

# Thyroid Disorders In Children

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# Objectives

## 1) Hypothyroidism

- At the end of the lecture, medical student will be able to:
  - Knowledge on anatomy, physiology of the thyroid gland and thyroid hormone biosynthesis
  - Description of the hypothalamic-pituitary regulation of Thyroid Gland
  - Enumerate various cause of primary, Secondary and tertiary hypothyroidism including congenital and acquired hypothyroidism
  - Description of the clinical features of congenital and acquired hypothyroidism
  - Knowledge on how to investigate and expected laboratory findings
  - Knowledge on importance of neonatal screening program for congenital hypothyroidism

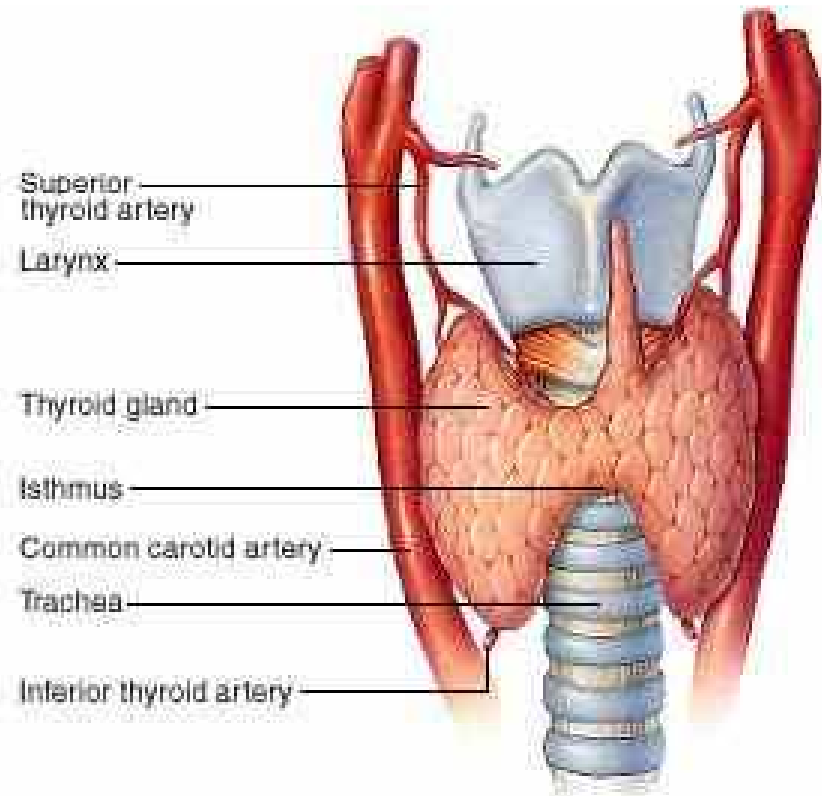
# Objectives

## 2) Hyperthyroidism

- At the end of the lecture, medical student will be able to:
  - Enumerate various causes of thyrotoxicosis including neonatal form
  - Description on Pathophysiology of thyrotoxicosis and association with other autoimmune endocrinopathy
  - Description of clinical presentation of thyrotoxicosis
  - Enumerate various causes of thyrotoxicosis.
  - Description clinical manifestation of eye disease in Grave's thyrotoxicosis.
  - Knowledge on different laboratory and radiological investigation tools in cases of thyrotoxicosis

# Anatomy

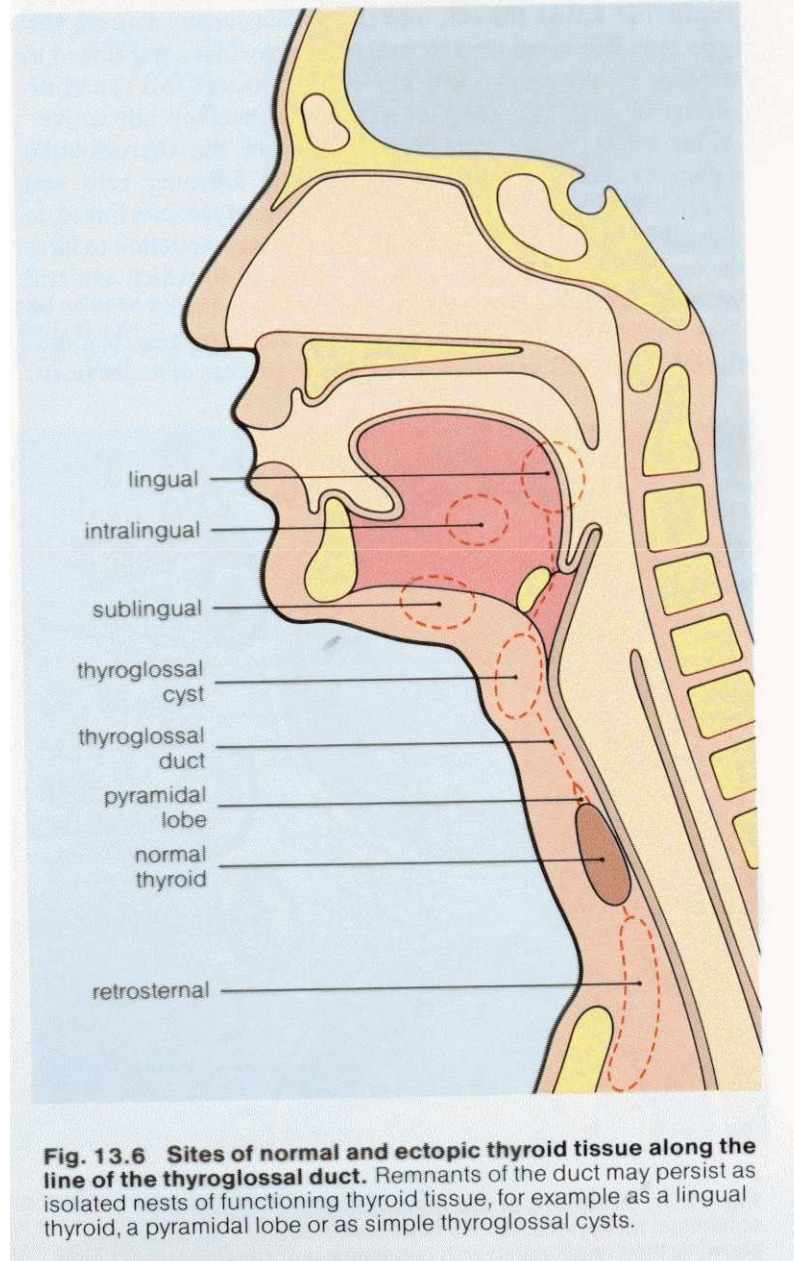
- Over Trachea
- Two Lobes connected together by an isthmus
- 15 to 20 g



# Thyroid gland

- Thyroid gland derives from the floor of embryonic pharynx
- Begins to develop around 4 weeks of gestation
- Moves down the neck while forming its characteristic bilobular structure
- Thyroid development is largely completed between 10-20 weeks of gestation
- Thyroid gland size increase gradually by 1g/year until age of 15 years where it achieves adult size (15-25 g)

