THYROID DISEASE

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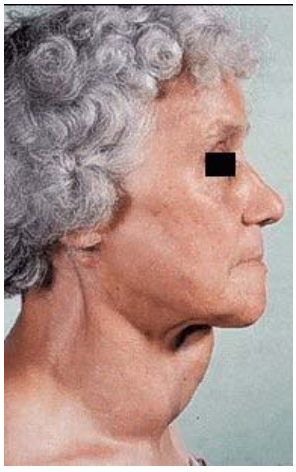
PHYSIOLOGY

- Axis (controlled via classic negative feedback)
  Thyrotropin-releasing hormone (TRH) from **hypothalamus** -> stimulates **anterior pituitary** to release **thyroid stimulating hormone (TSH)** -> stimulates thyroid
- TSH stimulates **thyroid** to produce primarily (90%) **thyroxine (T4)** and some (10%) T3
- T4 is converted in peripheral tissue to **triiodothyronine (T3**)
- T3 is the metabolically active form (more potent)
  - 10 % secreted by thyroid gland
  - 80-90% from T4 ->T3 conversion (sequential monodeiodination)
- T3 and T4 highly but reversibly bound to plasma **thyroid-bonding globulin (TBG)**
  - Also bound to a lesser extent to albumin and pre-albumin, transthyretin.
  - proteins synthesized in liver
  - overall 99.9% T4 and 99.7% T3 bound to plasma proteins
- Only minute, unbound (free) fractions are metabolically active
- **TSH is most sensitive indicator to thyroid status**
- TSH is controlled by classic negative-feedback mechanism (via unbound T3 and T4)
- TSH affects mainly pituitary but to a less extent hypothalamus (TRH)
- Both T3 and T4 metabolized hepatically via deiodination and conjugation

PATHOPHYSIOLOGY

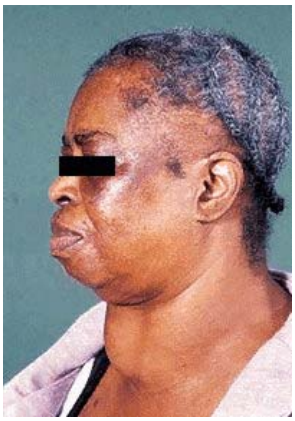
- 20 million Americans have thyroid disease
- **Primary disease** vs **Secondary disease:** usually used in reference to hypofunction
  - Primary hypothyroidism results from failure of thyroid gland (high TSH, low T3, T4)
  - Secondary disease from deficiency of pituitary TSH (low TSH, low T3, T4)
  - Tertiary disease if dysfunction is with hypothalamus

Goiter: enlargement of thyroid gland
- Can occur in hypothyroidism or hyperthyroidism)
- **Toxic goiter**: goiter where there is excess production of thyroid hormone (e.g. **Graves**)
- **Non-toxic goiter**: enlargement but no excessive hormone production (e.g. I2 deficiency)
  Thyroid enlarges under influence of TSH in response to low hormone levels
- **Adenomatous goiter**: caused by growth of encapsulated adenoma
- **Diffuse goiter**: thyroid tissue diffuse vs nodular form in adenomatous goiter
- Nodular goiter: contains nodules
- Substernal goiter: enlargement of lower portion of thyroid gland
- Suffocative: goiter causing SOB due to tracheal compression



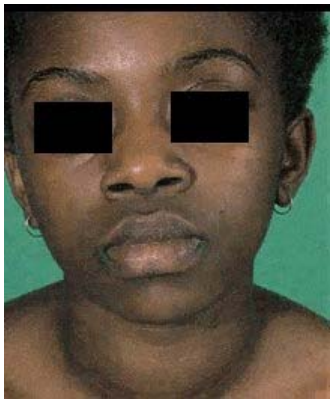
Right: Multinodular goiter
Left Endemic goiter (I2 deficiency)

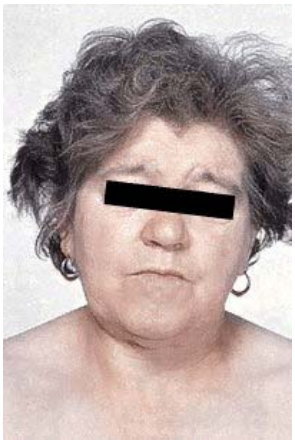
Both patients were euthyroid. Multinodular goiter required intervention due to tracheal compression. I2 deficiency can result in large goiter with or without hypothyroidism

