Thyroid Disorders

Duncan Bassett
Molecular Endocrinology Group
MRC Clinical Sciences Centre

Hypothyroidism

Non toxic goiter

Sick euthyroid syndrome

Thyrotoxicosis (Hyperthyroidism)

Amiodarone induced thyroid disease

TSHoma

Thyroid hormone resistance

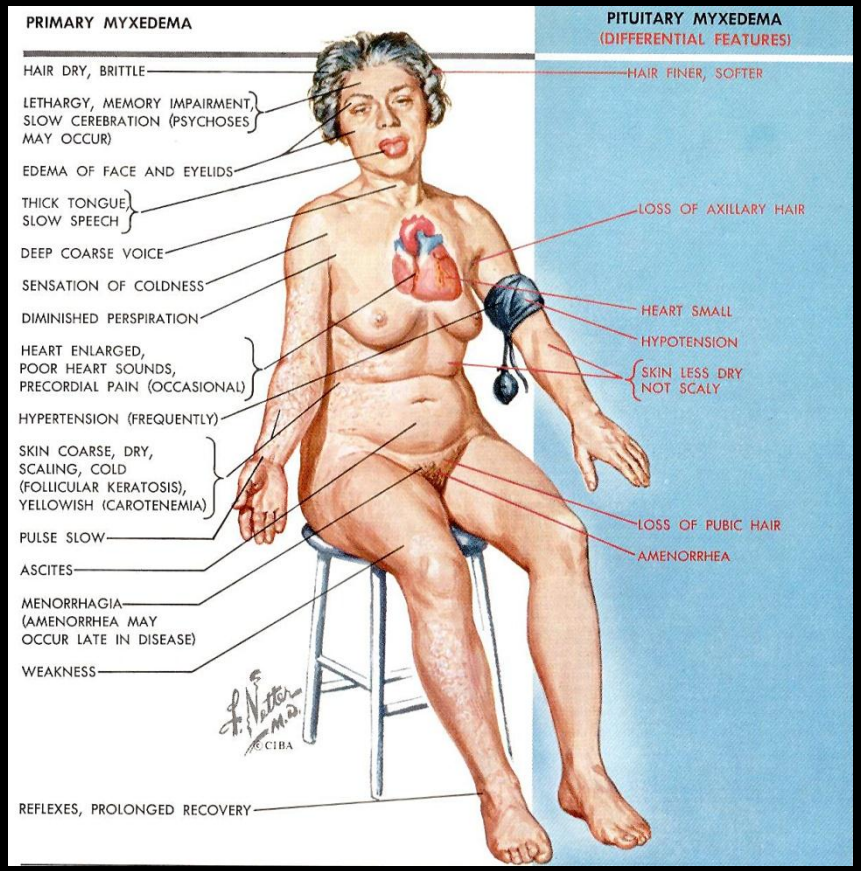
Thyroid nodules

Thyroid cancer

Hypothyroidism

Hypothyroidism

Incidence: 2% (women), 0.2% (men)



Signs and symptoms of hypothyroidism

Basic metabolic rate	low
Appetite	reduced
Body weight	Increased
Heart rate	reduced
Cardiac output	reduced
Bowel movements	constipation
Activity	lethargic
Sensitivity to cold	increased
Speech	slow
Mental function	impaired
Skin (*myxoedema)*	thickened
Hair	dry, brittle
Nails	brittle

Aetiology of hypothyroidism

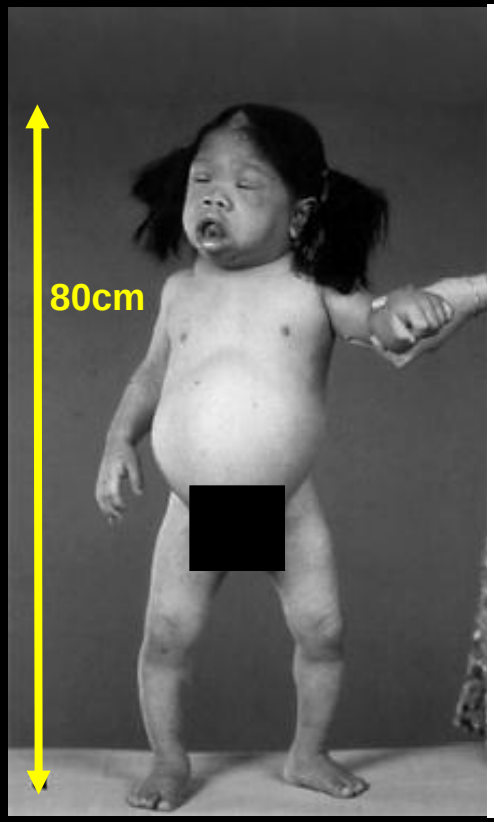
Primary Hypothyroidism (fT4 <9pmol/l and TSH>10mU/l)
- Hashimoto's thyroiditis (Autoimmune thyroid destruction TPO ab +ve)
- Subacute thyroiditis (Transient secondary to viral infection "deQuervain's")
- Transient Neonatal hypothyroidism (Maternal TSHR blocking ab)
- Excess iodine intake (Transient "Wolff–Chaikoff effect")
- Iatrogenic
  - Radioactive iodine (Graves')
  - Thyroid surgery (Goitre, thyroid cancer)
  - Lithium, Amiodarone

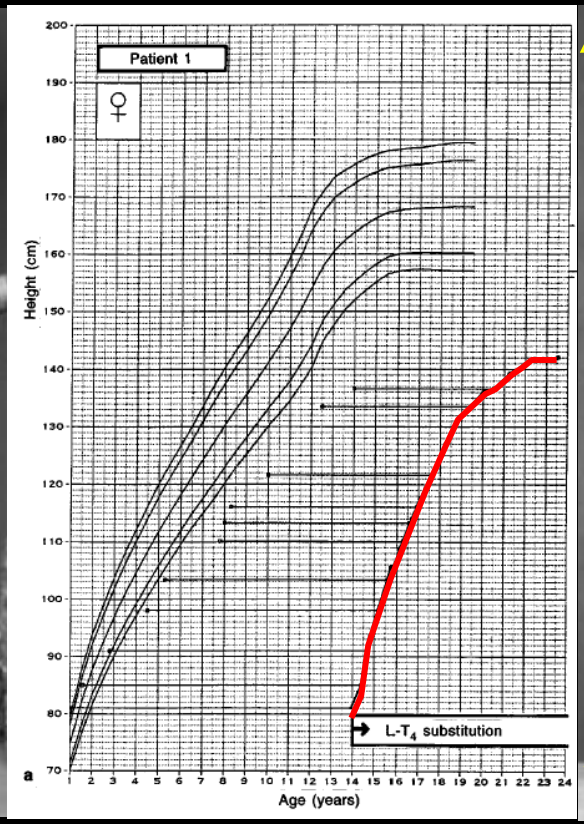
Secondary Hypothyroidism (fT4<9pmol/l and TSH<0.3mU/l)
- Hypopituitarism (Pituitary tumour, ablative pituitary therapy)

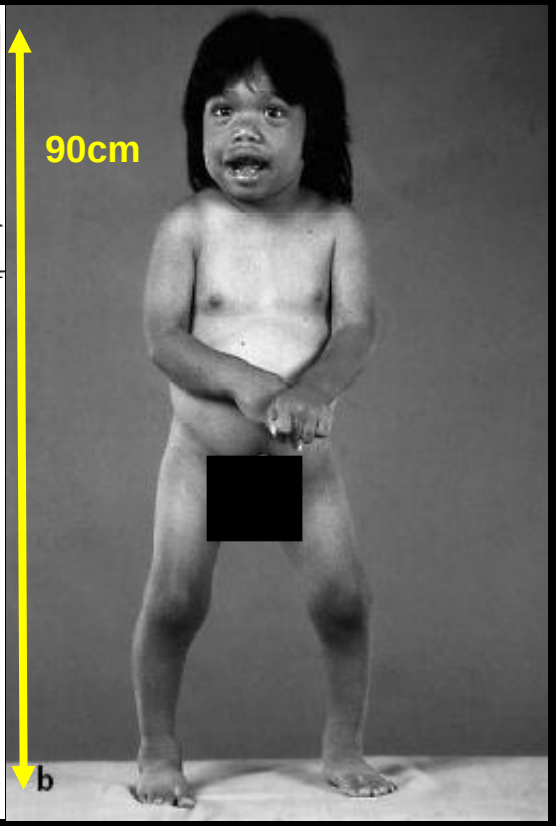
Neonatal hypothyroidism
- Cretinism (severe iodine deficiency in childhood, maternal goiter)
  - Growth arrest, immature body proportions, deaf mutism, mental retardation,
- Neonatal hypothyroidism (failure of thyroid development, inborn errors of thyroid hormone synthesis)
  - Less severe neurological phenotype (normal maternal thyroid hormone)

Newborn infants are screened for elevated TSH (Guthrie test)