# Sites of normal & ectopic thyroid tissue

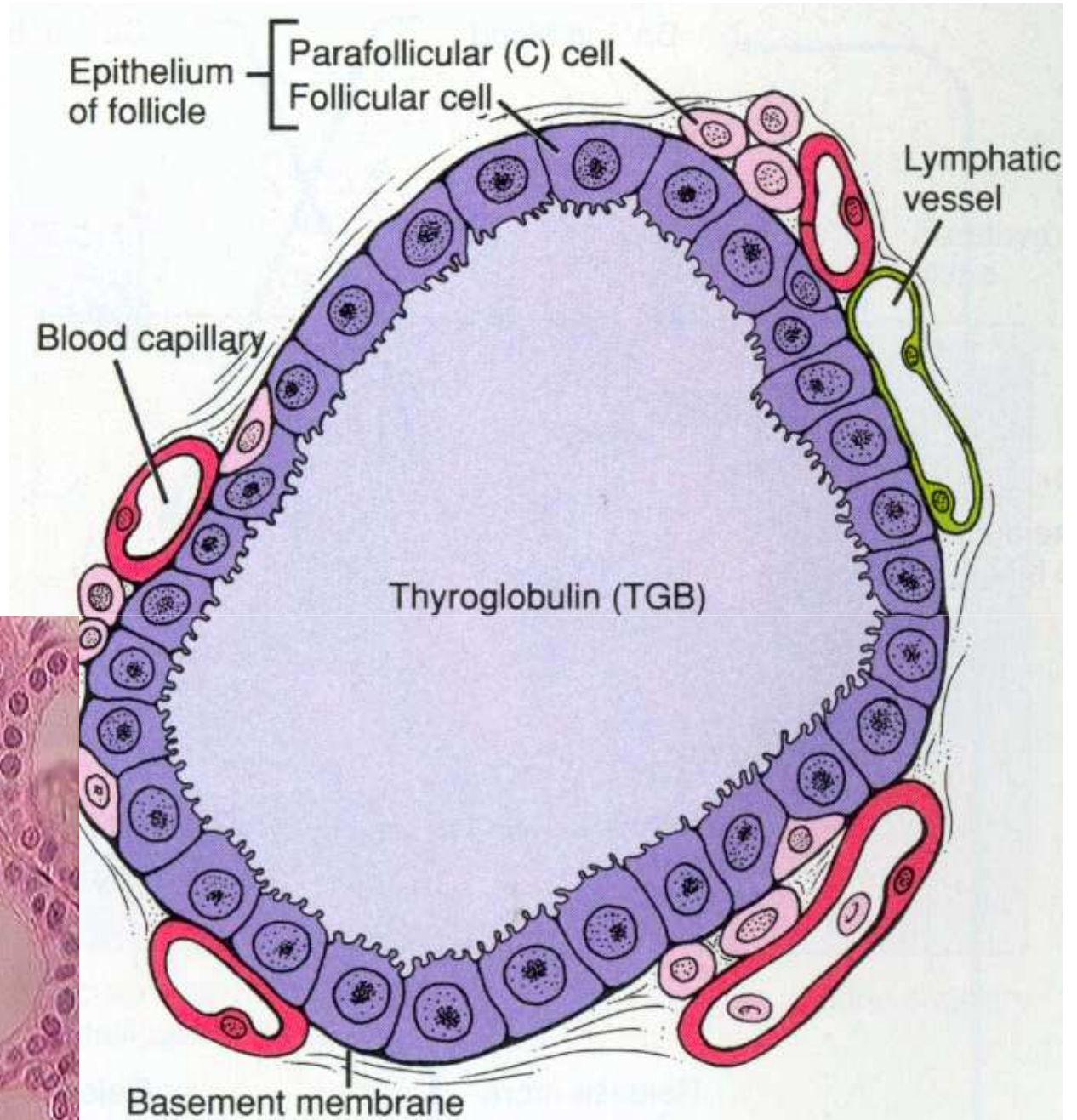


# Thyroid gland

- Thyroid gland is composed over a million cluster of follicles
- Follicles are spherical & consists of epithelial cells surrounding a central mass (colloid)
- Thyroglobulin is storage room
- Two main hormones:
  - Tetraiodothyronine (Thyroxin)
  - Triiodothyronine



# FUNCTIONAL UNIT IS THE FOLLICLE



(b) Diagram of a single thyroid follicle



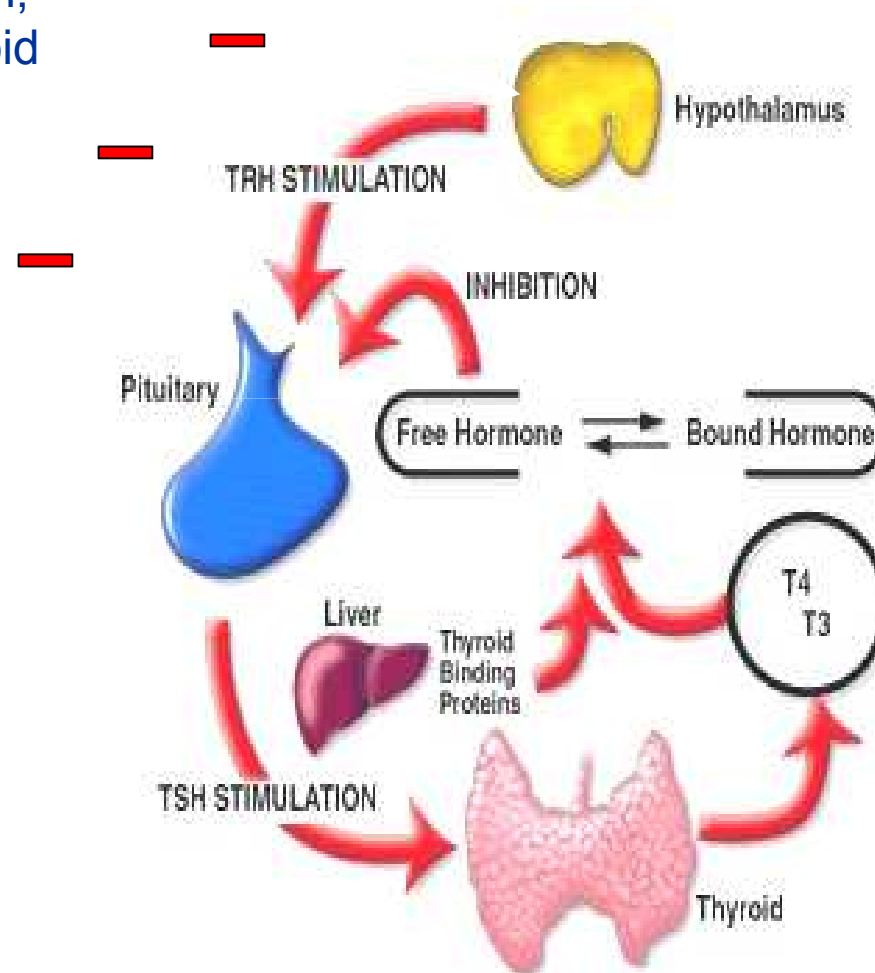
# Thyroid gland

- Thyroid gland normally secretes mainly T4
- 70 % of T3 derived from T4 in peripheral tissues
- T4 is converted to T3 by 5-deiodinase enzyme
- Both T4 and T3 are in bound form (TBG, pre albumin and albumin)
- Only 0.025% of T4 and 0.35% of T3 are free
- Free hormone concentration best correlates with thyroid status
- T4 production is 5-6  $\mu\text{g}/\text{kg}/\text{day}$  in infancy with gradual decrement to 1.5  $\mu\text{g}/\text{kg}/\text{day}$  in adult

# Thyroid Regulation

Somatostatin,  
Glucocorticoid

Dopamine



# Thyroid hormone synthesis

## 1) Iodide pump

- Rate –limiting step in thyroid hormone synthesis which needs energy
- Follicles have in their basement membrane an iodide trapping mechanism which pumps dietary I<sup>-</sup> into the cell
- Normal thyroid: serum iodine is 30-40:1
  - Iodide uptake enhancers:
    - TSH
    - Iodine deficiency
    - TSH receptors antibody
  - Iodide uptake inhibitors
    - Iodide ion
    - Drugs
      - Digoxin
      - Thiocynate
      - perchlorate