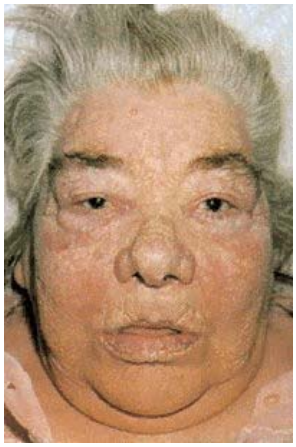


Hypothyroidism: (affects 1-3% of general population) - 11 million Americans

- Common in elderly; 10 % women > 65 have hypothyroidism; 15% of population by age 70
- More common in females vs males (10:1 ratio)
- Common causes
    - **Hashimoto's thyroiditis** is most common cause (see below)
    - S/P treatment for hyperthyroidism is common cause
        - Radioactive I2 for hyperthyroidism
        - S/P various antithyroid drugs
    - S/P **thyroid surgery**:
        - 5% within 1 year, 1-2% per yr subsequently
        - 50% by 25 yrs post-op
    - Lithium and amiodarone
    - Congenital hypothyroidism: agenesis or hypofunction of gland
    - I2 excess: kelp or seaweed supplements in susceptible persons
    - Neck irradiation esp for head/neck CA; radiation may cause thyroid CA
    - Pituitary or hypothalamic disorders
- Signs and symptoms may be subtle, easily missed; importance of **TSH screening**
- US Preventative Services Task Force recommends screening
    - Pts > 50 esp women
    - Pts with family history esp due to subtle presentation







- **Myxedema:** condition resulting from acquired (vs congenital) hypothyroidism

    Decreased metabolic rate, characteristic facial changes (large tongue, puffiness of face, skin changes) slow speech, puffiness of hands and face, coarse and thickened edematous skin, hair loss and dryness, mental apathy, drowsiness, cold sensitivity. Untreated will progress to **myxedema coma** and death

Hashimoto's Thyroiditis (left): most common cause of goitrous hypothyroidism. Patient shows marked goiter but few obvious signs of hypothyroidism

Hypothyroidism: (middle) generalized pallor, puffiness, coarsening features, coarse hair

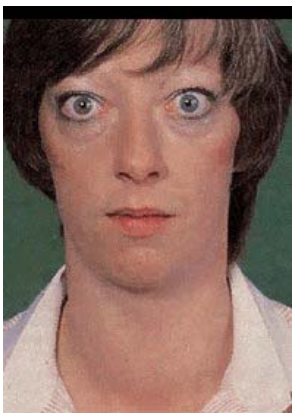
Severe clinical hypothyroidism (right) with non-pitting edematous changes in facial skin and characteristic clinical appearance; dry, puffy facial appearance with coarse hair. Patient was admitted with hypothermia and mental apathy

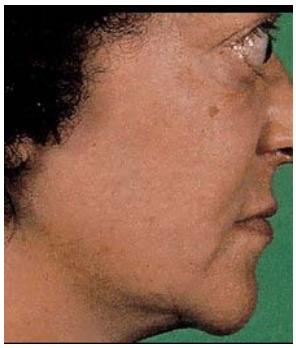
- **Cretinism:** congenital myxedema due to lack of thyroid secretion - now very rare
  (Rare due to perinatal screening)
  Lack of growth, bone dystrophy and profound mental retardation. Skin rough/dry, hair coarse, dry, brittle; teeth erupt slowly, poor quality, irregularly placed; tongue large and protruding; constant saliva drool; pot-bellied, swayback w umbilical hernia

Hyperthyroidism: less common vs hypothyroidism (1.9% women; 0.16% men); 15% in > 60 yrs

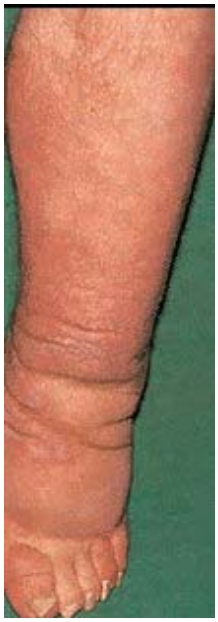
- **Graves disease**: autoimmune and familial
  - Most common cause hyperthyroidism in age < 40 yrs (90%)
  - Action of thyroid-stimulating immunoglobulin G antibody (TS Ab) on thyroid gland TSH receptors
  - Characterized by **exophthalmos** and **pretibial myxedema** *
  - Presents with a goiter