Hypothyroidism and linear growth







14 years old

6/12 treatment

(Boersma et al 1996 Eur J Pediatr 155:362)

Management of hypothyroidism

Investigation

- Thyroid function tests and thyroid auto antibodies

Diagnosis

- Low serum free T4 and TSH >10U/l
- Normal serum free T4 and TSH >10U/l (subclinical hypothyroidism)

Treatment

- Aim of treatment to normalise TSH levels 0.3-4.2mU/l
- Oral levothyroxine (thyroxine T4) 100-150mcg/d (T3 $T_{1/2}$ too short)

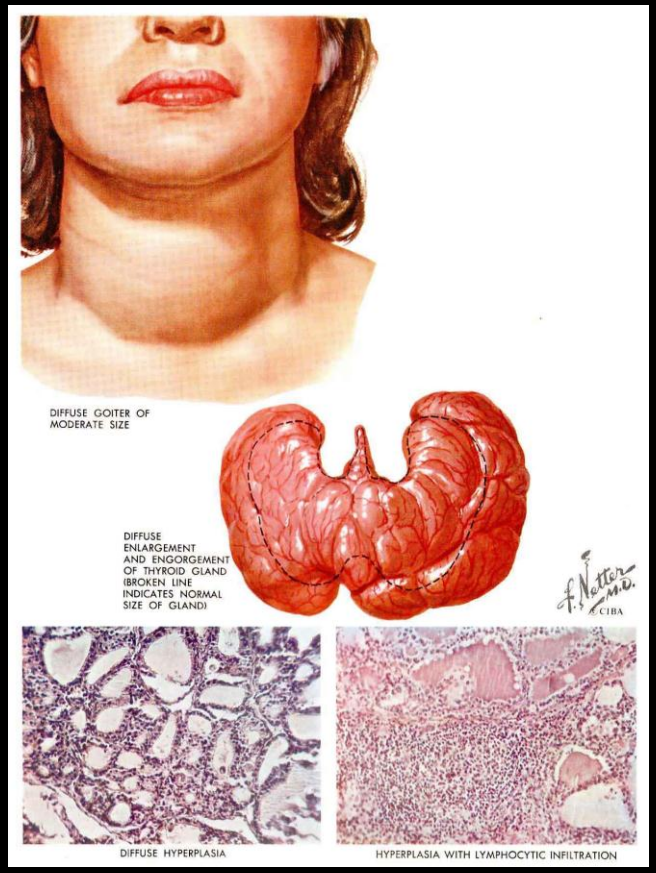
Pharmacokinetics

- T4 plasma half life of 7 days; peak effect 9 days;
- T3 plasma half life 1 day; peak effect 1-2 days;
- Almost 100% of T3 and T4 bound in the circulation to plasma proteins
  - plasma binding proteins increase in pregnancy, and phenothiazines phenytoin and salicylates compete for binding sites.

Adverse effects of T4

- TFTs should be monitored 6-12 weeks after a change of dose
- Excessive replacement (increased T4 and suppressed TSH)
  - Palpitations and AF, osteoporosis and fracture

Non toxic multinodular goiter



Aetiology of goiter

- Auto immune, sporadic, Iodine deficiency, Pregnancy, lithium, amiodarone, thyroiditis

Presentation of MNG (5% prevalence)

- Enlarging thyroid and cosmetic concerns
- Thyroid discomfort, stridor, dysphagia

Investigation

- Thyroid function test, auto antibodies
- Lung function and CT if retrosternal?
- FNA if dominant nodule palpable

Treatment

- Monitor by clinical examination
- Total or near total thyroidectomy
  - Compressive symptoms, cosmetic
  - Dominant nodule with suspicious FNA
- Radioiodine (in elderly)
  - May result in 50% shrinkage at 1year
  - Not if retrosternal

Non-thyroidal illness (sick euthyroid syndrome)

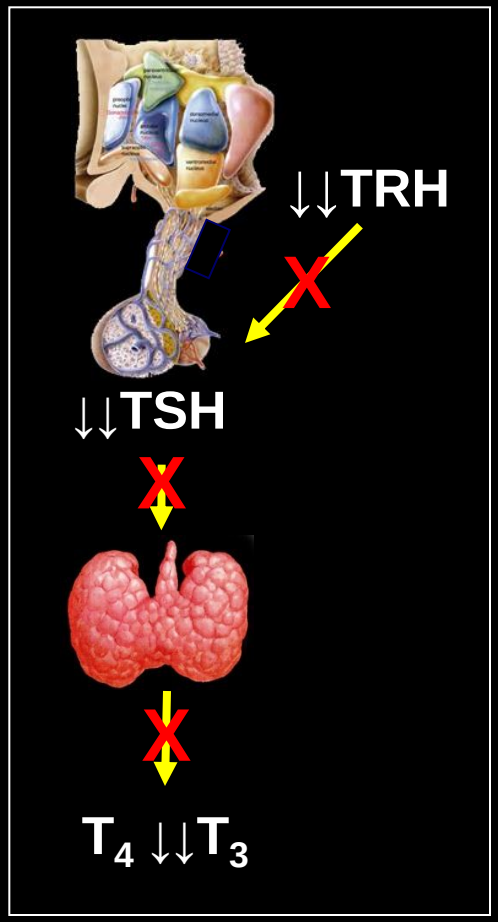
Stage 1 Low fT3 (high rT3)
Stage 2 Low fT3 low TSH (high rT3)
Stage 3 Low fT3 and fT4 low TSH (high rT3)

Mechanism
- Central reduction in TSH secretion
  - Reduced PVN TRH mRNA (dopamine, glucocorticoids, cytokines)
  - Reduced pulsatile TSH release
- Deiodinase activity
  - Reduced D1 and D2 (Impaired T4 to T3 conversion) (Impaired clearance of rT3 by D1)
  - Increased D3 (reduced T3 and increase rT3)
- Reduction in serum TH binding proteins
  - Reduced TBG, TTR, albumin (TH displaced from binding proteins)

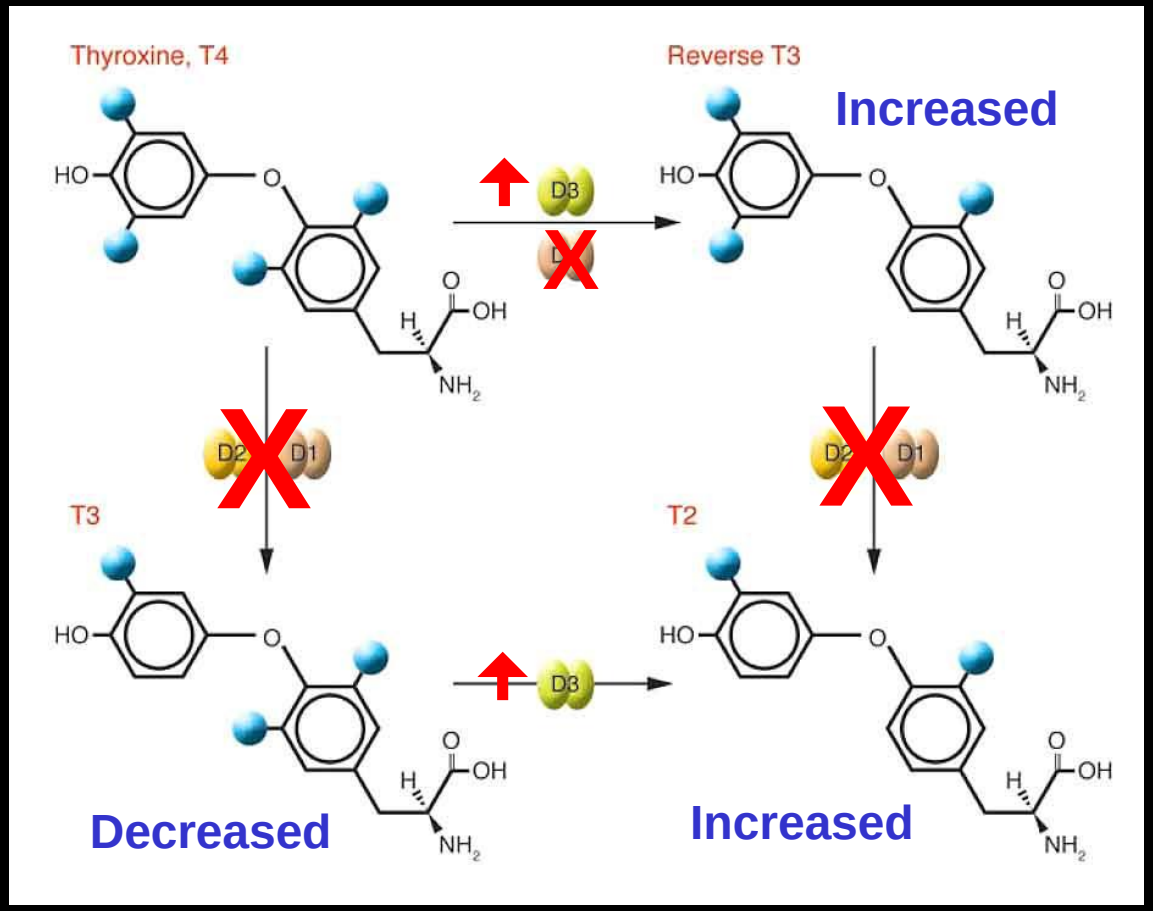
Management
- It remain unclear if T4 or T3 supplementation in even most severe cases is clinically beneficial