# Thyroid hormone synthesis

## 2) Iodide oxidation to iodine and Organification

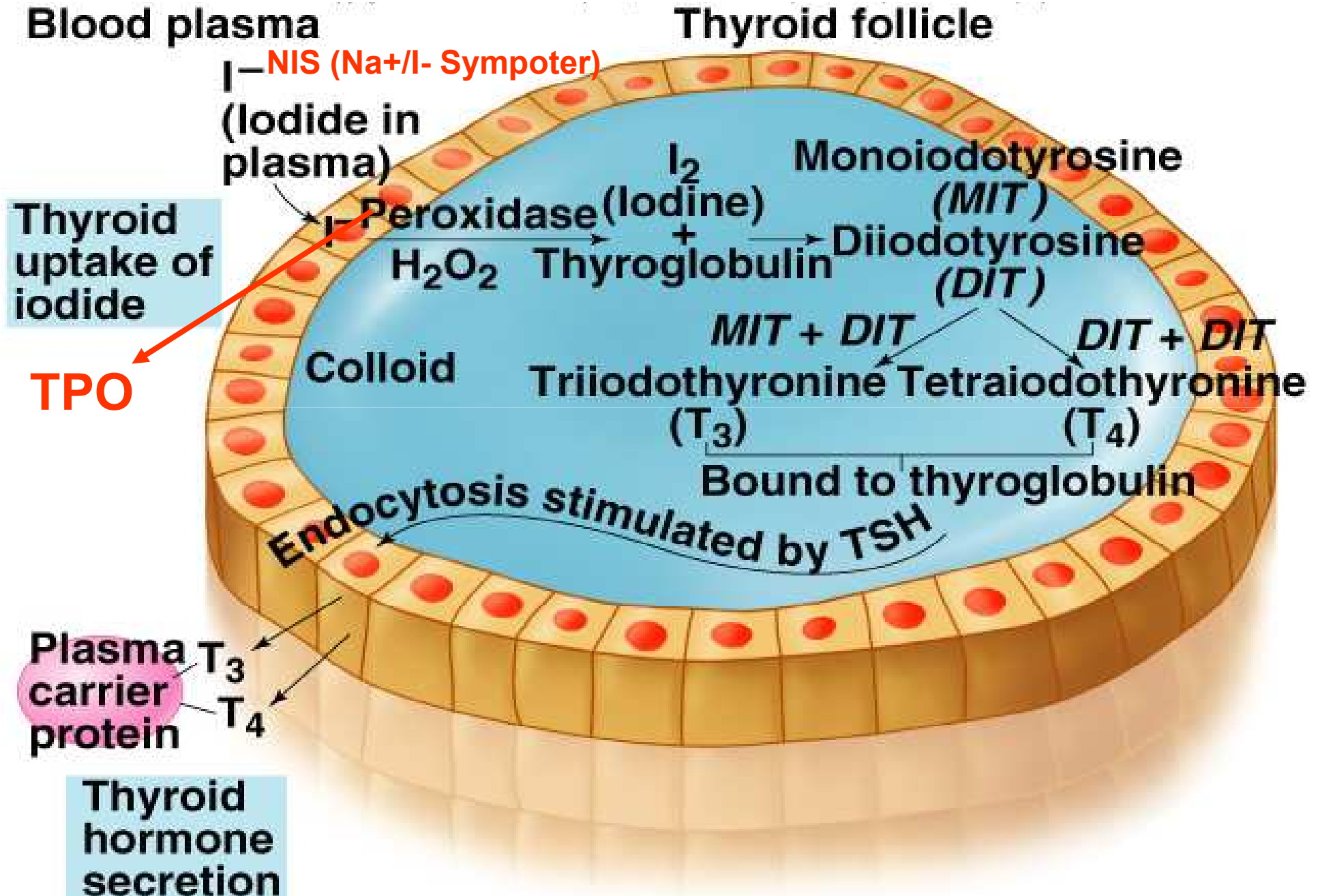
- Inside the cells, iodide is oxidized by peroxidase system to more reactive iodine
- Iodine immediately reacts with tyrosine residue on a thyroid glycoprotein called “thyroglobulin” to form :
  - T1= mono-iodotyrosyl thyroglobulin
  - T2= di-iodotyrosyl thyroglobulin
- Both processes are catalyzed by thyroid peroxidase enzyme

# Thyroid hormone synthesis

## 3) Coupling

- T1 & T2 couple together to form T3 & T4
- MIT + DIT = T3 (Tri-iodothyronine)
- DIT + DIT = T4 (Thyroxine)
- All attached to thyroglobulin and stored in the colloid Thyroglobulin molecule
- This process is stimulated by TSH

# Production of Thyroid Hormones





# Effects of thyroid hormones

- Fetal brain & skeletal maturation
- Increase in basal metabolic rate
- Inotropic & chronotropic effects on heart
- Increases sensitivity to catecholamines
- Stimulates gut motility
- Increase bone turnover
- Increase in serum glucose, decrease in serum cholesterol
- Conversion of carotene to vitamin A
- Play role in thermal regulation

## Increase BMR ( Basal Metabolic Rate )

- ↑ cellular metabolic activity by :
  - ↑ size, total membrane surface & number of mitochondria
- ↑ ATP formation
- ↑ active transport of ions (  $\text{Na}^+$ ,  $\text{K}^+$  )

Promote growth & development of the brain during fetal life and for the first few years of postnatal life

## Carbohydrate metabolism

- enhanced glycolysis, gluconeogenesis,
- GI absorption & insulin secretion

## Fat metabolism

- enhanced fat metabolism
- Accelerates the oxidation of free fatty acids by the cells
- plasma cholesterol, phospholipids & triglycerides

## Body weight

↑ the appetite, food intake, GI motility but ↓ the body weight

- **Cardiovascular system**
  - **vasodilatation**
  - **↑ blood flow**
  - **↑ cardiac output**
  - **↑ heart rate**
- **Respiratory**
  - **↑ the rate and depth respiration**
- **CNS**
  - **extreme nervous & psychoneurotic tendency**
- **Muscle**
  - **make the muscles react with vigor ----->**
  - **muscle tremor ( 10-15 times/sec )**
- **Sleep: extreme fatigue but is difficult to sleep**

# Causes , Clinical Features & Consequences of Hypothyroidism

Congenital Hypothyroidism

Acquired Hypothyroidism





# Etiology

- Congenital
- Acquired
  - Primary
  - Secondary
  - Tertiary

# Congenital Hypothyroidism

- Occurs in about 1/4000 live birth
- Thyroxin is important for CNS development and postnatal growth
- The most frequent cause is congenital absence of the thyroid gland (athyrosis)
- Presentations may include cyanosis, prolonged hyperbilirubinemia, poor feeding, hoarse cry, umbilical hernia, respiratory distress, macroglossia, large fontanelle, and delayed skeletal maturation
- Rarely, neonatal hypothyroidism is transient

# Congenital Hypothyroidism

## Etiology

### 1) Thyroid dysgenesis

#### Idiopathic:

- Commonest cause in 95% of cases
  - Athyreosis (40%)
  - Hypoplasia (40%)
  - Ectopia (base of tongue, midline) (20%)

### 2) Thyroid dyshormonogenesis (A.R) (10%)

### 3) Hypothalamic-pituitary hypothyroidism

- Anencephaly, holoprosencephaly, S.O.D
- idiopathic



# Congenital Hypothyroidism

- 4) Transient hypothyroidism
  - Maternal TRAB
  - Maternal ingestion of goitrogen
- 5) Drugs
- 6) Iodine excess
- 7) Iodine deficiency

# Anti-thyroid Drugs and fetus

- Thionamides
  - PTU & MZT
- Iodide
- Lithium
- Amiodarone
- Radioiodine
  - After 10-12 wk gestation can damage fetal thyroid gland



# Presentations of congenital hypothyroidism

- Macroglossia
- Prolonged hyperbilirubinemia
- Poor feeding
- Hoarse cry
- Decreased activity
- Constipation
- Umbilical hernia
- Dry yellow skin
- large fontanelle
- Delayed skeletal maturation

# Neonatal screening for congenital hypothyroidism

- Routine in most countries worldwide
- Filter paper blood spot measuring TSH
  - Why ??
- Clinical manifestations at birth, usually are subtle or even absent (passive transplacental maternal thyroxin)
- At birth, surge of TSH (stress of delivery) up to 30 -40  $\mu\text{u/ml}$
- Early detection will prevent mental retardation or decreasing IQ of affected neonates
- Thyroxin is important for CNS development from birth till 3 years of life
- Screening program will miss 2ry/ tertiary cases
- The program is hampered by a high rate of false positive results

