedel's thyroiditis, sarcoidosis etc.	+	++
Secondary hypothyroidism		
TSH deficiency	–	–


↑TSH and ↓T4
Scenario?
TSH < 20 mU/L1
Any features of secondary hypothyroidism? 4
Possible sick euthyroidism2
Repeat when acute illness has resolved
No
TSH > 20 mU/L
Any features of transient thyroiditis?
• Neck pain
• < 12 months post-partum
• Recent symptoms of thyrotoxicosis
• < 6 months since 131I or thyroidectomy
No
Relevant drugs?
• Amiodarone
• Lithium
No
Thyroid ablation?
• > 6 months since 131I or thyroidectomy
No
Positive anti-thyroid peroxidase antibodies?3
No
Goitre?
Yes
Yes
Yes
Yes
No
Yes
Temporary T4 replacement4
• After 4 months with normal TSH, reduce to 50 μg/day for 6 weeks and repeat TSH
• If normal, stop T4 for 6 weeks and repeat
T4 replacement for as long as other drug is required
Hashimoto's thyroiditis
Spontaneous atrophic hypothyroidism
Permanent T4 replacement
Consider rare causes and refer to specialist4

Clinical features

- The clinical presentation depends on the duration and severity of the hypothyroidism.
- A consequence of prolonged hypothyroidism is the infiltration of many body tissues by the mucopolysaccharides, hyaluronic acid and chondroitin sulphate, resulting in a low-pitched voice, poor hearing, slurred speech due to a large tongue, and compression of the median nerve at the wrist (carpal tunnel syndrome).
- Infiltration of the dermis gives rise to non-pitting oedema (myxoedema) which is most marked in the skin of the hands, feet and eyelids.
- The resultant periorbital puffiness is often striking and, when combined with facial pallor due to vasoconstriction and anaemia, or a lemon-yellow tint to the skin due to carotenaemia, purplish lips and malar flush, the clinical diagnosis is simple.

- Most cases of hypothyroidism are not clinically obvious, however, and a high index of suspicion needs to be maintained so that the diagnosis is not overlooked in the middle-aged woman complaining of non-specific symptoms such as tiredness, weight gain, depression or carpal tunnel syndrome.
- Care must be taken to identify patients with transient hypothyroidism, in whom life-long thyroxine therapy is inappropriate.
- This is often observed during the first 6 months after subtotal thyroidectomy or ^{131}I treatment of Graves' disease, in the post-thyrotoxic phase of subacute thyroiditis and in post-partum thyroiditis. In these conditions thyroxine treatment is not always necessary as the patient may be asymptomatic during the short period of thyroid failure.

Investigations

- In the vast majority of cases hypothyroidism results from an intrinsic disorder of the thyroid gland (primary hypothyroidism). In this situation serum T4 is low and TSH is elevated, usually in excess of 20 mU/L.
- Measurements of serum T3 are unhelpful since they do not discriminate reliably between euthyroidism and hypothyroidism.
- The rare condition of secondary hypothyroidism is caused by failure of TSH secretion in a patient with hypothalamic or anterior pituitary disease. This is characterised by a low serum T4 but TSH may be low, normal or even slightly elevated

Management

- Treatment is with thyroxine replacement. It is customary to start with a low dose of 50 µg per day for 3 weeks, increasing thereafter to 100 µg per day for a further 3 weeks and finally to a maintenance dose of 100–150 µg per day.
- Thyroxine has a half-life of 7 days so it should always be taken as a single daily dose and at least 6 weeks should pass before repeating thyroid function tests and adjusting the dose, usually in increments of 25 µg per day.
- Patients feel better within 2–3 weeks. Reduction in weight and periorbital puffiness occurs quickly, but the restoration of skin and hair texture and resolution of any effusions may take 3–6 months.

- The dose of thyroxine should be adjusted to maintain serum TSH within the reference range.
  - To achieve this, serum T4 often needs to be in the upper part of the normal range or even slightly raised, because the T3 required for receptor activation is derived exclusively from conversion of T4 within the target tissues, without the usual contribution from thyroid secretion.
- Some patients remain symptomatic despite normalisation of TSH and may wish to take extra thyroxine which suppresses TSH values.
  - However, there is evidence that suppressed TSH is a risk factor for osteoporosis and atrial fibrillation, so this approach cannot be recommended.