    * misnomer due to its resemblance to skin of myxedema facies



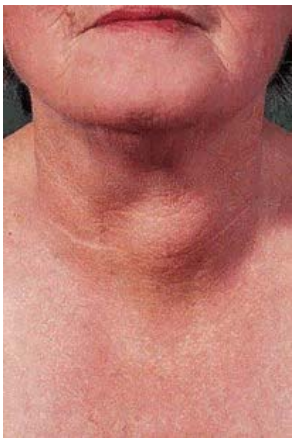


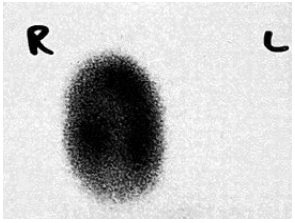
Graves Disease: diffuse goiter with vascular bruit and eye signs
Exophthalmos (proptosis) results from enlargement of muscles and fat within orbit resulting in mucopolysaccharide infiltration
Pretibial myxoedema (right)



Plummer's disease: non-toxic multinodular goiter
- Most common cause hyperthyroidism in age > 40 yrs
- Multinodular goiter develops autonomous hyperfunctioning nodules

- **Toxic adenoma:** least common cause hyperthyroidism
  One or more hyperfunctioning thyroid adenomas capable of functioning independent of TSH or thyroid stimulators





Toxic adenoma s/p partial thyroidectomy with recurring toxic nodule confirmed with scan

"Hot" Nodule on scan takes up isotope whereas rest of gland does not

- **Thyroiditis:** transient hyperthyroidism
    - Hormone leaks from inflamed gland)
    - Transient hypothyroidism may follow (intrathyroidal stores of hormone depleted)

- **Hashimoto's thyroiditis** aka lymphocytic thyroiditis - autoimmune disorder
    - Most common cause of hypothyroidism in adults
    - Leads to gradual destruction of gland

- **Post-partum thyroiditis**: short-term change in thyroid function which affects 10%
    - Transient overactivity -> underactivity; abates after several months
    - May be misdiagnosed as post-partum depression due to mood swings
    - Type I DM patients are at greater risk
    - Avoid thyroid scan as will preclude breast-feeding for 6 months

DIAGNOSING HYPERTHYROIDISM

S/S hyperthyroidism plus abnormal thyroid profile testing
- **Suppressed sTSH and elevated FTI**
- If normal FTI: meas T3 to r/o T3 thyrotoxicosis

H and P critical to distinguish etiology
- **Graves disease**: IS, NN, NT - proptosis, pretibial myxedema, bruit (50%)
- **Subacute thyroiditis**: IS, NN, T- recent viral illness in many
- **Silent thyroiditis**: modest IS, NN, NT
    - consider Hashimoto's
    - some post partum
- **Toxic multinodular goiter**: IS, multiple-N, NT - consider Hashimoto's
- **Extra-thyroid source**: DS, NN, NT
- **Toxic adenoma**: DS, single-N, NT

IS = increased size DS = decreased size NN = non-nodular;
N = nodular NT = non-tender T = tender

Radioactive iodine (123I) uptake: can help clarify uncertain etiology
- Graves disease: diffuse increase in uptake
- Toxic adenoma: nodular concentration
- Multinodular goiter: nodular concentration
- Exogenous hyperthyroxemia: decreased uptake*
- Thyroiditis: decreased uptake*
- Iodine-induced thyrotoxicosis: decreased uptake*
- struma ovarii: decreased uptake*

* **Thyroglobulin measurement** can help distinguish
- Increased: thyroiditis, iodine-induced thyrotoxicosis, struma ovarii
- Decreased: exogenous (factitious) hyperthyroxemia

LAB MEASUREMENT

Total T4 and T3 measure both bound and unbound
- Radioassay measurement
- Affected by changes in thyroid-binding protein

Free T4: expensive; not commonly ordered
- Measured reliably via equilibrium dialysis
- Major indication: severe/chronic non-thyroid illness which affects other types free T4 assay