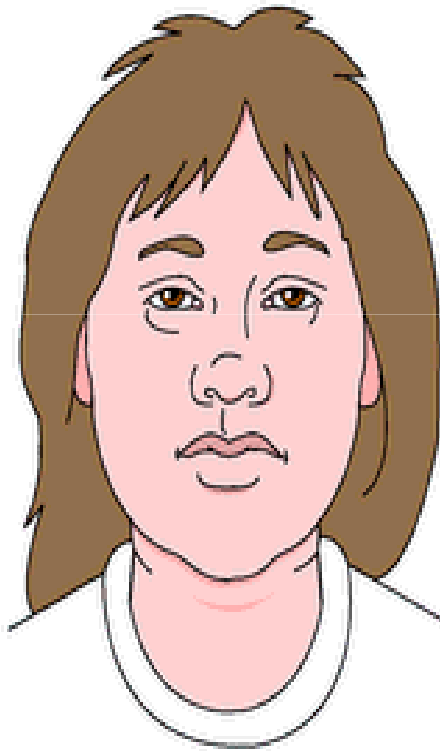
# Acquired Hypothyroidism

- More common than hyperthyroidism
- 99% is primary (< 1% due to TSH deficiency)
- Hashimoto's
  - most common thyroid problem (4% of population)
  - most common cause in iodine-replete areas
  - chronic lymphocytic thyroiditis
  - Associated with TPO antibodies (90%), less commonly Tg antibodies
- Iatrogenic Hypothyroidism from radioactive iodine therapy

# Acquired Hypothyroidism

- Subacute thyroiditis
  - Painful, often radiates to the ear
  - c/o malaise, pharyngitis, fatigue, fever, neck pain/swelling
  - Viral etiology (URI/ pharyngitis)
  - self-limited. Can tx inflammation w/ ASA, NSAID's or steroids
- Suppurative/ Acute Infectious thyroiditis
  - Infections of the thyroid are rare
    - normally protected from infection by its thick capsule
  - Bacterial >> fungal, mycobacterial or parasitic
  - Pt's are acutely ill w/ a painful thyroid gland
    - assoc w/ fever/chills, anterior neck pain/swelling, dysphagia and dysphonia

# Acquired Hypothyroidism



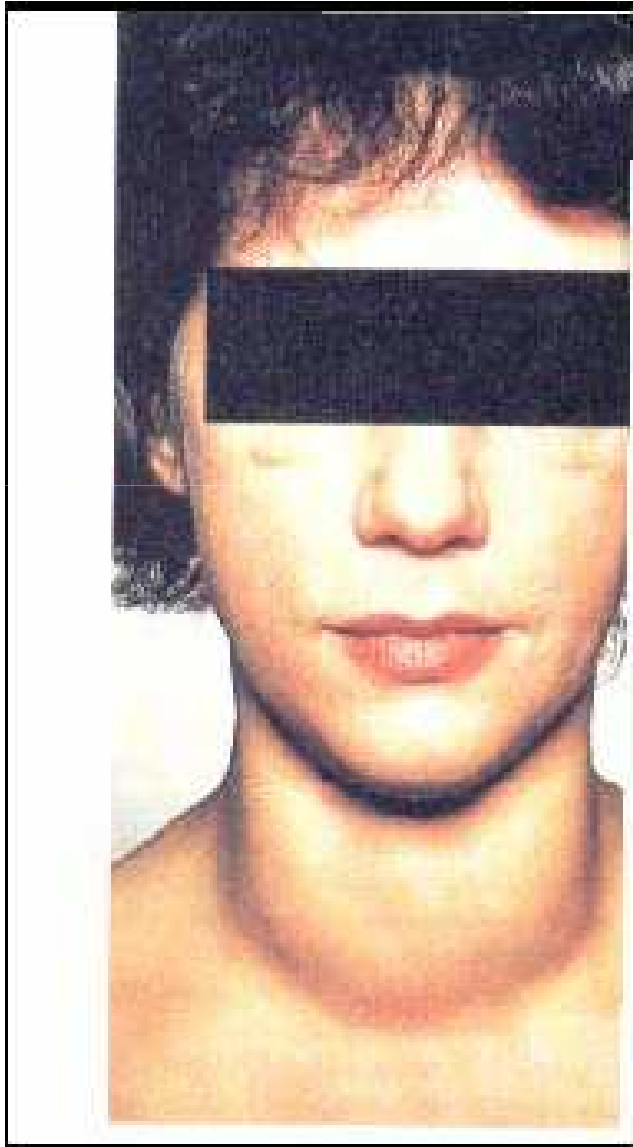
- Symptoms
  - General Slowing Down
  - Lethargy/somnolence
  - Depression
  - Modest Weight Gain
  - Cold Intolerance
  - Hoarseness
  - Dry skin
  - Constipation (↓ peristaltic activity)
  - General Aches/Pains
    - Arthralgias or myalgias (worsened by cold temps)
  - Brittle Hair
  - Menstrual irregularities
    - Excessive bleeding
    - Failure of ovulation
  - ↓ Libido

# Acquired Hypothyroidism

## Examination

- Dry, pale, coarse skin with yellowish tinge
- Periorbital edema
- Puffy face and extremities
- Sinus Bradycardia
- Diastolic HTN
- ↓ Body temperature
- Delayed relaxation of reflexes
- Megacolon (↓ peristaltic activity)
- Pericardial/ pleural effusions
- Congestive heart failure
- Non-pitting edema
- Hoarse voice
- Myopathy

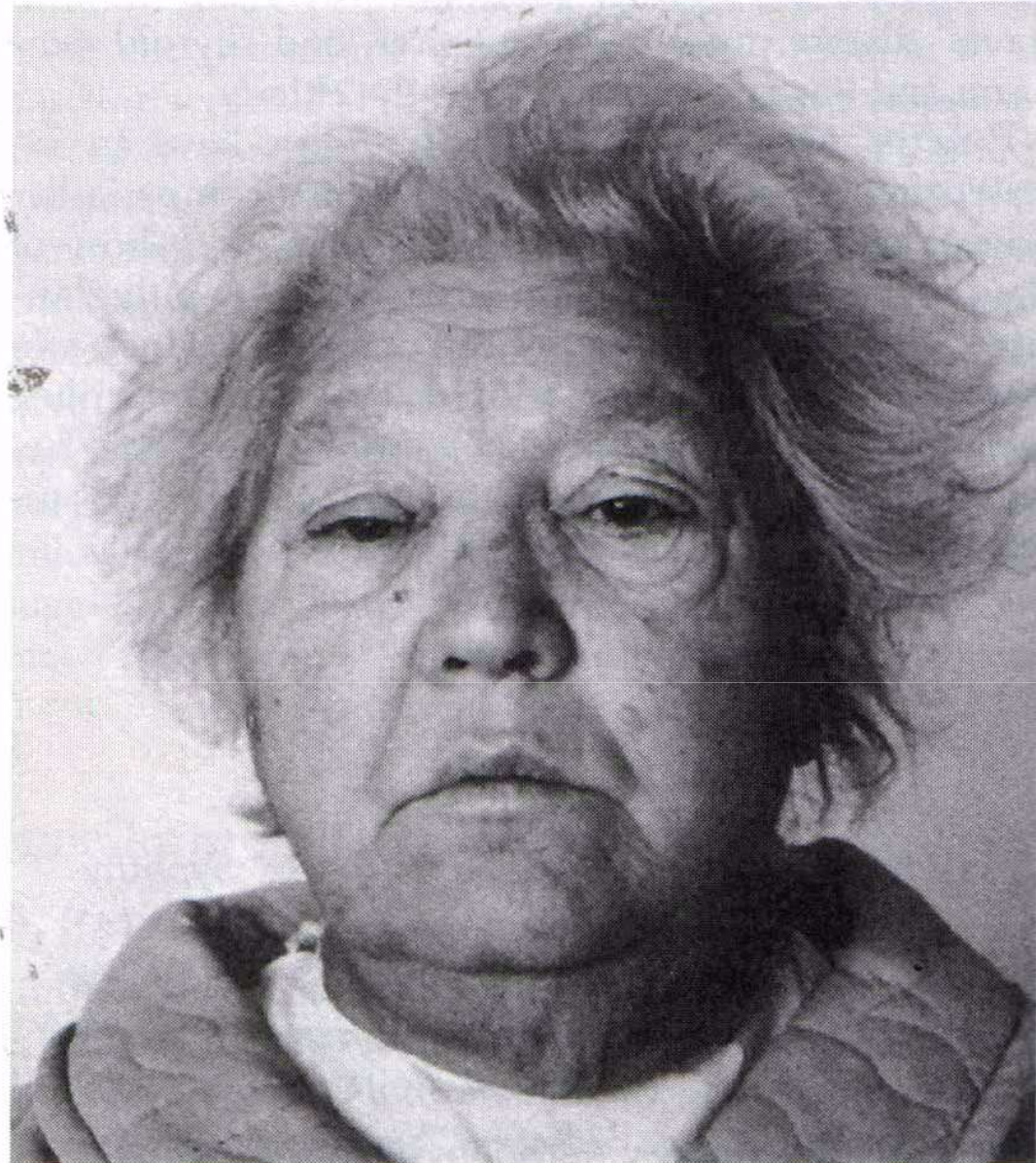
# Goiter



- A swollen thyroid gland
- Assessment;
  - how big, how quickly has it developed, is it smooth or nodular, is it painful, any associated lymph nodes, any sudden changes, is it big enough to cause local symptoms (e.g. breathing problems)