Non-thyroidal illness (sick euthyroid syndrome)

Synthesis



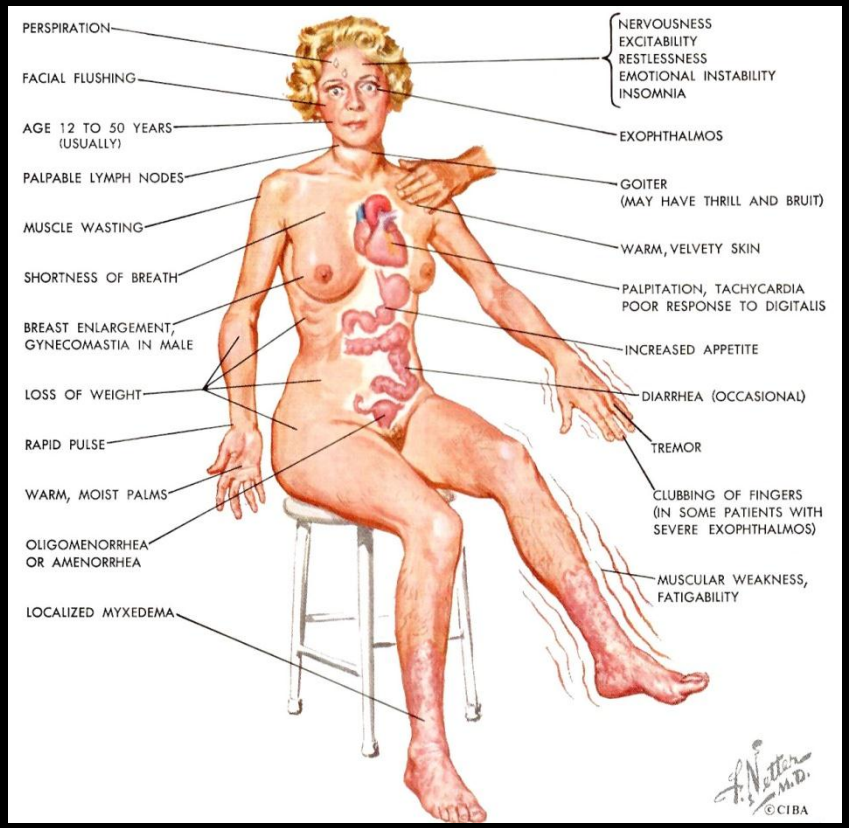
Metabolism



Hyperthyroidism

Thyrotoxicosis (Hyperthyroidism)

Incidence: 0.8% (women) 0.2% (men)



Signs and symptoms of hypothyroidism

Basic metabolic rate	**increased**
Appetite	**increased**
Body weight	**reduced**
Eyes	**lid lag**
Heart rate	**marked tachycardia**
Cardiac output	**increased (murmur)**
Bowel movements	**increased**
Activity	**increased (tremor)**
Temperature	**Heat intolerant of heat**
Mental function	**Agitation (inappropriate behaviour)**
Skin (*myxoedema)*	**sweaty, clubbing**

Aetiology of hyperthyroidism

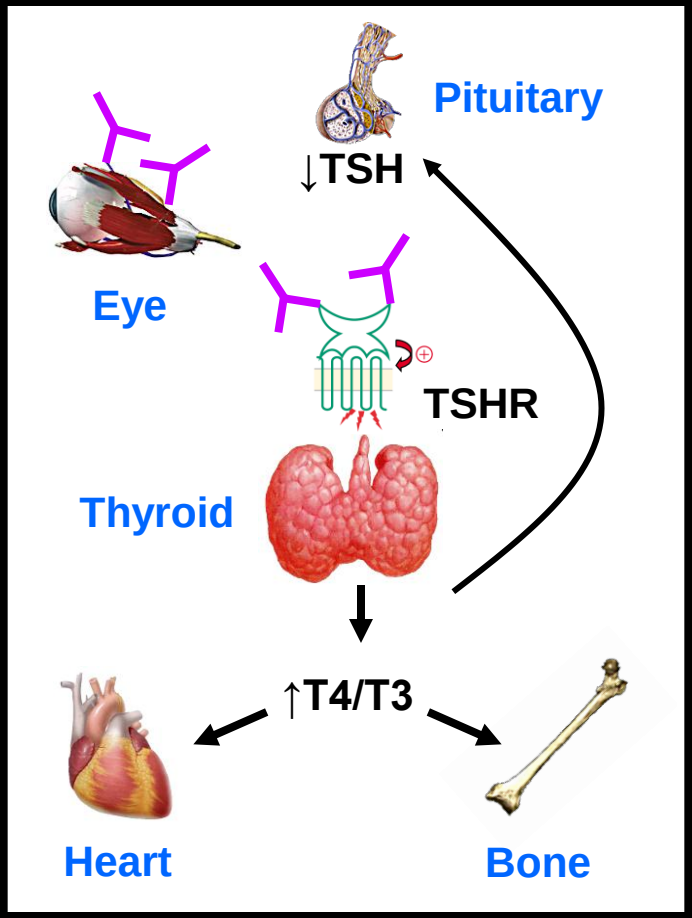
Differential diagnosis of elevated thyroid hormone levels

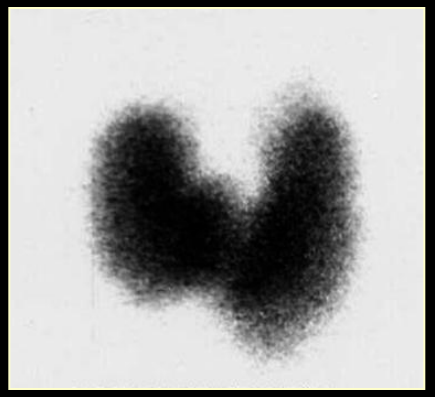
- **Diffuse toxic goitre (Graves' Disease; TSH stimulating antibodies)**
- **Toxic adenoma (Somatic mutation of TSHR and GNAS)**
- **Toxic multinodular goiter (Plummer's disease)**
- **Subacute thyroiditis (De Quervain's) acute viral infection**
- **Gestational thyrotoxicosis (GTT)**
- **Amiodarone induced thyrotoxicosis (Iodine excess or cytotoxic)**
- **TSHoma (TSH secreting pituitary adenoma)**
- **Resistance to thyroid hormone (dominant negative TRβ mutation)**

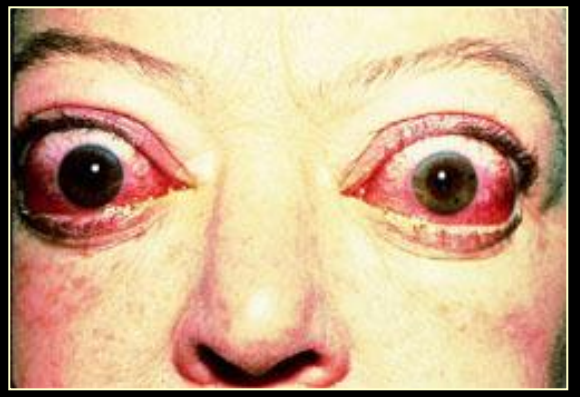
Graves' disease

Most common form of thyrotoxicosis (F:M 5:1 peak age 20-30)
T4/T3 elevated TSH suppressed (If T4 is normal T3-toxicosis)

Graves' Disease







TSHR antibodies cause Graves' disease

- Autoimmune hyperthyroidism
- Opthalmopathy (smokers)
- TSHR stimulating antibodies (ectodomain)
- Stimulates growth and hormone secretion
- Shedding of α-subunit may be antigenic
- Genetic component DZ twins 35% concordant (HLA DRβ1, CTLA4, PTNP22, CD40 and Tg)
- Transient congenital hyperthyroidism