- It is important to measure thyroid function every 1–2 years once the dose of thyroxine is stabilised.
  - This encourages patient compliance with therapy and allows adjustment for variable underlying thyroid activity and other changes in thyroxine requirements

Thyroxine replacement in ischaemic heart disease

- Hypothyroidism and ischaemic heart disease are common conditions which often occur together.
- Although angina may remain unchanged in severity or paradoxically disappear with restoration of metabolic rate, exacerbation of myocardial ischaemia, infarction and sudden death are recognised complications of thyroxine replacement, even using doses as low as 25 µg per day.
- In patients with known ischaemic heart disease, thyroid hormone replacement should be introduced at low dose and increased very slowly under specialist supervision.
- It has been suggested that T3 has an advantage over T4 since T3 has a shorter half-life and any adverse effect will reverse more quickly, but the more distinct peak in hormone levels after each dose of T3 is a disadvantage.
- Coronary artery surgery or angioplasty is required in the minority of patients with angina who cannot tolerate full thyroxine replacement therapy despite maximal anti-anginal therapy.

Hypothyroidism in pregnancy

- Most pregnant women with primary hypothyroidism require an increase in the dose of thyroxine of approximately 50 µg daily to maintain normal TSH levels.
- This may reflect increased metabolism of thyroxine by the placenta and increased serum thyroxine-binding globulin during pregnancy, resulting in an increase in the total thyroid hormone pool to maintain the same free T4 and T3 concentrations.
- Recent research suggests that inadequate maternal T4 therapy is associated with impaired cognitive development in their offspring. Serum TSH and free T4 should be measured during each trimester and the dose of thyroxine adjusted to maintain a normal TSH.

Myxoedema coma

- This is a rare presentation of hypothyroidism in which there is a depressed level of consciousness, usually in an elderly patient who appears myxoedematous.
- Body temperature may be as low as 25°C, convulsions are not uncommon and cerebrospinal fluid (CSF) pressure and protein content are raised.
- The mortality rate is 50% and survival depends upon early recognition and treatment of hypothyroidism and other factors contributing to the altered consciousness level, such as phenothiazines, cardiac failure, pneumonia, dilutional hyponatraemia and respiratory failure.

- Myxoedema coma is a medical emergency and treatment must begin before biochemical confirmation of the diagnosis.
- Suspected cases should be treated with an intravenous injection of 20 µg triiodothyronine followed by further injections of 20 µg 8-hourly until there is sustained clinical improvement. In survivors there is a rise in body temperature within 24 hours and, after 48–72 hours, it is usually possible to switch patients on to oral thyroxine in a dose of 50 µg daily.
- Unless it is apparent that the patient has primary hypothyroidism, the thyroid failure should also be assumed to be secondary to hypothalamic or pituitary disease and treatment given with hydrocortisone 100 mg i.m. 8-hourly, pending the results of T4, TSH and cortisol measurement
- Other measures include slow rewarming, cautious use of intravenous fluids, broad-spectrum antibiotics and high-flow oxygen. Occasionally, assisted ventilation may be necessary.

Autoimmune thyroid diseases

- Thyroid diseases are amongst the most prevalent antibody- mediated autoimmune diseases and are associated with other organ-specific autoimmunity
- Autoantibodies may produce inflammation and destruction of thyroid tissue resulting in hypothyroidism, goitre (in Hashimoto's thyroiditis) or sometimes even transient thyrotoxicosis ('Hashitoxicosis'), or they may stimulate the TSH receptor to cause thyrotoxicosis (in Graves' disease).
- There is overlap between these conditions, since some patients have multiple autoantibodies.

Graves' disease

- Graves' disease can occur at any age but is unusual before puberty and most commonly affects women aged 30–50 years.
- The most common manifestation is thyrotoxicosis with or without a diffuse goitre.
- Graves causes clinical features shown in previous lectures
- Graves' disease also causes ophthalmopathy and rarely pretibial myxoedema
  - These extrathyroidal features usually occur in thyrotoxic patients, but can occur in the absence of thyroid dysfunction.