# Myxedema



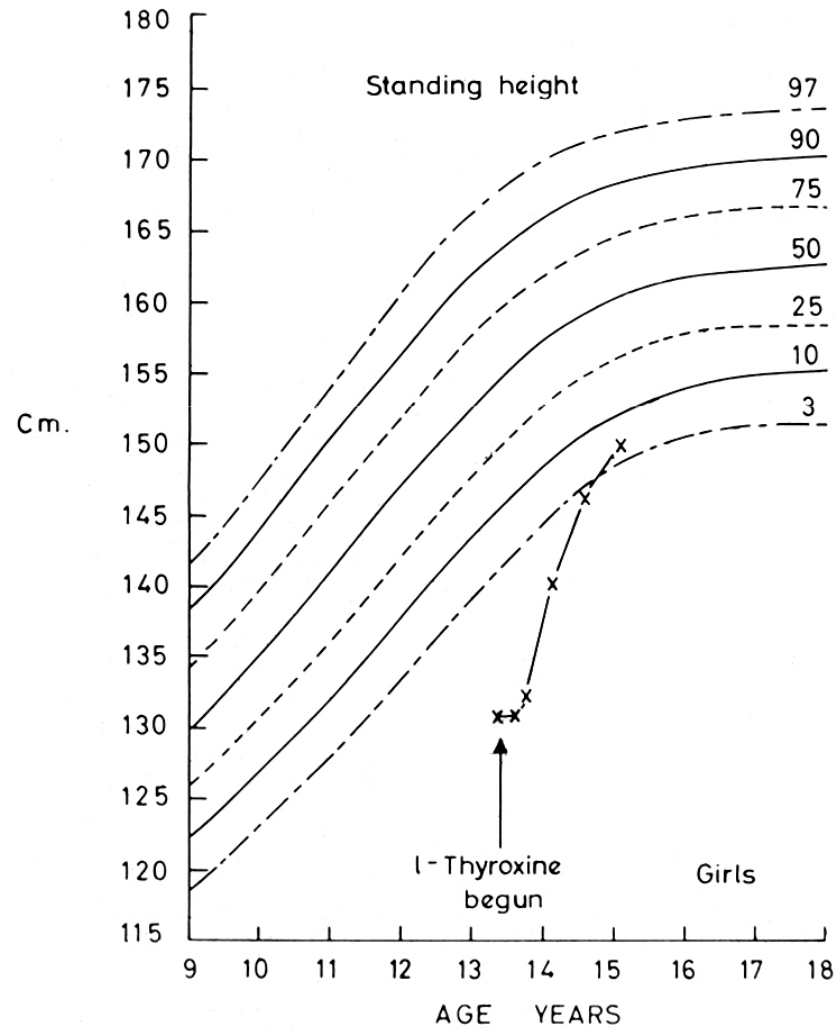
**Figure 20–8.** Myxedema. (Reproduced, with permission, from Greenspan FS, Gardner DG [editors]: *Basic and Clinical Endocrinology*, 6th ed. McGraw-Hill, 2001.)



# Hypothyroidism --- loss of scalp hair



# Hypothyroidism with short stature



# Diagnosis

## Congenital hypothyroidism

- Thyroid hormone level
- TSH
- Thyroid scan

## Acquired Hypothyroidism

- TSH
- fT4
- Thyroid antibodies
- Thyroid ultrasound
- **TSH**: low in secondary hypothyroidism  
high in primary hypothyroidism
- **TRH test**: to differentiate between secondary & Tertiary hypothyroidism

# Euthyroid sick syndrome

- Abnormalities in thyroid function tests observed with systemic non thyroidal illness
- Cytokine mediated
- Reduced TRH release, TSH response, T4 production/release, T4 to T3 conversion and TBG production
- Increased somatostatin secretion
- Inhibitory effects of dopamine and glucocorticoid on TRH action
- Very low T4 values have a poor prognosis

# Treatment

- L-thyroxin replacement should be started as soon as possible
- If treatment is delayed  $> 2$  months of life,  $> 75\%$  risk of hypothyroidism
- On the other hand, delayed treatment of hyperthyroidism will lead to advanced skeletal maturation, craniosynostosis and intellectual deficits
- L-Thyroxin is the main drug for treatment of hypothyroidism, whatever is the cause

# Treatment

Age	L-Thyroxin dose Total dose ( $\mu\text{g}/\text{day}$ )	L-Thyroxin dose $\mu\text{g}/\text{kg}/\text{day}$
0-6	25-50	8-10
6-12	50-75	6-8
1-5	75-100	5-6
6-12	100-150	4-5
>12	150-200	2-3

# Causes , Clinical Features & Consequences of Hyperthyroidism

# Hyperthyroidism (Thyrotoxicosis)

## Definition

- Excessive secretion of T3 & T4
- Affects metabolic processes in all body organs
- Hyperthyroidism is 4-10 times more prevalent in women
- Most common endocrine disease second only to diabetes as the most occurring endocrine disease



# Thyrotoxicosis

## Causes

### Transient

1. Neonatal thyrotoxicosis
2. Infectious : Acute & subacute thyroiditis
3. Drug – induced: Amiodarone, interferon & interleukin
4. Iatrogenic

# Thyrotoxicosis

## Causes

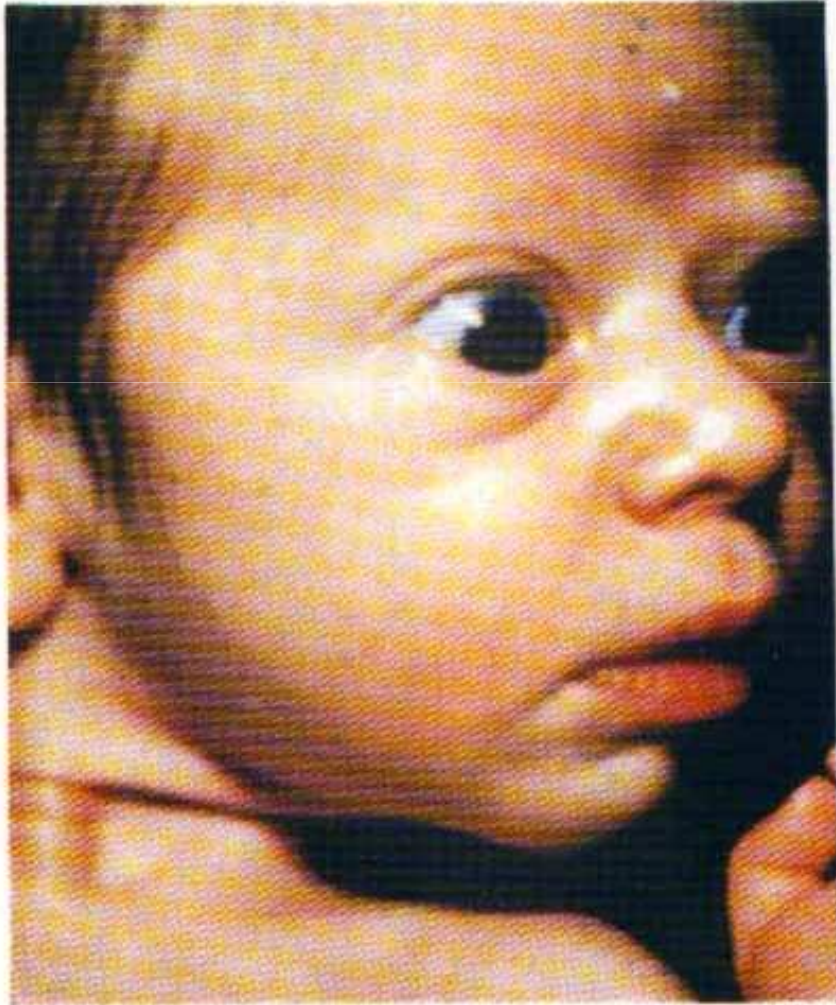
### Persistent

- 1.Graves' disease
- 2.Toxic multinodular goiter
- 3.Toxic solitary adenoma
- 4.Central (pituitary origin)