De Quervain's thyroiditis

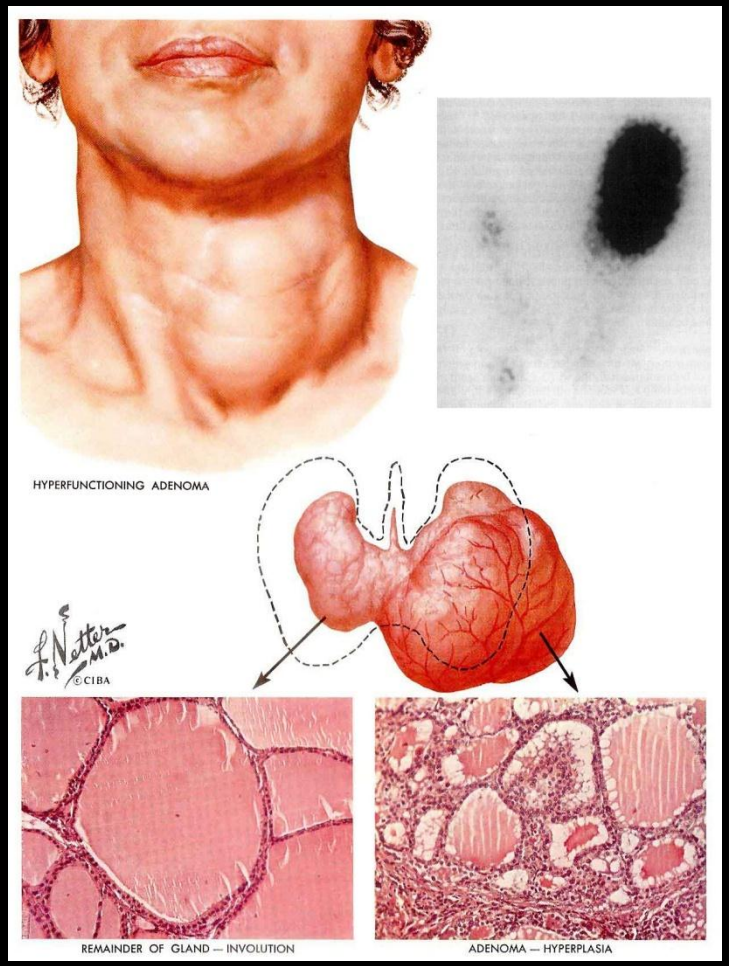
Acute viral inflammation (coxsackie virus, adenovirus)
- Fever, malaise, neck tenderness
- Initial symptoms of thyrotoxicosis followed by hypothyroidism

Investigations
- Elevated T4, T3 and suppressed TSH in initial phase
- Negative TPO and TSHR antibodies and elevated ESR
- Thyroid uptake scans show no uptake
  - May be helpful to distinguish from Graves'

Treatment
- NSAIDs for symptomatic relief in most cases
- In more severe cases
  - β-blocker during hyperthyroid phase
  - T4 replacement in hypothyroid phase

Prognosis
- Hypothyroid phase frequently resolves over a few months
- Stop T4 replacement after 6 months and repeat TFTs
- 90% remain euthyroid 10% have permanent hypothyroidism

Solitary toxic adenoma



Autonomously functioning thyroid nodule

- Symptoms of thyrotoxicosis
- Nodule may be palpable
- Usually >40 years

Aetiology

- 60% somatic constitutive activating mutation TSHR
- 5% have activating mutation of G proteins (GNAS)
- Suppression of normal thyroid tissue

Investigation

- T3 elevated, TSH suppressed, (T4 may be normal)
- TSH receptor antibodies negative
- Uptake scans (rarely necessary)
  - Hot nodule
  - No uptake in the rest of thyroid
- if nodule is palpable do FNA (benign)

Plummers' Disease (Toxic MNG)

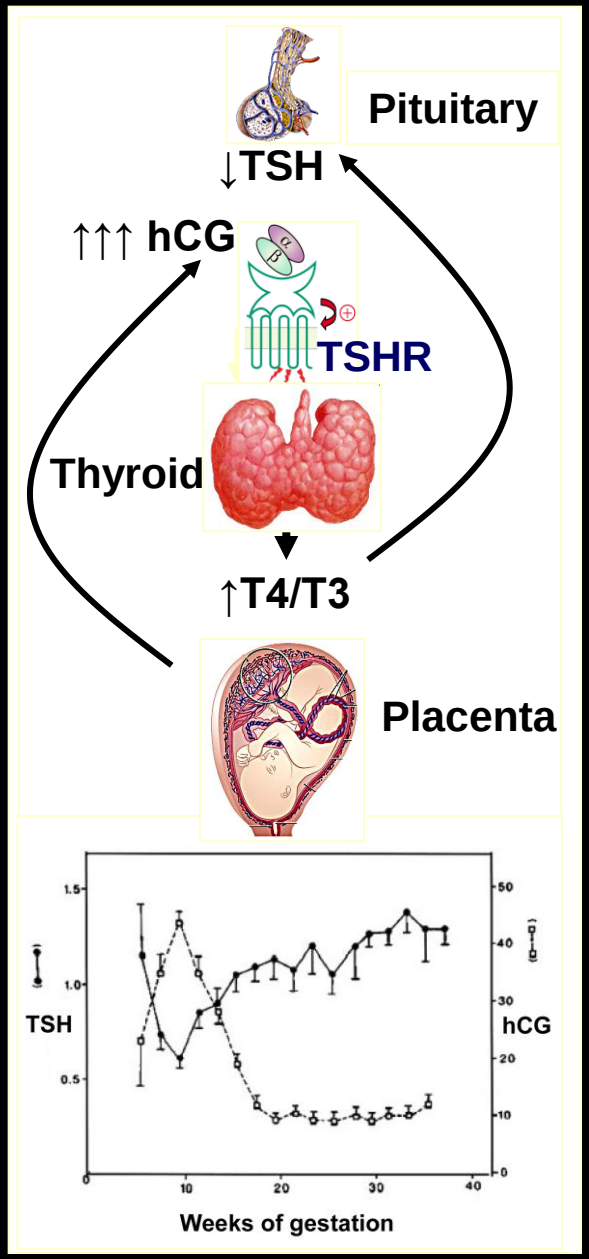
Aetiology

- Usually in >50 year old patients F>M
- Atrial fibrillation and heart failure may occur
- Precipitated in a longstanding non toxic multinodular goiter
- One or more discrete active nodules
- May be precipitated by iodine load (Jod-Basedow effect)

Investigation

- Marginal elevation of T3, T4 but fully suppressed TSH,
- TSH receptor antibodies negative
- Thyroid uptake scans often shows multiple hot nodule.
  - But rarely necessary

Gestational thyrotoxicosis (GTT)



Promiscuous activation of TSHR by hCG
(hCG in µmol/l range activates TSHR)
1st trimester gestational hyperthyroidism
Inverse relationship between TSH and hCG
hCG is µmol/l (TSH/FSH/LH are pmol/l)
Occurs in 4% of pregnancies (twins)
(hyperemesis gravidarium vomiting and wt loss)
Trophoblastic tumours
(Choriocarcinoma/Hydatidiform mole)

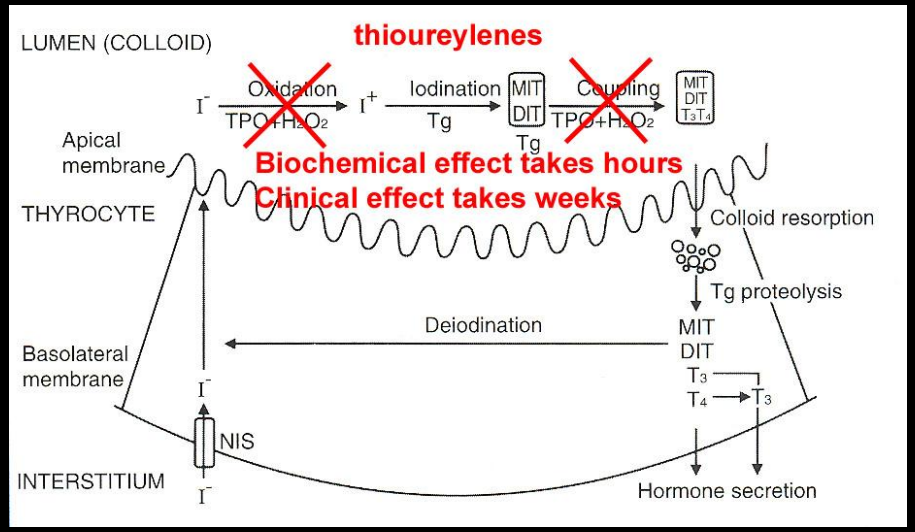
Investigation
Elevated T4, suppressed TSH, negative auto antibodies

Does not require treatment
Resolves by 20 weeks of gestation

Rodien P 1998 NEJM 339:1823; Glinoer G 1997 Endo Rev 18:404

Treatment of hyperthyroidism

Inhibition of thyroid hormone synthesis



Thionamides/Thioureylene (Propylthiouracil & Carbimazole)

