THYROID DISEASES

For Class- B.Pharmacy 2nd Semester

Subject- Pathophysiology (BP204T)

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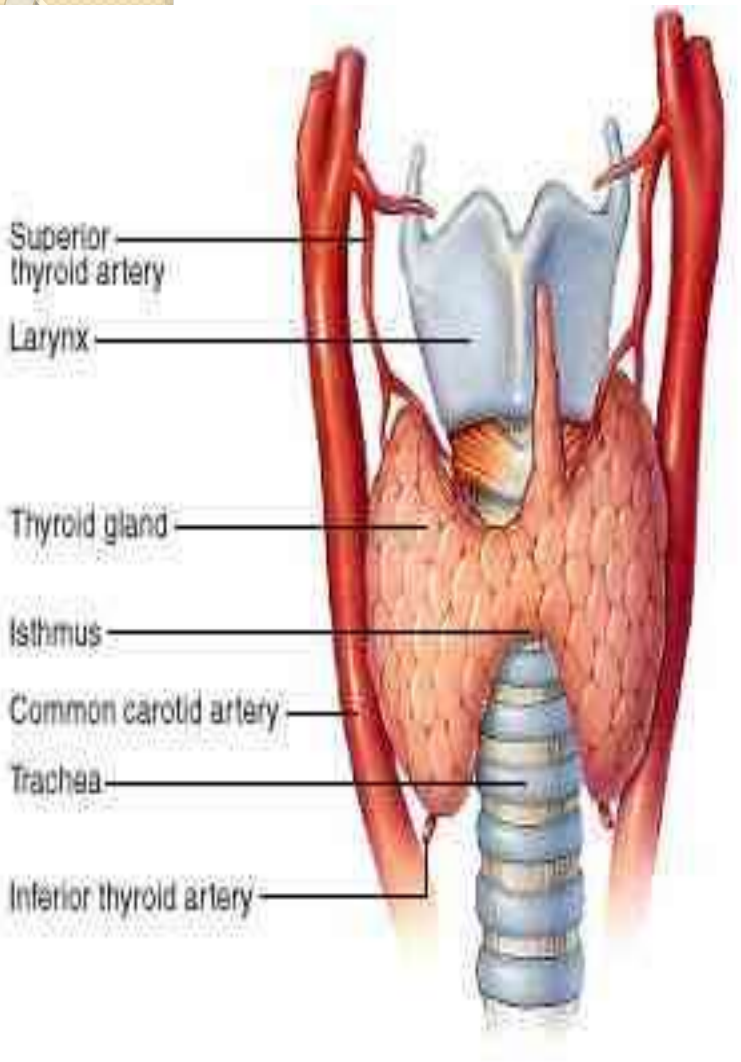
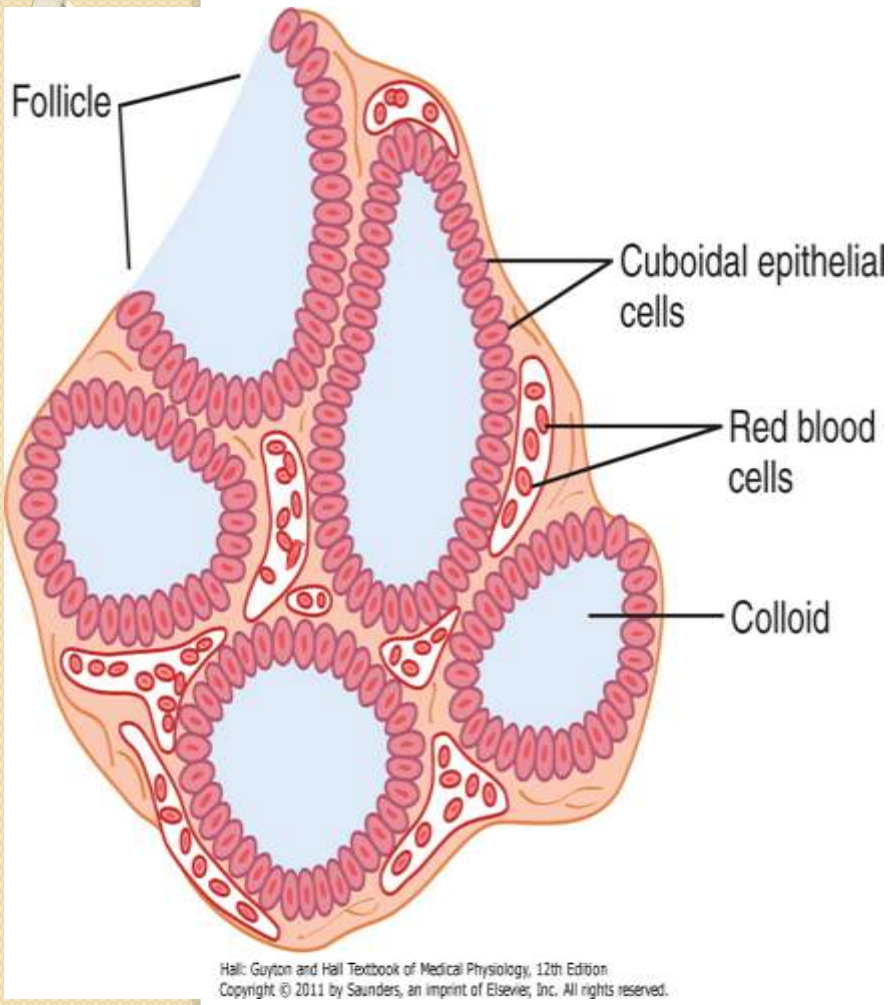
Thyroid gland