Free T4 index (FTI): most widely used test for free T4 - calculated value - T3 or T4 resin uptake

Estimate free T4; adjusts for variation secondary to altered protein binding
- T4 concentration via thyroid hormone binding ratio (THBR)
- Inverse estimate of TBG concentration and expressed as a percent (%)
- THBR reduced if high capacity of serum binding proteins; increased if diminished capacity

T3 resin uptake (T3 RU): lab measure of protein binding of T4 and T3; NOT measure of circ T3
- Inversely proportional to unsaturated hormone binding sites on thyroid binding globulin
- Useful to help interpret given level of T4

sTSH - sensitive TSH assays - **choice for initial screen**
- First assays (1965) dual antibody approach: good dx only primary hypothyroidism
  - Could not reliably measure lower limit to normal
  - Radioimmune assay approach
- Sensitive TSH (1985) - detects both hypothyroidism and hyperthyroidism
  - Dual antibody approach
  - Expansion of assay detection limit below normal range
- Proved that subnormal levels were common in asymptomatic patients
  - 15% hospitalized pts w abnormal TSH; no dysfunction on recovery
  - 20-30% pts > 60 yrs have subnormal TSH w normal FTI (subclinical disease)
- Clinical implications (conclusions) re: sTSH testing
  - Normal TSH is sensitive and specific to ID normal pts
  - Subnormal (suppressed) TSH sensitive but not specific to hyperthyroidism
  - Abnormal TSH requires additional workup (biochemical/clinical eval) to dx disease

THYROID NUCLEAR SCANNING: measures **uptake of radioactive iodine**

- Gives thyroid outline (e.g. size) and nodularity (hot spots vs cold spots) of thyroid gland
- Can distinguish toxic versus non-toxic goiters
- If ordered post-postpartum (thyroid dysfunction common) will limit breast feeding for 8 months

THYROID ASSAYS

FUNCTION ASSAY	NORMAL VALUE
TSH	0.15-4.5 Mu/L
Total Serum Thyroxine (T4)	5.5-12.4 ug/dl
Free T4	10-27 pmol/L
Total serum triiodothyronine (T3)	260-480 pg/dl
Thyroid scan	Symmetrical gland; uniform uptake
Thyroid antibody	Positive suggests autoimmune disease

INDICATIONS FOR HYPOTHYROIDISM SCREENING

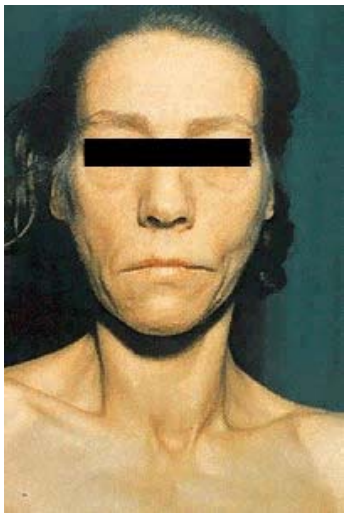
Well Established Benefit to Screening
- Congenital hypothyroidism
- Neck irradiation
- Patients taking amiodarone or lithium
- Pituitary gland surgery
- Treatment of hyperthyroidism
- Women > 50 yrs

Probably Worthwhile To Screen
- Autoimmune conditions e.g. Addison's disease, pernicious anemia, vitiligo, DM type I
- Premature menopause
- Previous episode of postpartum thyroiditis
- Refractory depression; bipolar affective disorder w rapid cycling
- Type I DM antepartum (check thyroid antibodies 1st trimester; if positive: TSH postpartum
- Turner's syndrome; Down syndrome
- Unexplained infertility or recurrent miscarriage
- Woman > 40 yrs with nonspecific complaints

Screening Has Uncertain Benefit
- Breast cancer
- Dementia
- Idiopathic edema
- Obesity
- Pts w family hx of autoimmune thyroid disease
- Pregnancy looking for postpartum thyroiditis