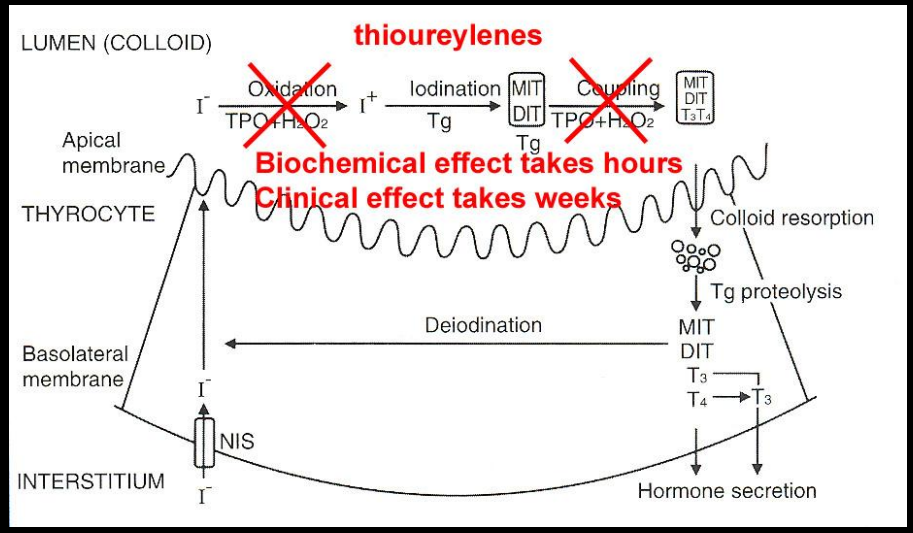
- Inhibit the thyroperoxidase (TPO)
- Blocks organification of iodine and MIT/DIT coupling reaction
- Carbimazole may also suppress antibody production in Graves disease
- Propylthiouracil inhibits D1 and reduces conversion of T4 to T3

Adverse effects

- Agranulocytosis/granulocytopenia – More frequent with high doses
  - All patients must be given advice literature prior to starting drug
  - Rare and reversible on withdrawal (antibiotics and G-CSF)
- Rashes (relatively common), headaches, nausea, jaundice, joint
- PTU may cause liver disease in children and should not be used

Treatment of hyperthyroidism

Inhibition of thyroid hormone synthesis



Carbimazole 5-40mg/d oral (low risk of teratogenicity)

- **Prodrug ($T_{1/2}$ 6-15 hours, crosses placenta and is secreted in milk, metabolised in liver and secreted in urine)**

Propylthiouracil 50-400mg/d oral

- **Use at lowest possible dose in pregnancy and breast feeding (less in milk)**

1 to 2 years of treatment (can be continued long term at low dose)

- **Thyroid hormone levels normalise by 4 to 12 weeks**
- **Dose reduced every 3 months depending on thyroid function**
- **After cessation monitor for relapse initially every 3 months then annually**

Treatment of hyperthyroidism

Initial symptomatic control

- **β-Adrenergic blockers (reduce symptoms before T4 and T3 normalise)**
  - **Nadolol 80-160mg od po (long acting compared to propranolol)**
  - **Propranolol 20-80mg tds po**
- **Treat for 4 to 8 weeks to reduces anxiety, palpitations, tremor**

Thyroidectomy rarely required but indicated if

- **Pregnant inadequately controlled by PTU or adverse effects**
  - **Perform surgery in 2nd trimester**
- **Large multinodular goitre with compressive symptoms**
- **Allergy to carbimazole or PTU and decline radioiodine**
- **Poor compliance with treatment**

Iodide

- **Can be used in preparation for surgery**
  - **Potassium iodide 60mg tds po for 10 days (max effect)**
- **Wolf-Chaikoff effect Inhibition of secretion of thyroid hormones in thyrotoxic patients and reduces vascularity and size of thyroid gland**

Treatment of hyperthyroidism

Radioiodine (^{131}I treatment)

- Given as single oral capsule after stopping carbimazole for 2 days

Indications

- relapsed Graves', toxic adenoma and toxic multinodular goiter
  - (In USA commonly used as 1st line treatment of Graves' disease)

Contraindications

- Young children (potential risk of thyroid cancer)
- Pregnancy and breast feeding
- Active Graves opthalmopathy (unless steroid cover for 7 weeks)

Mechanism of action

- ^{131}I concentrated in thyroid and incorporated into thyroglobulin.
- Short range β-particles (1mm) are cytotoxic to thyroid follicular cells
  - (^{131}I $T_{1/2}$ is 8 days and radioactivity is background by 2 months)

Adverse effects

- No close personal contact (<1m) for 1-2 weeks (difficult if young children)
- Avoid pregnancy for 6 moths after treatment
- Hypothyroidism is inevitable and life long T4 replacement will be required
- Repeat dose required in approximately 10%

Thyroid crisis “thyroid storm” (very rare)

This is a medical emergency and requires aggressive management

- Usually occurs in Graves’ Disease patients
- Presentation
  - Abrupt onset precipitated by
    - Infection, trauma, surgery, DKA, delivery
  - Abdominal pain, sweating, tachycardia, arrhythmias, pulmonary oedema and congestive cardiac failure, tremulous, delirium and psychosis, stupor and coma
- Management (in ITU)
  - β-Adrenergic blockers (Control of arrhythmias)
    - Propranolol 2mg iv every 10 minute until 10mg total
    - 80mg po every 6 hours thereafter
  - Propylthiouracil 250mg iv every 6 hours
    - Inhibits synthesis and blocks T4 to T3 conversion
  - Iodine (Lugols iodine 10 drops bd)
    - Wolf Chaikoff effect (retards release of TH)
  - Hydrocortisone (50mg iv every 6 hours)
    - Inhibits release of TH from thyroid
    - Induced D3 activity and T4 and T3 inactivation
  - Careful IV fluid and electrolyte balance and cooling
  - Oxygen, digoxin and diuretics for heart failure

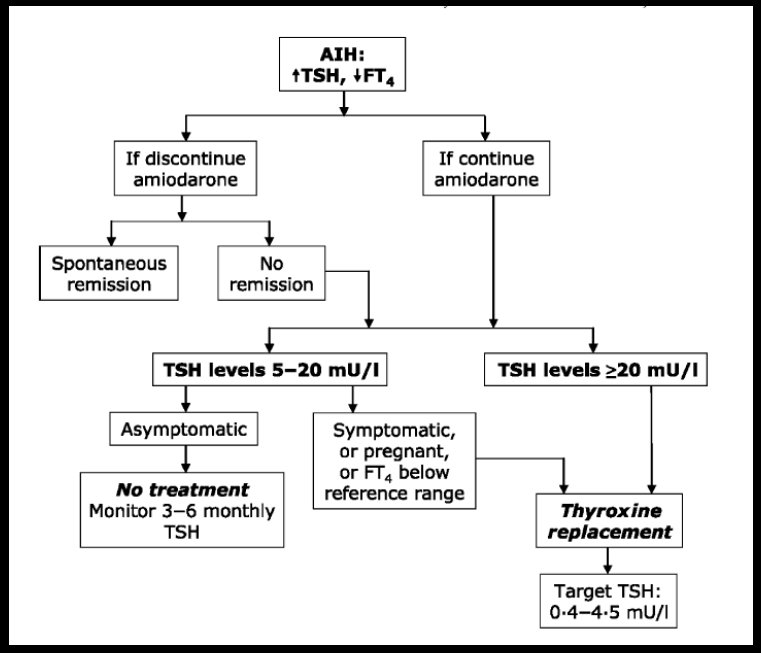
Amiodarone induced thyroid disease

Amiodarone induced thyroid disease

Amiodarone is 37% iodine by weigh ($T_{1/2}$ 60 days)

Due to direct destructive effect on thyroid and increased iodine supply

Amiodarone induced hypothyroidism



Immune mediated thyroid dysfunction

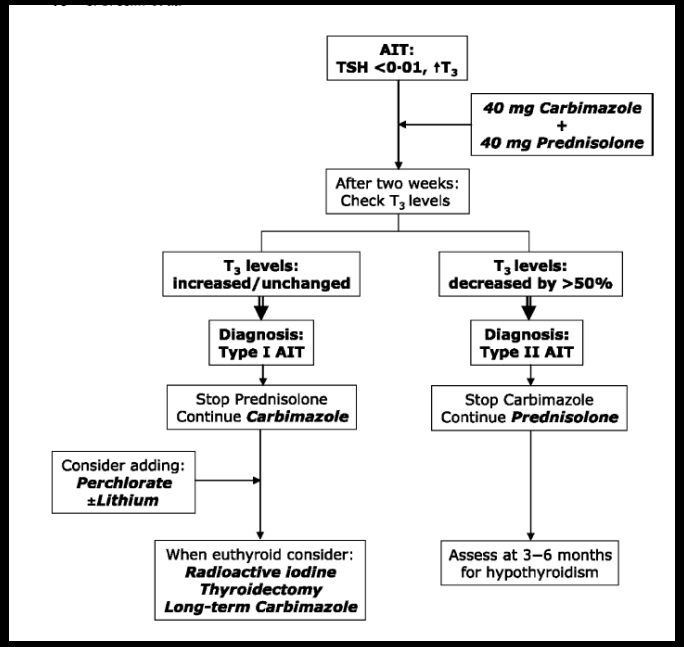
7% of patients of treated patient

Failure to escape Wolf-Chaikoff effect

Decreased free T4 and increased TSH

TPO antibody positive

Amiodarone induced thyrotoxicosis



Type I Jod-Basedow (increase iodine supply to a hyper-functioning nodule)