Graves' thyrotoxicosis-Pathophysiology

- The thyrotoxicosis results from the production of IgG antibodies directed against the TSH receptor on the thyroid follicular cell, which stimulate thyroid hormone production and proliferation of follicular cells, leading to goitre in the majority of patients. These antibodies are termed thyroid-stimulating immunoglobulins or TSH receptor antibodies (TRAb) and can be detected in the serum of 80–95% of patients with Graves' disease.
- The concentration of TRAb in the serum is presumed to fluctuate to account for the natural history of Graves' thyrotoxicosis
- The thyroid failure seen in some patients may result from the presence of blocking antibodies against the TSH receptor, and from tissue destruction by cytotoxic antibodies and cell-mediated immunity.

Features of Graves disease in addition to diffuse goitre

- Periorbital oedema
- Conjunctival irritation
- Exophthalmos
- Diplopia
- Pretibial myxoedema
- Thyroid acropachy

- A suggested trigger for the development of thyrotoxicosis in genetically susceptible individuals may be infection with viruses or bacteria.
- Certain strains of the gut organisms Escherichia coli and Yersinia enterocolitica possess cell membrane TSH receptors; antibodies to these microbial antigens may cross-react with the TSH receptors on the host thyroid follicular cell.
- In regions of iodine deficiency, iodine supplementation can precipitate thyrotoxicosis, but only in those with pre-existing subclinical Graves' disease. Smoking is weakly associated with Graves' thyrotoxicosis, but strongly linked with the development of ophthalmopathy.

Management

- Symptoms of thyrotoxicosis respond to β-blockade, but definitive treatment requires control of thyroid hormone secretion.

Comparison of treatments for the thyrotoxicosis of Graves' disease

Management	Common indications	Contraindications	Disadvantages/ complications
Antithyroid drugs	First episode in patients < 40 yrs		
Subtotal thyroidectomy	Large goitre Poor drug compliance, especially in young patients Recurrent thyrotoxicosis after course of antithyroid drugs in young patients		
Radio-iodine	First episode in patients < 40 yrs		

Comparison of treatments for the thyrotoxicosis of Graves' disease

Management	Common indications	Contraindications	Disadvantages/ complications
Antithyroid drugs		Breastfeeding (propylthiouracil suitable)	
Subtotal thyroidectomy		Previous thyroid surgery Dependence upon voice, e.g. opera singer, lecturer	
Radio-iodine		Pregnancy or planned pregnancy within 6 months of treatment Active Graves' ophthalmopathy	

Comparison of treatments for the thyrotoxicosis of Graves' disease

Management	Common indications	Contraindications	Disadvantages/ complications
Antithyroid drugs			Hypersensitivity rash 2% Agranulocytosis 0.2% > 50% relapse rate usually within 2 years of stopping drug
Subtotal thyroidectomy			Hypothyroidism (~25%) Transient hypocalcaemia (10%) Permanent hypoparathyroidism (1%) Recurrent laryngeal nerve palsy1 (1%)
Radio-iodine			Hypothyroidism, ~40% in first year, 80% after 15 years Most likely treatment to result in exacerbation of ophthalmopathy