# Neonatal Thyrotoxicosis

- Only occur with 5% of thyrotoxic mothers
- Severity consistent in future pregnancies
- 20% mortality if untreated
- Evolves rapidly, evident by day 7 of life, unless TRAB blocking antibody is present
- Associate with cranial synostosis and learning difficulties, if not treated
- Fetal thyrotoxicosis in rats leads to abnormal CNS myelination
- Parents should be aware of potential learning problems (early school years should be monitored)

# Neonatal hyperthyroidism born to mother with Graves' disease



# Grave's disease

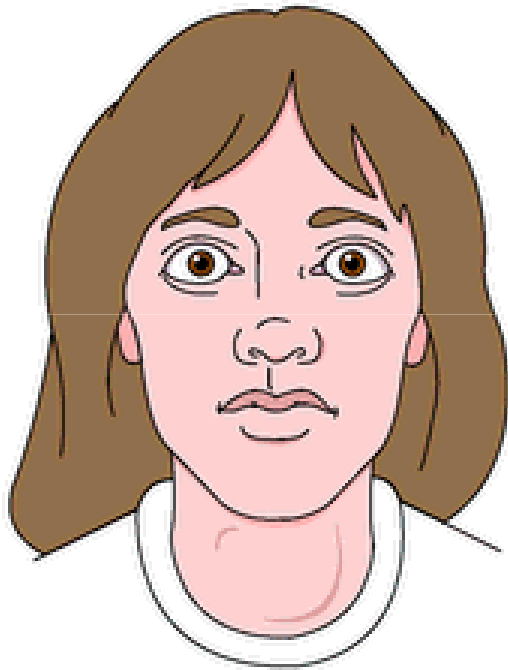
## Pathogenesis

- T-cell dependent autoimmune disease
- 60% have HLA association with A1, B8, DR3, DR4, DR5
- Autoimmune disorder that results in production of antibodies directed against thyroid antigens:
  - TSH receptors
  - Thyroglobulin
  - Thyroid peroxidase

# Subacute Thyroiditis

- Clinical course lasts weeks to months
- Acute phase (2-6/52) with clinical and biochemical hyperthyroidism
- Recovery phase (weeks-months) transient hypothyroidism then euthyroidism
- Clinically, history of sore throat, fever, tender goiter, cervical lymphadenopathy
- High ESR, negative antibodies and absent radioactive I<sup>131</sup> uptake

# Hyperthyroidism

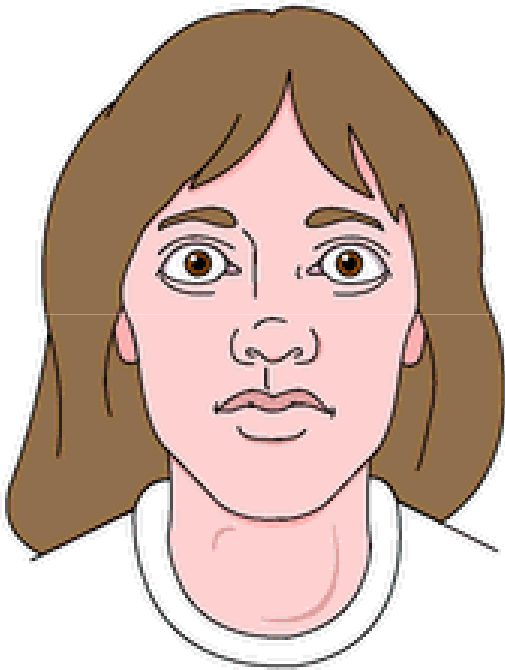


- May result in significant morbidity, mortality & even death
- Symptoms
  - Jittery, shaky, nervous
  - Difficulty concentrating
  - Emotional lability
  - Insomnia
  - Rapid HR, palpitations, Feeling Hot
  - Weight Loss
  - Diarrhea
  - Fatigue
  - Menses : lighter flow, shorter duration

# Hyperthyroidism

- Exam

- Eye findings (20%)
- Goiter
- Thyroid bruit or thrill
- Tachycardia: Sinus Tachycardia, Atrial Fibrillation
- Flow murmur
- Systolic hypertension
- Hyperreflexia
- Tremors
- Proximal muscle weakness
- Clubbing
- Onycholysis (<1%)
  - separation of nail from the nailbed
- Dermopathy (1%)





# Thyrotoxicosis

- Heart: Increased heart rate, contractility and cardiac output
- Skeletal muscles: Proximal myopathy, easy fatigability and muscle atrophy
- Gonads: Irregular menstrual cycles, impotence
- Liver: Low cholesterol LDL & apolipoprotein
- Bone: Increased bone turnover, osteoporosis & increased risk of fracture

# Grave's ophthalmopathy

- The pathogenesis of infiltrative ophthalmopathy is poorly understood
- It may occur before the onset of hyperthyroidism or as late as 15 to 20 years
- The clinical course of ophthalmopathy is independent of the clinical course of hyperthyroidism
- Infiltrative ophthalmopathy may result from immunoglobulins directed to specific antigens in the extraocular muscles & orbital fibroblasts
- The antibodies are distinct from those initiating Graves'-type hyperthyroidism

## Clinical Characteristics of Exophthalmos

- ◆ Proptosis
- ◆ Corneal Damage
- ◆ Periorbital edema
- ◆ Chemosis
- ◆ Conjunctival injection
- ◆ Extraocular muscle impairment
- ◆ Optic neuropathy



## Graves' Disease

- ◆ Goiter
- ◆ Hyperthyroidism
- ◆ Exophthalmos
- ◆ Localized myxedema
- ◆ Thyroid acropachy
- ◆ Thyroid stimulating immunoglobulins



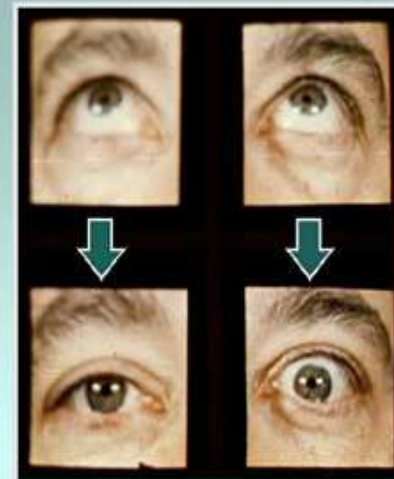
## Clinical Characteristics of Goiter in Graves' Disease

- ◆ Diffuse increase in thyroid gland size
- ◆ Soft to slightly firm
- ◆ Non-nodular
- ◆ Bruit and/or thrill
- ◆ Mobile
- ◆ Non-tender
- ◆ Without prominent adenopathy