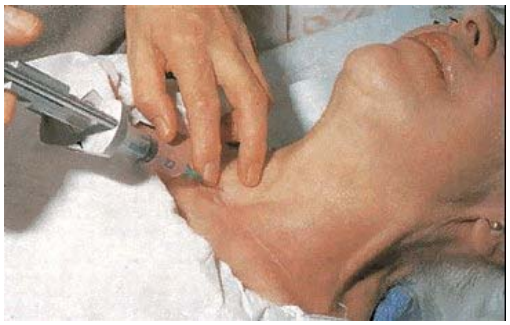
Screening is Not Indicated: Acutely ill pts w no clinical reason to suspect thyroid disease

Reference : Weetman AP. Hypothyroidism: Screening and subclinical disease *BMJ.* 1997; 314: 1175-1178



"Masked" hyperthyroidism (apathetic hyperthyroidism)

Commonly caused by toxic multinodular goiter. Eye signs and pretibial myxedema lacking since patient does not have Grave's disease. Clinical diagnosis is less obvious. Patients classically present with atrial fibrillation and/or tachycardia; heart failure and weight loss are common in patients over age 60 yrs



Fine-needle aspiration of thyroid nodule - Diagnostic of choice in patient with solitary nodule. Cells sent for cytology to rule out carcinoma. Usually done under local.

CLASSIC SIGNS AND SYMPTOMS

HYPOTHYROIDISM	HYPERTHYROIDISM
Cold intolerance	Frequent/looser bowel movements
Muscle weakness	Frequent or lighter menses
Changes in bowel (usually constipation)	Heart palpitations, SOB
Hearing loss	Emotional instability, sleep disturbances
Lethargy	Inability to concentrate, nervousness
Myalgia	Hyperactivity and tremors
Menorrhagia; frequent periods	Heat intolerance
Wt gain (less common than believed)	Double vision (exophthalmos)
Bradycardia	Shakiness and tremors
Diastolic hypertension	Tachycardia
Hypothermia	Widened pulse pressure
Puffiness around face/eyes	Cardiac arrhythmia
Slow, hoarse speech	Heart murmur
Cold, thick skin	Warm, velvety, smooth skin
Dull, brittle hair/nails	Increased sweating
Goiter (dyspnea if large	Wt loss despite increased appetite
	Exophthalmos, pretibial myxedema (Grave's)
	Proximal muscle weakness in shoulders and hip

CLINICAL PRESENTATION

HYPERTHYROIDISM

- Not all patients present with classic s/s; some w opposite of what expected (see Table below)
- Signs/symptoms hyperthyroidism can be subtle to non-existent
- **Apathetic hyperthyroidism** very common in elderly - suspect in any elderly w a-fibrillation
    - Fail to exhibit signs and symptoms despite significant disease
    - **Atrial fibrillation**, CHF, muscle weakness or wt loss
- Atypical presentation of hyperthyroidism
    - Depression, apathy and psychomotor retardation (difficult to differentiate from depression)
    - Risk osteoporosis, organ system damage, heart failure, dehydration if undetected

-**Thyroid storm -** medical emergency - life-threatening
- Sudden development of extremely overactive thyroid
- Generally affects persons with neglected health
- Precipitating factors: infection, flu, MI, DKA, pregnancy/labor, physical stressor
- Extreme tachycardia, extreme fever, shock

Diagnostic Screening for Hyperthyroidism
- Low TSH diagnostic; not useful for pts who are acutely ill (falsely low)
- Dx supported by increased T4, free T4 and T3
- Low TSH with normal FTI: evaluate T3 levels
- Controversy re treating pt w low TSH and normal T4/T3 (subclinical hyperthyroidism)
    - Some normal thyroid glands; most have few s/s hyperthyroidism
    - Some have thyroid antibodies (autoimmune); some no antibodies
    - Consider endocrine referral for close monitoring

HYPOTHYROIDISM

- Subclinical presentation is very common esp among older females
- Misdiagnosis of subtle symptomatology in elderly is very common
    - Fatigue, myalgia, mental confusion may be dismissed as normal aging
    - Dazed, forgetfulness or confusion may be misdiagnosed as Alzheimer's
- Must maintain high index of suspicion
- Sequelae of untreated hypothyroidism
    - Hyperlipidemia
    - Vascular disease
    - Anemia
    - Carpal tunnel
    - Increased susceptibility to infection
    - Cardiac hypertrophy from pericardial dilation/effusion -> heart failure
    - Rarely: psychosis or **myxedema madness/coma** (life threatening)
        - Severe agitation, alternating periods of restlessness and lethargy, psychosis
        - Seizures and coma
- Sequelae of pediatric disease
    - Decline in growth rate; abnormal sexual maturation (early or late development)
    - Impaired alertness, learning, cognitive function