- The thyroid gland is one of the largest endocrine glands.
- The thyroid gland is located immediately below the larynx and anterior to the upper part of the trachea. It weighs about 15-20g.
- It consists of 2 lateral lobes connected by a narrow band of thyroid tissue called the isthmus.
- The isthmus usually overlies the region from the 2nd to 4th tracheal cartilage.

- 4 tiny parathyroid glands located posteriorly at each pole of thyroid gland.
- **Hormone secreted-**
- Thyroxine(T4)
- Tri iodothyronine (T3)
- Reverse T3
- Calcitonin

HISTOLOGY



- The lobes of the thyroid contain many hollow, spherical structure called follicles, which are the functional units of the thyroid gland.
- Between the follicles there are C cells, which secrete calcitonin.
- Each follicle is filled with a thick sticky substance called colloid.

- The major constituent of colloid is a large glycoprotein called thyroglobulin.

- Unlike other endocrine glands, which secretes their hormones once they are produced, the thyroid gland stores considerable amount of the thyroid hormones in the colloid until they are needed by the body.

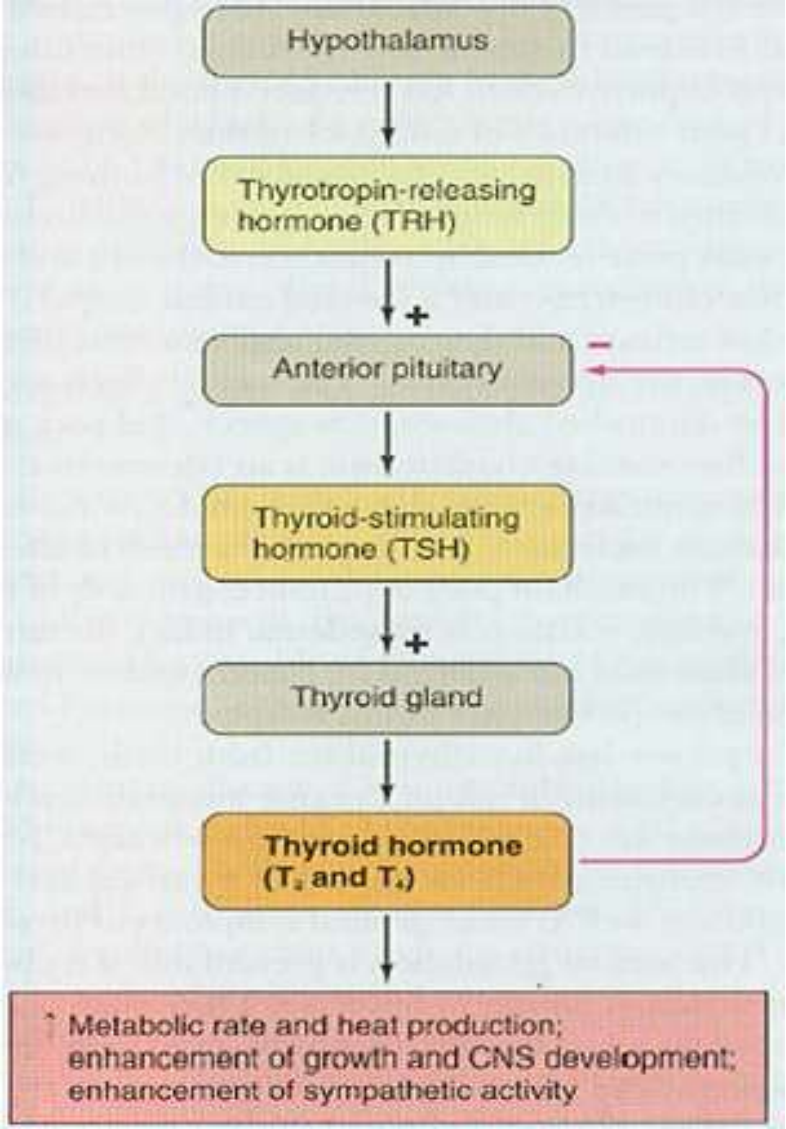
Iodine Metabolism

- Raw material, essential for thyroid synthesis
- Source-
- Sea foods, milk, iodized salt.