## Lid Lag in Thyrotoxicosis

Normal      Lid Lag



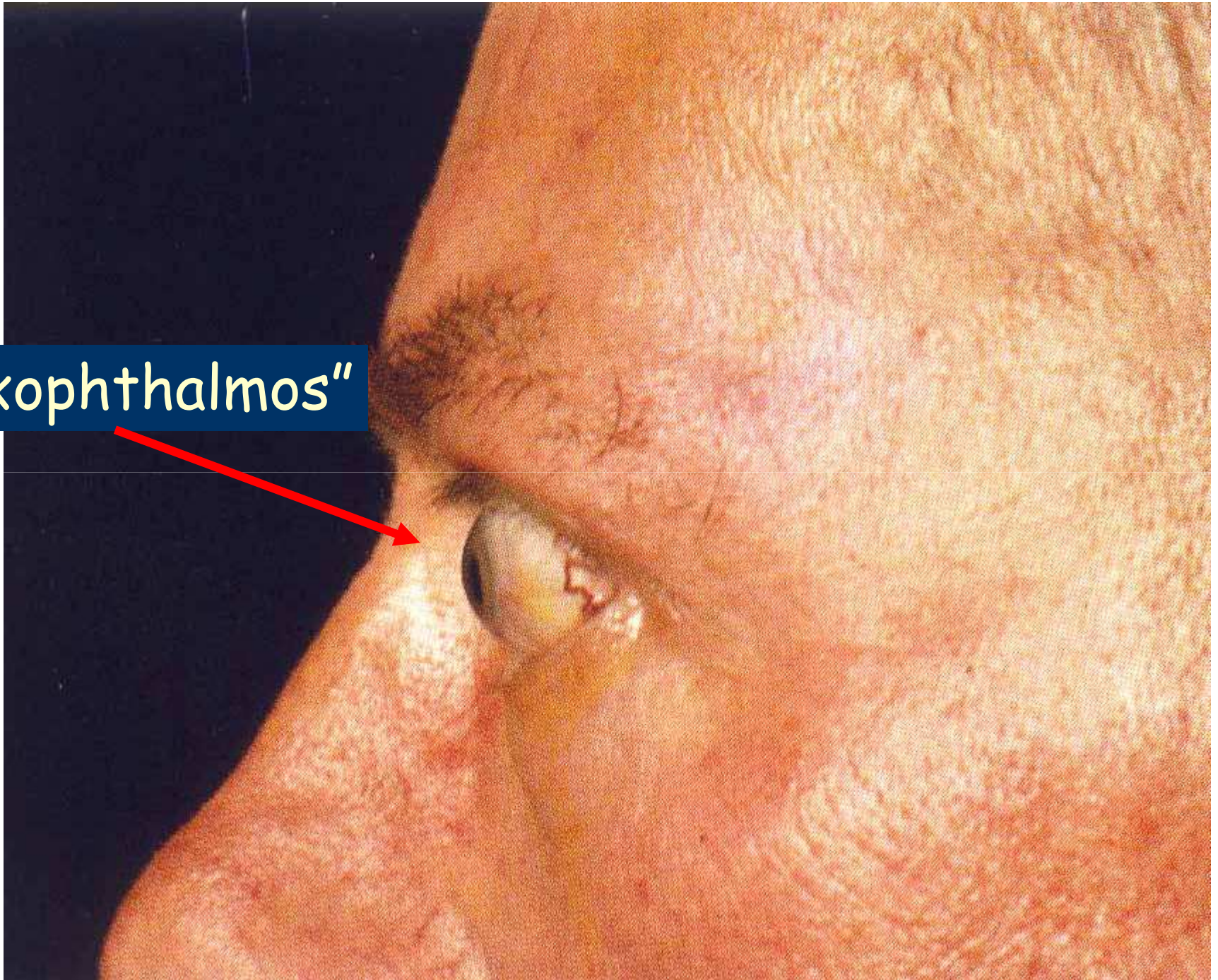
# Hyperthyroid Eye Disease



- Hyperthyroidism (any cause)
  - Lid lag, lid retraction and stare
  - Due to increased adrenergic tone stimulating the levator palpebral muscles.
- True Graves' Ophthalmopathy
  - Proptosis
  - Diplopia
  - Inflammatory changes
    - Conjunctival injection
    - Periorbital edema
    - Chemosis
  - Due to thyroid autoAb's that cross-react w/ Ag's in fibroblasts, adipocytes, + myocytes behind the eyes.



"Exophthalmos"