Type II Destructive thyroiditis (may lead to hypothyroidism)

6-12% of patients male to female ratio 3:1

(Han TS et al 2009 Clin Endocrinol 70: 2-13)

Rare causes of elevated T4 and T3

TSH secreting pituitary tumour (very rare)

Less than 1% of all pituitary tumours

TSHoma are usually large (90% macro) and invasive (60%)

Symptoms

- Hormone excess: Mild thyrotoxicosis and goitre
- Hormone deficiency: Gonadotrophins may be reduced
- Size: Bitemporal hemianopia, headache

Investigation

- T4 and T3 elevated TSH inappropriately normal
- Thyroid antibodies negative
- Serum α-subunit markedly elevated
  - (α-subunit (µg/l)/TSH (IU/l) ratio >5.7 normal range (<1))
- MRI demonstrates pituitary adenoma

Management

- Somatostatin analogues +/- PTU to control thyrotoxicosis
- Pituitary surgery
- If incomplete resection
  - Somatostatin analogues and pituitary radiotherapy
  - (Radioactive iodine and T4 replacement have been used)

Resistance to thyroid hormone (very rare)

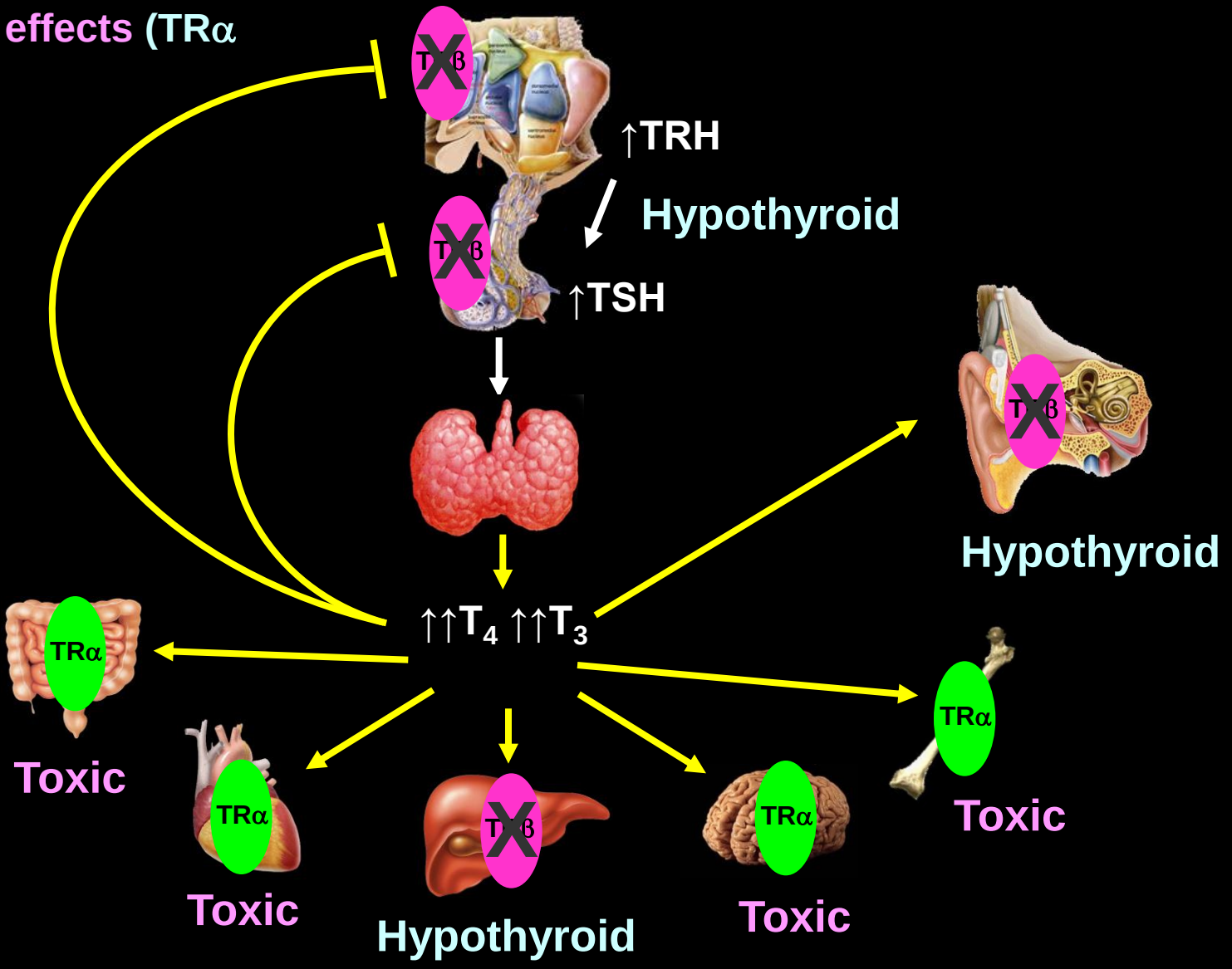
Mutant TRβ acts as a dominant negative receptor

- Resistance to thyroid hormone (autosomal dominant, TRβ mutation)
  - Mutant TRβ heterodimerises with RXR
  - Mutant TRβ heterodimerises with normal TRβ and TRα
- Presentation (variable and depend on mutation)
  - Combination of hyper and hypothyroid symptoms and signs
    - Hypothalamic and pituitary resistance to T4, goiter, palpitations, growth retardation, ADHD, hearing defects
- Investigations
  - Elevated T4, T3, elevated or inappropriately normal TSH,
  - Normal α-subunit/TSH ration and normal pituitary MRI
- Diagnosis test
  - TSH responses to TRH determined during the graded T3-suppression
  - Sequencing *THRB*
- Management
  - Controversial but frequently none required
    - Some may benefit from supra-physiological doses of T4
    - others may require beta blockade to alleviate tachycardia

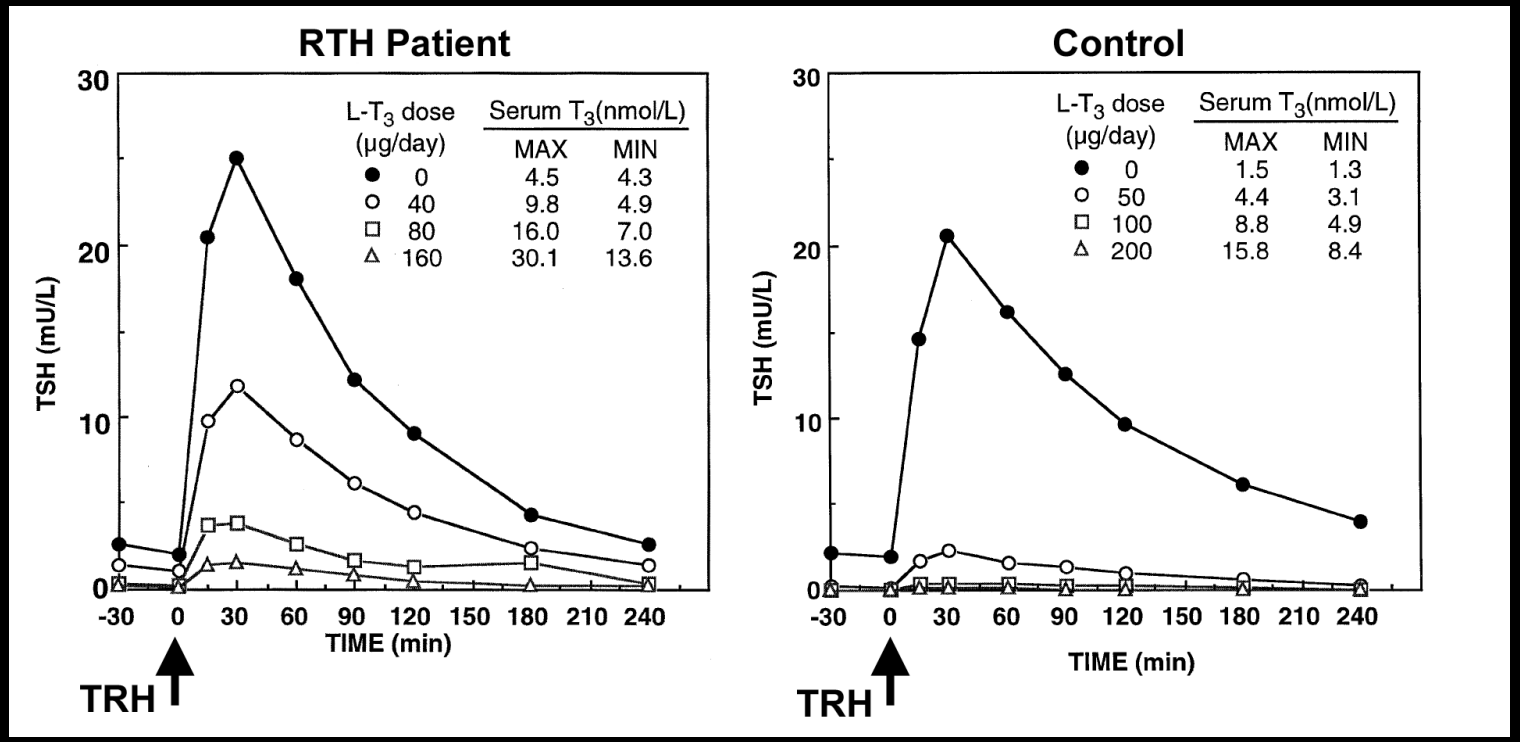
RTH is caused by a dominant negative mutation of TRβ