Thyrotoxicosis in pregnancy

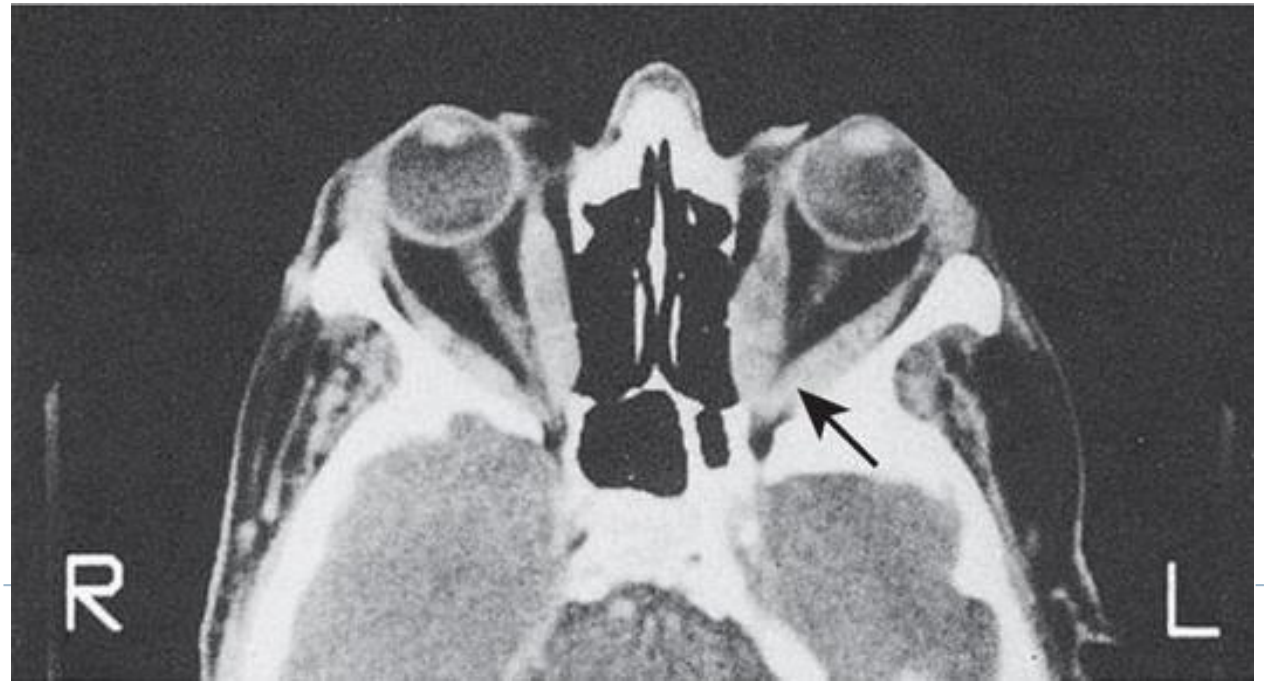
- The coexistence of pregnancy and thyrotoxicosis is unusual, as anovulatory cycles are common in thyrotoxic patients and autoimmune disease tends to remit during pregnancy, when the maternal immune response is suppressed.
- Thyroid function tests must be interpreted in the knowledge that thyroid-binding globulin, and hence total T_4 and T_3 levels, are increased in pregnancy and that TSH normal ranges may be lower
- A fully suppressed TSH with elevated free thyroid hormone levels indicates thyrotoxicosis.
- The thyrotoxicosis is almost always caused by Graves' disease.
- Both mother and fetus must be considered, since maternal thyroid hormones, TRAb and antithyroid drugs can all cross the placenta to some degree, exposing the fetus to the risks of thyrotoxicosis, iatrogenic hypothyroidism and goitre.

- Thyrotoxicosis should be treated with antithyroid drugs which cross the placenta and also treat the fetus, whose thyroid gland is exposed to the action of maternal TRAb. Propylthiouracil may be preferable to carbimazole since the latter might be associated with a skin defect in the child, known as aplasia cutis.
- In order to avoid fetal hypothyroidism and goitre, it is important to use the smallest dose of antithyroid drug (optimally less than 150 mg propylthiouracil per day) that will maintain maternal (and presumably fetal) free T_4, T_3 and TSH within their respective normal ranges.
- After delivery, if antithyroid drug is required and the patient wishes to breastfeed, then propylthiouracil is the drug of choice, as it is excreted in the milk to a much lesser extent than carbimazole.

- If subtotal thyroidectomy is necessary because of poor drug compliance or drug hypersensitivity, it is most safely performed in the second trimester.
- Radioactive iodine is absolutely contraindicated, as it invariably induces fetal hypothyroidism.

Graves' ophthalmopathy

- This condition is immunologically mediated, but the autoantigen has not been identified.
- Within the orbit (and the dermis) there is cytokine-mediated proliferation of fibroblasts which secrete hydrophilic glycosaminoglycans.
- The resulting increase in interstitial fluid content, combined with a chronic inflammatory cell infiltrate, causes marked swelling and ultimately fibrosis of the extraocular muscles and a rise in retrobulbar pressure.
- The eye is displaced forwards (proptosis, exophthalmos) and in severe cases there is optic nerve compression.
- The majority of patients require no treatment other than reassurance.
- Methylcellulose eye drops and gel counter the gritty discomfort of dry eyes, and tinted glasses or side shields attached to spectacle frames reduce the excessive lacrimation triggered by sun or wind.
- Severe inflammatory episodes are treated with glucocorticoids (e.g. daily oral prednisolone or pulsed i.v. methylprednisolone) and sometimes orbital irradiation.
- Loss of visual acuity is an indication for urgent surgical decompression of the orbit. In 'burnt out' disease, surgery to the eyelids and/or ocular muscles may improve conjunctival exposure, cosmetic appearance and diplopia.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Pretibial myedema