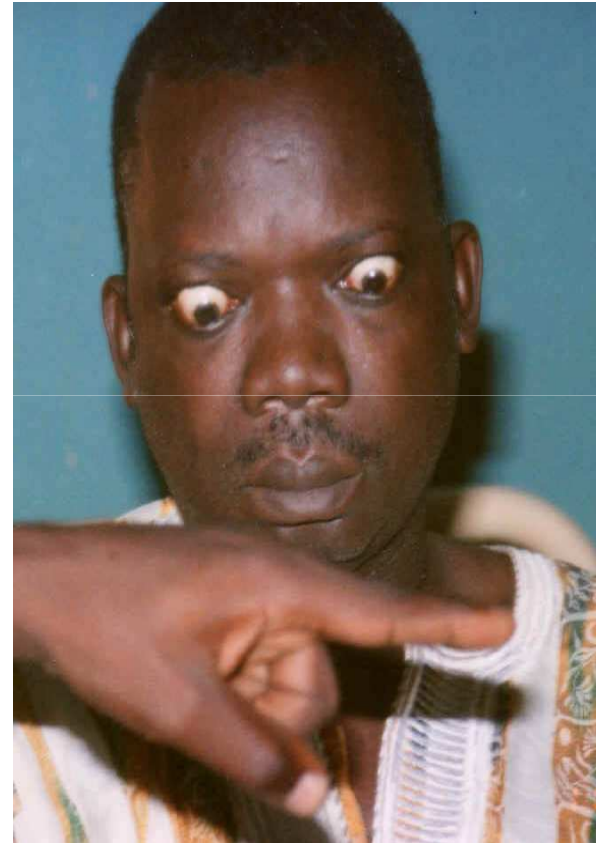


# Grave's ophthalmopathy

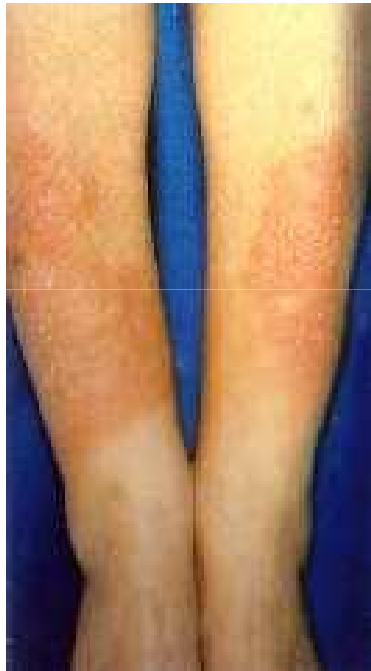




# Hyperthyroid Eye Disease



# Graves' Dermopathy



## Thyroid Dermopathy

- Thickening and redness of the dermis
  - Due to lymphocytic infiltration



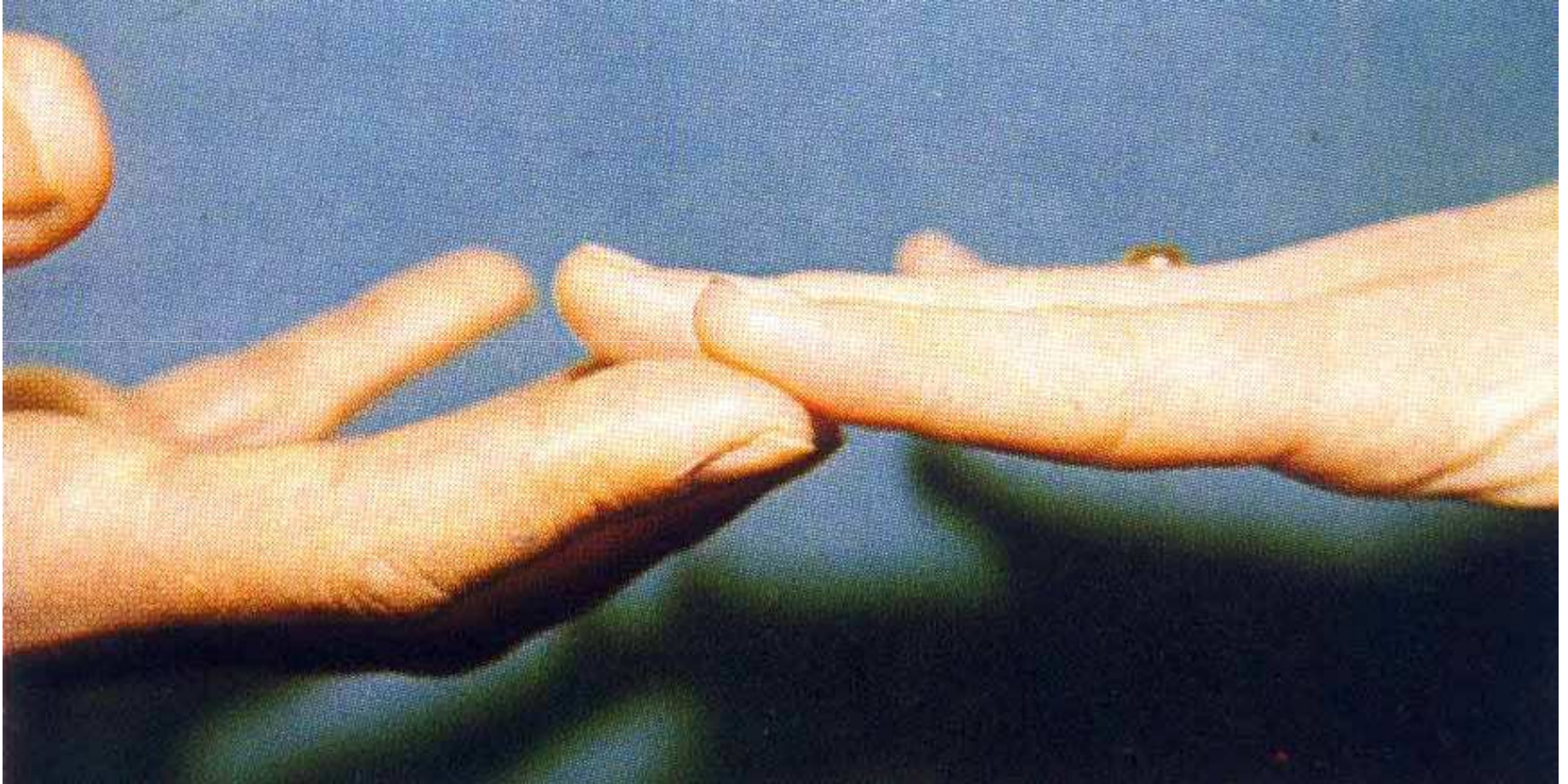
# Thyroid Acropachy



Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner  
Elsevier Science Ltd

**Thyroid acropachy. This is most marked in the index fingers and thumbs**

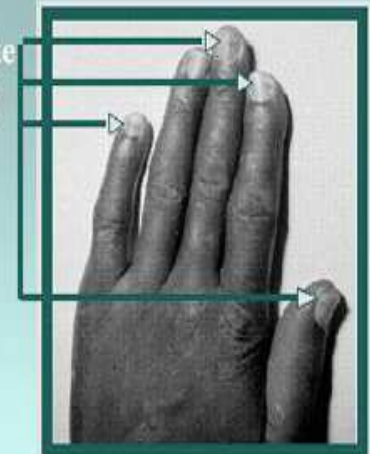
# Tremor of the hand





## Onycholysis of Thyrotoxicosis

Distal separation of the nail plate from nail bed (Plummer's nails)



## Thyroid Acropachy

- ◆ Clubbing of fingers
- ◆ Painless
- ◆ Periosteal bone formation and periosteal proliferation
- ◆ Soft tissue swelling that is pigmented and hyperkeratotic

Periosteal Proliferation



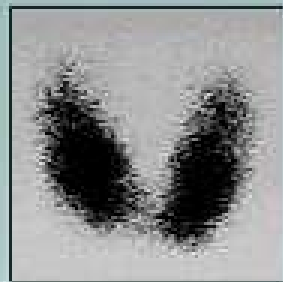
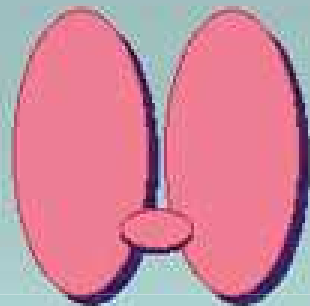
Clubbing of fingers



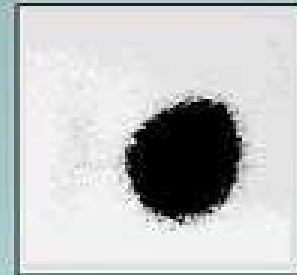
# Diagnosis

- TSH level usually  $< 0.05 \mu\text{u} / \text{ml}$
- 95 % of cases, high FT4 & FT3
- In 5% high FT3 with normal T4 (T3 Thyrotoxicosis)
- Thyroid receptor (TRAB) are usually elevated at diagnosis
- Antibodies against thyroglobulin, peroxidase or both are present in the majority of patients

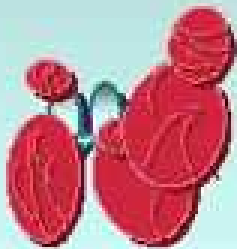
# Thyroid Scan in Thyrotoxicosis



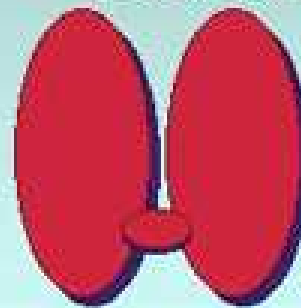
**Graves' Disease**



**Follicular Adenoma**



**Multinodular Goiter**



**Subacute Thyroiditis**

# Thyrotoxicosis- Treatment

- Three modalities for more than last 50 years
- Radioactive iodine, antithyroid drugs & surgery
- None is optimal
- None interrupts the autoimmune process
- Each has a drawbacks
- There is no treatment for underlying cause
- No other research options so far

# Neonatal Thyrotoxicosis

## Treatment

### 1) Lugol's iodine

- 1 drop tid for 1-2 / 7
- Dramatic coarse therapy
- Blocks T4 release, synthesis and I uptake (Wolf Chaikoff effect)

### 2) Propranolol

### 3) Carbimazole

will take several days to have an effect on T4 synthesis

# Hyperthyroidism (Treatment)

## 1) $\beta$ -blockers (symptom control)

- Propranolol (Inderal ®)
- Atenolol (Tenormin ®)
- Metoprolol (Lopressor ®)

## 2) $^{131}$ -RAIA (70% thyroidologists prefer)

- Dosing
  - Graves: 10-15 mCi
  - Toxic MNG/Adenoma: 20-30 mCi
- Absolute contraindications
  - Pregnancy and lactation (excreted in breast milk)!
- Pregnancy should be deferred for at least 6 months following therapy with radio-active  $^{131}$
- It is advisable to avoid  $^{131}$ -Radio-active iodine therapy in patients with active moderate → severe Graves' ophthalmopathy.



# Hyperthyroidism (Treatment)

## 3) Antithyroid Drugs (30% thyroidologists prefer)

- Propylthiouracil (PTU)
  - 100 mg bid-tid to start
- Methimazole
  - 10X more potent than PTU
  - 10 mg bid-tid to start
- Complications of ATD's
  - Agranulocytosis (1/200-500)
    - usually presents w/ acute pharyngitis/ tonsillitis or pneumonia.
  - Rash
  - Hepatic necrosis, Cholestatic jaundice
  - Arthralgia

# Hyperthyroidism (Treatment)

## 4) Surgery (sub-total thyroidectomy)

- Indications
  - Patient preference
  - Large or symptomatic goiters
  - When there is question of malignancy
- Need to be euthyroid prior to surgery
  - To ↓ the risk of arrhythmias during induction of anesthesia
  - To ↓ the risk of thyroid storm post operatively
  - ATD's +  $\beta$ -blockers
- Risks
  - Permanent hypoparathyroidism
  - Recurrent laryngeal nerve problems
  - Permanent hypothyroidism