Mixed Hypo/Toxic effects (TRα and TRβ)

- BMR
- Thermogenesis
- Adipogenesis
- Vasculature
- Skin
- Hair
- Muscle
- Bone marrow
- Kidney
- Lung



Effect of increasing doses of T3 on TSH responsiveness to TRH stimulation



TSH response to TRH not suppressed by 160μg/d T3

TSH response to TRH suppressed by 50μg/d T3

Thyroid nodules and thyroid cancer

Thyroid nodules

Palpable thyroid nodules are very common (4% of adults, F:M 4:1)

- 95% of thyroid nodules are benign
- 95% of thyroid cancer presents as asymptomatic nodule

Differential diagnosis

Common

- Colloid nodule
- Cyst
- Lyphocytic thyroiditis
- Benign neoplasm
  - Follicular adenoma
  - Hurthle cell
- Malignant neoplasm
  - Papillary thyroid cancer
  - Follicular thyroid cancer

Rare

- Granulomatous thyroiditis
- Infection
- Malignancy
  - Medullary thyroid cancer
  - Anaplastic thyroid cancer
  - Metastic disease
  - Lymphoma

Thyroid nodules

Risk factors for malignancy

- Childhood exposure to ionizing radiation
  - Early papillary thyroid carcinoma

Low risk

- Female, soft nodule, MNG, positive TPO antibodies

High risk

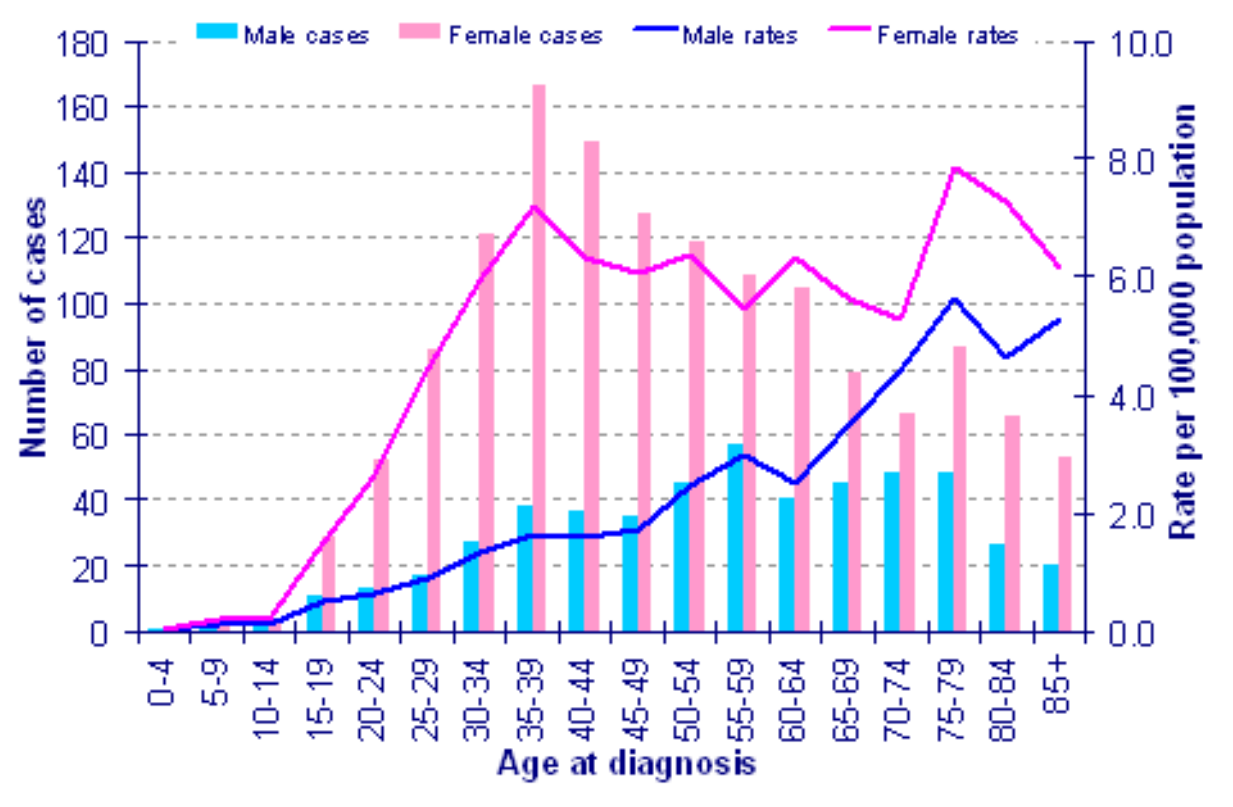
- Younger age or elderly, male, solitary firm nodule, horse voice, LN

Investigation of thyroid nodule if >1cm

- Thyroid function tests, thyroid auto antibodies,
- Fine needle aspiration cytology (2% false +ve, 5% false -ve)
  - Classification:
    - THY1 inadequate
    - THY2 benign
    - THY3 indeterminate
    - THY4 suspicious
    - THY5 malignant

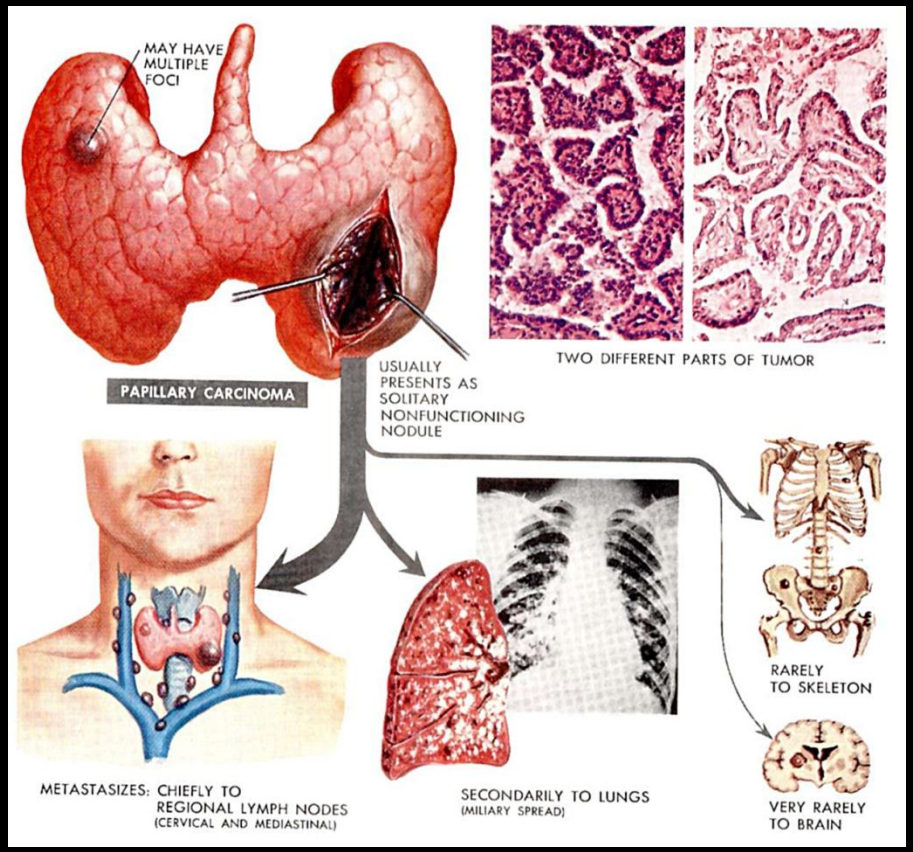
Thyroid cancer incidence

Approximately 2000 cases of thyroid cancer per year in UK



Must be managed in specialist centres

Differentiated thyroid cancer



Frequency of thyroid cancers

Papillary thyroid carcinoma	80%
Follicular thyroid carcinoma	10%
Medullary thyroid carcinoma	5%
Anaplastic carcinoma	1%

Differentiated thyroid cancer

Papillary carcinoma (PTC)
- BRAF (V600E) mutations and RET/PTC translocations
- Commonly multifocal and metastatic to local LN
  - May also invade locally
  - Indolent course and excellent survival (>95%)
- Tumour cells concentrate iodine (^{131}I treatment)