- This infiltrative dermopathy occurs in fewer than 10% of patients with Graves' disease and has similar pathological features as occur in the orbit.
- It takes the form of raised pink-coloured or purplish plaques on the anterior aspect of the leg, extending on to the dorsum of the foot.
- The lesions may be itchy and the skin may have a 'peau d'orange' appearance with growth of coarse hair; less commonly, the face and arms are affected.
- Treatment is rarely required, but in severe cases topical glucocorticoids may be helpful.

Hashimoto's thyroiditis

- Hashimoto's thyroiditis is characterised by destructive lymphoid infiltration of the thyroid, ultimately leading to a varying degree of fibrosis and thyroid enlargement.
- There is an increased risk of thyroid lymphoma, although this is exceedingly rare.
- Many present with a small or moderately sized diffuse goitre, which is characteristically firm or rubbery in consistency.
- The goitre may be soft, however, and impossible to differentiate from simple goitre by palpation alone.
- Around 25% of patients are hypothyroid at presentation. In the remainder, serum T4 is normal and TSH normal or raised, but these patients are at risk of developing overt hypothyroidism in future years.
- Antithyroid peroxidase antibodies are present in the serum in more than 90% of patients with Hashimoto's thyroiditis. In those under the age of 20 years, antinuclear factor (ANF) may also be positive.

Hashimoto's thyroiditis

- Levothyroxine therapy is indicated as treatment for hypothyroidism, and also to shrink an associated goitre. In this context, the dose of thyroxine should be sufficient to suppress serum TSH to low but detectable levels.

Transient thyroiditis

Subacute (de Quervain's) thyroiditis

- In its classical painful form, subacute thyroiditis is a transient inflammation of the thyroid gland occurring after infection with Coxsackie, mumps or adenoviruses.
- There is pain in the region of the thyroid that may radiate to the angle of the jaw and the ears, and is made worse by swallowing, coughing and movement of the neck.
- The thyroid is usually palpably enlarged and tender. Systemic upset is common.
- Affected patients are usually females aged 20–40 years.
- Painless transient thyroiditis can also occur after viral infection and in patients with underlying autoimmune disease.
- The condition can also be precipitated by drugs, including interferon-α and lithium.

- Irrespective of the clinical presentation, inflammation in the thyroid gland occurs and is associated with release of colloid and stored thyroid hormones, but also with damage to follicular cells and impaired synthesis of new thyroid hormones.
- As a result, T4 and T3 levels are raised for 4–6 weeks until the pre-formed colloid is depleted.
- Thereafter, there is usually a period of hypothyroidism of variable severity before the follicular cells recover and normal thyroid function is restored within 4–6 months
- In the thyrotoxic phase, the iodine uptake is low, because the damaged follicular cells are unable to trap iodine and because TSH secretion is suppressed.
- Low-titre thyroid autoantibodies appear transiently in the serum, and the erythrocyte sedimentation rate (ESR) is usually raised.
- High-titre autoantibodies suggest an underlying autoimmune pathology and greater risk of recurrence and ultimate progression to hypothyroidism.

- The pain and systemic upset usually respond to simple measures such as non-steroidal anti-inflammatory drugs (NSAIDs).
- Occasionally, however, it may be necessary to prescribe prednisolone 40 mg daily for 3–4 weeks.
- The thyrotoxicosis is mild and treatment with a β-blocker is usually adequate.
- Antithyroid drugs are of no benefit because thyroid hormone synthesis is impaired rather than enhanced.
- Careful monitoring of thyroid function and symptoms is required so that
- levothyroxine can be prescribed temporarily in the hypothyroid phase.
- Care must be taken to identify patients presenting with hypothyroidism who are in the later stages of a transient thyroiditis, since they are unlikely to require life-long levothyroxine therapy