DIAGNOSTIC EVALUATION VERSUS SCREENING - Persons found to have thyroid disease

- 78% of those with 5 or more findings; 2.9% of those with 3 or 4 findings
- 0.45% of those with 1 or 2 findings

HYPOTHYROIDISM		HYPOTHYROIDISM		HYPERTHYROIDISM	
SIGN/SYMPTOM	% cases	SIGN/SYMPTOM	% cases	SIGN/SYMPTOM	% cases
Weakness	99	Poor heart sounds	30	Goiter	87
Dry skin	97	Precordial pain	25	Dyspnea	81
Course skin	97	Poor vision	24	Tiredness	80
Lethargy	91	Fundus changes	20	Hot hands	76
Slow speech	90	Dysmenorrhea	18	Palpitations	75
Eyelid edema	90	Loss of wt	13	Preference for cold	73
Sensation of cold	89	Atrophic tongue	12	Hands sweating	72
Decrease sweating	89	Emotional instability	11	Excessive sweating	68
Cold skin	83	Choking sensation	9	Resting pulse > 90	68
Thick tongue	82	Fineness of hair	9	Finger tremor	66
Edema of face	79	Cyanosis	7	Lid lag	62
Coarse hair	76	Dysphagia	3	Nervousness	59
Cardiomegaly	68			Wt loss	52
Pallor of skin	67			Goiter: diffuse	49
Memory impairment	66			Hyperkinesis	39
Constipation	61			Exophthalmos	34
Wt gain	59			Goiter: nodular	32
Loss of hair	57			Increased appetite	32
Pallor of lips	57			Atrial fibrillation'	19
Dyspnea	55			Scant menses	18
Peripheral edema	55			Constipation	15
Hoarseness	52			Diminished appetite	13
Anorexia	45			Diarrhea	8
Nervousness	35			Wt gain	4
Menorrhagia	32			Goiter: single adenoma	4
Palpitation	31			Excessive menses	3
Deafness	30				

TREATMENT: HYPOTHYROIDISM

- Levothyroxine preferred for routine replacement - avoid switching brands: significant variation
- Levothyroxine (T4)
    - Long half life -> qd administration
    - Steady state requires q 6-8 weeks (don't recheck TSH before that time frame)
    - Toxicity - (f) thyroxine levels
        - nervousness, heart palpitations/tachycardia
        - Heat intolerance and unexplained weight loss

- Thyroid hormone replacement is the only treatment regardless of etiology
    - Primary (thyroid: 98%)
    - Secondary (pituitary) or rare tertiary (hypothalamus)

- **Sodium L thyroxine aka thyroxine or T4:**
    - **Synthroid, Levoxyl, Levothroid** (all are synthetic levothyroxine)
    - Preferred therapy
    - T4 converts to T3 in vivo
    - Most nearly mimics the normal levels of circulating T3 and T4

    - Other preps (rarely if ever used currently; most no longer available)
        - Desiccated thyroid: dried prep of animal thyroid
        - Synthetic T3
        - Purified TGB
        - Mixtures of T3 and T4
    - Previously used levothyroxine to treat non-thyroid conditions
        - This application is no longer considered valid
        - Examples: dry skin, obesity, infertility
        - Osteoporosis is one of main side effects of misuse or excessive dosing

- Brand vs generic is an important issue
    - Exception to the rule of preferred prescribing of generics for cost purposes
    - Minute quantity of hormone in the tablet which is largely inert
    - Small variations in amount of activity can have large impact on clinical results

- Adverse effects: presents with all s/s hyperthyroidism
    - Adverse effects should not occur with proper dosing
    - Some have more symptoms even with proper dose
        - Especially moderate to severe heart disease (angina)
        - Use caution with these patients

- Dosing:
    - Adults: 1.7 ug/day for full replacement with average maintenance dose of 125 ug/day.
    - Use full replacement dose in pt < 50 yrs initially *
    - Caution with other patients - start with 12.5 - 50 mcg/d
        - Age > 50 yrs
        - Cardiac patients start with 12.5-50 ug/day
    - Reevaluate q 6-8 weeks until dose **titrated to normal TSH**