Follicular carcinoma
- Associated with Pax8-PPARγ fusion genes and Ras mutation
- More aggressive than PTC but good survival
  - local spread and metastasis to bone and lung
- Tumour cells concentrate iodine (^{131}I treatment)

Risk stratification
- Low risk: <45 years, <2cm, no intra or extra-glandular spread
- High risk: >45 years, >2cm, intra or extra-glandular spread

Anaplastic carcinoma
- Associated with P53 mutation
- Very aggressive and poor survival, surgery is palliative

Management of differentiated thyroid cancer

Low risk patients (<45 years, <2cm, no intra or extra-glandular spread)
- Total thyroidectomy and life long T4 and follow up
  - Degree of TSH suppression is controversial
  - Some patient may also require ^{131}I ablation

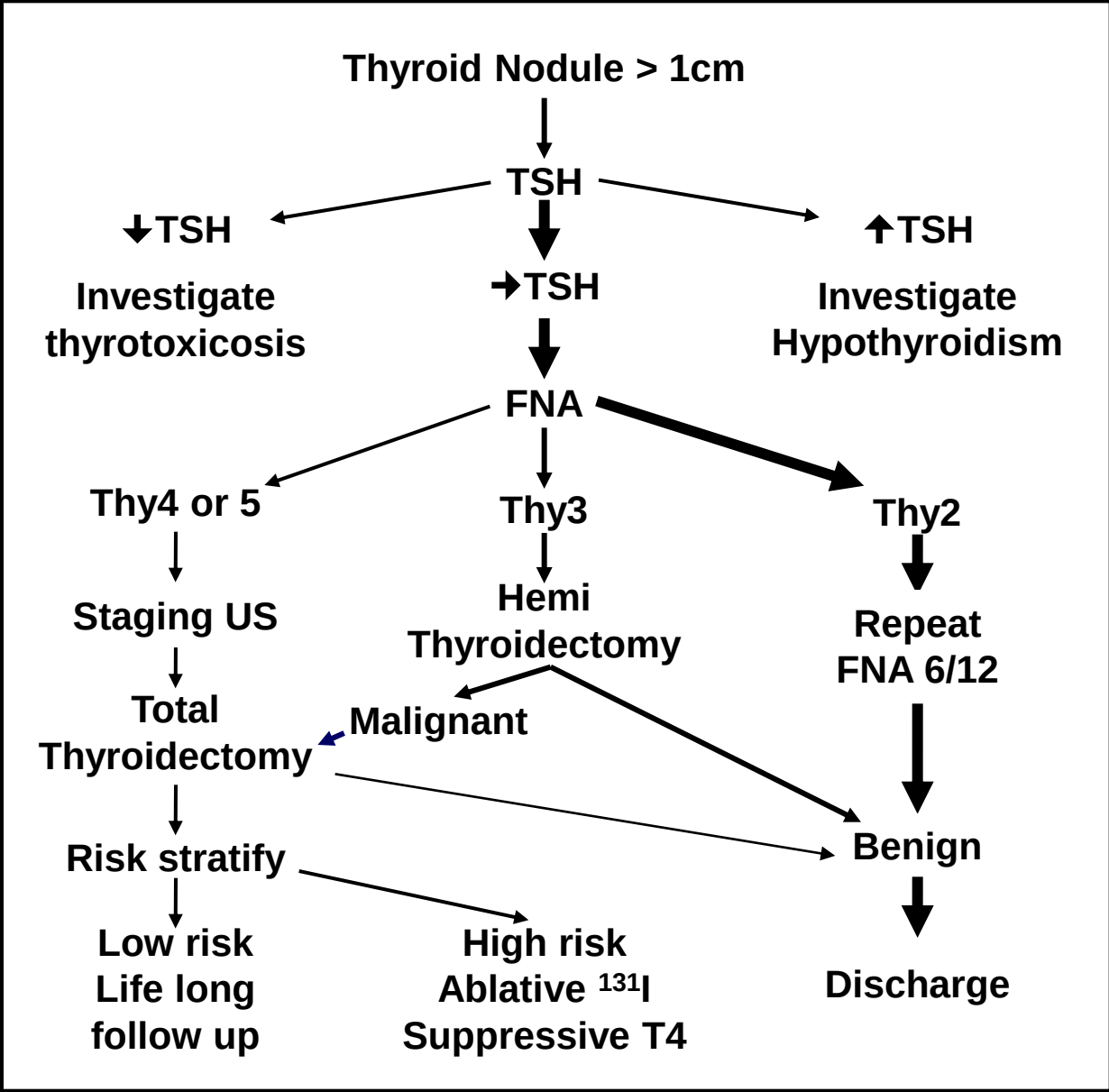
High risk patients (>45 years, >2cm, intra or extra-glandular spread)
- Total thyroidectomy and LN dissection as appropriate
  - T4 sufficient to suppress TSH <0.1mU/L
  - Remnant ablation with ^{131}I with rhTSH stimulation
  - (Post ablation scan performed at day 4)
- At 6 months post ablation
  - rhTSH stimulated scan and thyroglobulin
  - Negative scan and undetectable thyroglobulin is best evidence of tumour eradication

Follow up
- Annual neck ultrasound, TFTs
- non stimulated thyroglobulin and anti-thyroglobulin antibodies

Prognosis: 95-99% 30 year survival if
- Total thyroidectomy at initial surgery
- Appropriate suppression of TSH

(ATA Guidelines Cooper DS et al 2009 Thyroid 19:1167)

Algorithm for thyroid nodules



Medullary thyroid carcinoma (MEN2)

Rare malignancy of the thyroid parafollicular cells (C-cells)
- 1 in 250 thyroid nodule FNAs (3-5% of all thyroid cancers)
- But accounts for 14% of thyroid cancer related deaths
- Surgery is the only effective treatment
  - TSH suppression and ^{131}I cannot be used
- Only chance of cure is complete resection at initial surgery

Optimal management requires diagnosis prior to surgery
- Surgical requires extensive LN dissection
- Phaeochromocytoma must be excluded prior to surgery
- No specific FNA or US features but atypical
- Serum or FNA calcitonin may aid diagnosis if MTC suspected

80% Sporadic
20% Familial (MEN2A, FMTC, MEN2B : Germline RET mutations)

Patients may survive may years with significant residual tumour

Medullary thyroid carcinoma

Diagnosis

- May be diagnosed as a result
  - serum calcitonin, FNA cytology or at surgery
- All MTC patients should have RET genetic testing
  - If RET mutation identified family screening is mandatory
  - RET mutation dictates the timing of prophylactic thyroidectomy

Follow up

- Annual ultrasound and serum calcitonin

Management

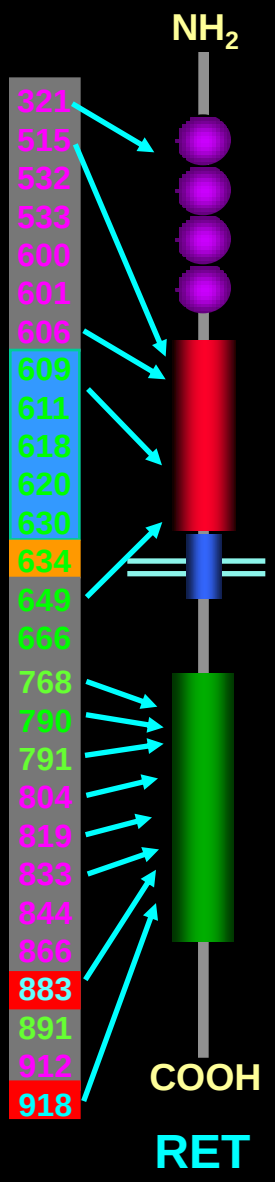
- Local recurrence : Neck exploration
- Increasing calcitonin without evidence of local recurrence
  - Imaging (Thoracic CT, Liver MRI and Bone scintigraphy/MRI)
  - Surgical excision, radiotherapy (TK inhibitors)

Prognosis

- Prophylactic surgery cures MTC
- Complete resection at initial surgery is best chance of cure
- Clinical course if often indolent (MEN2B (RET M918T) more aggressive)
- Long term survival is common even with metastatic disease

(ATA Guidelines Kloos RT et al 2009 Thyroid 19:565)

American Thyroid Association risk levels 2009



MEN2A/FMTC	FMTC	MEN 2B
609	321	A883F
611	515	M918T
618	532	
620	533	
630	600	
634	601	
649	606	
666	777	
768	V804M	
790	819	
791	833	
804	844	
891	866	
	912	

Level A: TTx may be delayed if normal U/S and Ct <40

Level B: TTx by 5 years but may be delayed if normal U/S and Ct

Level C: TTx before 5 years

Level D: TTx ASAP and within the first year

Kloos RT 2009 thyroid 19:565

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