Post-partum thyroiditis

- The maternal immune response, which is modified during pregnancy to allow survival of the fetus, is enhanced after delivery and may unmask previously unrecognised subclinical autoimmune thyroid disease.
- Surveys have shown that transient biochemical disturbances of thyroid function occur in 5–10% of women within 6 months of delivery
- Those affected are likely to have anti-thyroid peroxidase antibodies in the serum in early pregnancy.
- Symptoms of thyroid dysfunction are rare and there is no association between postnatal depression and abnormal thyroid function tests.
- However, symptomatic thyrotoxicosis presenting for the first time within 12 months of childbirth is likely to be due to post-partum thyroiditis and the diagnosis is confirmed by a negligible radio-isotope uptake. The clinical course and treatment are similar to those of painless subacute thyroiditis
- Postpartum thyroiditis tends to recur after subsequent pregnancies, and eventually patients progress over a period of years to permanent hypothyroidism.

Iodine-associated thyroid disease

- Thyroid enlargement is extremely common in certain mountainous parts of the world, such as the Andes, the Himalayas and central Africa, where there is dietary iodine deficiency (endemic goitre). Most patients are euthyroid with normal or raised TSH levels, although hypothyroidism can occur with severe iodine deficiency. Iodine supplementation programmes have abolished this condition in most developed countries.

Iodine-induced thyroid dysfunction

- Iodine has complex effects on thyroid function.
- Very high concentrations of iodine inhibit thyroid hormone release and this forms the rationale for iodine treatment of thyroid storm and prior to thyroid surgery for thyrotoxicosis
- Iodine administration initially enhances, but then inhibits, iodination of tyrosine and thyroid hormone synthesis
- The resulting effect of iodine on thyroid function varies according to whether the patient has an iodine-deficient diet or underlying thyroid disease.
- In iodine-deficient parts of the world, transient thyrotoxicosis may be precipitated by prophylactic iodinisation programmes.
- In iodine-sufficient areas, thyrotoxicosis can be precipitated by radiographic contrast medium or expectorants in individuals who have underlying thyroid disease predisposing to thyrotoxicosis, such as multinodular goitre or Graves' disease in remission.
- Induction of thyrotoxicosis by iodine is called the Jod–Basedow effect.
- Chronic excess iodine administration can, however, result in hypothyroidism. Increased iodine within the thyroid gland down-regulates iodine trapping, so that uptake is low in all circumstances.

Amiodarone

- The anti-arrhythmic agent amiodarone has a structure that is analogous to that of T4 and contains huge amounts of iodine; a 200 mg dose contains 75 mg iodine, compared with a daily dietary requirement of just 125 µg.
- Amiodarone also has a cytotoxic effect on thyroid follicular cells and inhibits conversion of T4 to T3.
- Most patients receiving amiodarone have normal thyroid function, but up to 20% develop hypothyroidism or thyrotoxicosis and so thyroid function should be monitored regularly.
- The ratio of T4:T3 is elevated and TSH provides the best indicator of thyroid function.

Amiodarone

- The thyrotoxicosis can be classified as either:
  - type I: iodine-induced excess thyroid hormone synthesis in patients with an underlying thyroid disorder, such as nodular goitre or latent Graves' disease
  - type II: thyroiditis due to a direct cytotoxic effect if amiodarone administration results in a transient thyrotoxicosis.
- Antithyroid drugs may be effective in patients with the type I form, but are ineffective in type II thyrotoxicosis. Prednisolone is beneficial in the type II form.
- A pragmatic approach is to commence combination therapy with an antithyroid drug and glucocorticoid in patients with significant thyrotoxicosis.
- A rapid response (within 1–2 weeks) usually indicates a type II picture and permits withdrawal of the antithyroid therapy; a slower response suggests a type I picture, when antithyroid drugs may be continued and prednisolone withdrawn.
- If the cardiac state allows, amiodarone should be discontinued, but it has a long half-life (50–60 days) and so its effects are long-lasting.
- To minimise the risk of type I thyrotoxicosis, thyroid function should be measured in all patients prior to commencement of amiodarone therapy, and amiodarone should be avoided if TSH is suppressed.

- Hypothyroidism should be treated with levothyroxine, which can be given while amiodarone is continued.