    * **More common approach** is to start with lowest available dosing e.g. 0.025 mg/d and titrate up ward q 6 weeks pending TSH level

- Monitoring patients on therapy
    - Monitor with TSH and H/P once TSH is stable
    - At minimal monitor patients annually

- Drug interactions with levothyroxine
    - Drugs which interfere with absorption
        - **Cholestyramine** and **ferrous sulfate**
        - **Sucralfate** and **antacids with aluminum hydroxide** (**Maalox, Gaviscon**)
    - Drugs which elevate metabolism thus require higher doses of drug
        - **Phenytoin, carbamazepine, rifampin**

TREATMENT: HYPOTHYROIDISM

ANTITHYROID DRUGS

Methimazole and **propylthiouracil (PTU)** * (classification: thioamides)
- Inhibit thyroid hormone synthesis
- PTU inhibits peripheral conversion T4 to T3
- Suppress thyroid antibodies
- Decrease TS Ab
- Lead to remission in some pt w Grave's disease

- Concentrated in thyroid
- Inhibit necessary oxidative processes needed for normal physiology
    - Iodination of tyrosyl groups
    - Coupling of iodotyrosines to form T3 and T4
- No effect on thyroglobulin already stored in gland (must deplete stores)
- Clinical effect may be delayed until stores are depleted
- Well absorbed from GI tract but short half-life
- Several doses of PTU required but single dose of methimazole (duration of antithyroid effect)
- Slow in onset thus not effective to treat thyroid storm
- Rare s/e: agranulocytosis, rash and edema

* Dosing is not covered here as usually is an endocrine referral; PDR will guide dosing.

Radioactive iodine (RAI-131):

- Usually administered orally
- Concentration in thyroid gland: destroys follicular cells.
- Single dose permanently controls hyperthyroid in 90%
- Second dose p 3-6 mo if symptomatic
- Full effect over 2-3 months; f/u q 4-6 wks
- Most common complication: early or late development of **hypothyroidism**
    - Thyroid replacement therapy is needed as FTI and sTSH pass into hypothyroid range
    - End point replacement is normal sTSH
- Contraindicated in pregnancy; avoid pregnancy for at least 6 months after administration
    - Not shown to cause CA/infertility
    - No ill effects in subsequent children

SURGERY

- Declined in popularity due to availability of because of antithyroid drugs (ATDs) and I-131
- Used for patients unwilling or unable to take ATDs or R-131
- Used where there is large problematic goiters
    - Neck obstructions
    - Large goiters resistant to I-131
    - Cosmetic concerns
- Surgical candidates are often pretreated with methimazole till euthyroid
    - Avoids post-op thyrotoxic crisis
    - Other drugs used in combo with methimazole: K-iodide and beta blockers

- Potential complications (mortality: 0%; complication <4%)
    - Transient hypocalcemia, transient hypothyroidism, thyroid crisis
    - Permanent hypoparathyroidism, recurrent laryngeal nerve damage, post-op hemorrhage
- Recurrent hyperthyroidism: 10%

- Hypothyroidism (permanent)
    - 5% wi year 1
    - 1-2% per year subsequently
    - 50% hypothyroid 25 yrs post-op

ADJUVANT MEDICAL THERAPIES

- Used to relieve s/s in transient forms or pts undergoing definitive therapy with other treatment.
- Beta-blockers (B-adrenergic antagonists)
    - blunts widespread sympathetic stimulation
    - prompt symptomatic relief of hyperadrenergic manifestations.
    - **Propranolol (Inderal)** most widely used (
        Dosing: 20-40 mg qid adjusted to control tachycardia and other s/s

- CaCh blockers - **diltiazem, verapamil -** used where beta blockers are contraindicated
- Pharmacologic dose of iodide: rarely used as sole therapy
    - Inhibits iodination of tyrosines thus decreasing supply of stored thyroglobulin
    - Used to treat potentially fatal **thyrotoxic crisis (thyroid storm)** or prior to surgery
    - Decreases vascularity in thyroid gland
    - Not useful long term: thyroid ceases to respond after a few weeks
    - Administered PO; S/E minor
        - Sore mouth and throat, rashes, ulcerations of mucus membrane
        - Metallic taste in mouth