- Daily req- 100-200 microgram/day
- From the total amount of Iodine entering the ECF, 20% enters the thyroid gland and 80% excreted in urine.
- Thyroid contain 95% of total iodine content of body.

- Thyroid gland stores enough hormone to maintain euthyroid state for 3 months.
- Daily secretion-
- 93% Thyroxine (3-8 mgm/dl)
- 7% T3(0.15 mgm/dl)
- T3 is 4 times more potent than T4

REGULATION OF THYROID HORMONE SECRETION



Thyrotropin Releasing Hormone (TRH)

- A tripeptide: pyro-Glutamate-histidine-proline-amide
- Synthesized from a 29 kDa precursor protein
- Produced by hypothalamus

Thyrotropin (TSH; Thyroid Stimulating Hormone)

28 kDa glycoprotein dimer composed of alpha and beta chains.

Autoregulation

- Depending upon the body Iodine availability-
- ↑ Iodine ingestion- Thyroid gland depressed
- ↓ Iodine ingestion- Hyperactive
- High dose of iodine ↓ the formation and release of thyroid hormone, called **Wolff Chaikoff effect.**
- Done by-
- ↓ iodine trapping
- Preventing oxidation of Iodide to iodine.
- Preventing incorporation of iodine to hormone

SYNTHESIS, STORAGE & SECRETION

- Iodine trapping
- Synthesis and secretion of thyroglobulin
- Oxidation of iodine
- Organification of thyroglobulin
- Coupling reaction
- Storage
- Secretion

Iodide trapping

- Plasma iodide enters through the sodium iodide symporter (NIS) at the baso lateral membrane of thyrocyte facing the capillaries.
- It transport 2 Na^+,1 I^- into cell, against electrochemical gradient.
- Energy given- Na+ K+ ATPase pump
- Process- secondary active transport
- TSH promote this uptake.
- Anti thyroid drugs- Thiocynate,Perchlorate inhibit this

Synthesis and Secretion of Thyroglobulins

- •Thyroglobulin (Tg), a large glycoprotein, is synthesized within the thyroid cell by RER, then modified in GA and packed into secretary vesicle.
- Tg released in the lumen by exocytosis.
- Each molecule of Tg- 123 tyrosine residue, which serve as subtract for iodine for synthesis of hormone.

Oxidation of iodine

- Once within the gland, iodide rapidly moves to apical surface of epithelial cell.
- From there ,it is transported into the lumen of follicle by Chloride Iodide ion counter transporter Pendrin.
- Thyroid peroxidase (TPO) sits on the luminal membrane. Iodide ion immediately oxidized into iodine by TPO and its accompanying H2O2.
- Anti thyroid drugs- Thiouracil,Methemazole inhibit this conversion.

Organification of thyroglobulin

- Binding of iodine with Tg molecule
- Oxidized iodine bind directly with tyrosine.
- After release Tg into lumen, Iodine binds about 1/6 th tyrosine residue in Tg.
- Iodinates specific tyrosines in Tg, creating mono-and di-iodotyrosines.

Coupling reaction

- •The iodotyrosines combine to form T3 and T4 within the Tg protein.
- TPO both involve in iodination and coupling reaction.
- MIT+ DIT→T3
- DIT+ DIT→ T4
- DIT+MIT→ reverse T3

Storage

- MIT, DIT, T3,T4 are all in peptide linkage with Tg which occurs as a colloidal aggregate with in the follicle.

- Store is sufficient to supply for 2-3 months.

Secretion

- Tg itself is not release into circulation.
- T3,T4 must cleaved from Tg and release.
- The apical surface of thyroid cells send pseudopodia which close around small portion of colloid to form pinocytic vesicle that enter apex of thyroid cell by endocytosis.
- Endocytosis facilitated by Tg receptor Megalin on apical membrane.
- Lysosome fuse with this vesicle to form digestive vesicle.

- Protease digest the Tg molecule releasing MIT, DIT, T3,T4
- As T3, T4 lipid soluble,they diffuse through plasma membrane into interstitial fluid then into blood.
- MIT, DIT rapidly deiodinated in follicular cell by the enzyme Iodotyrosine deiodinase.
- Iodine is reutilized to produce thyroid hormone.

- In patient with congenital absence of deiodinase enzyme MIT, DIT appear in urine and there are symptoms of iodine deficiency.
- Salivary gland, gastric mucosa,placenta,cilliary body of eye,choroid plexus, mammary gland, post pitutary and adreanal cortex also transport iodide.
- There uptake are not dependent by TSH and they can't form thyroid hormone.

Plasma thyroid hormone binding proteins

- ~99.97% of plasma T4 and 99.7% of T3 are non-covalently bound to proteins.
- Thyroxine Binding Globulin(TBG) is the major binding protein for T4 and T3. TBG's affinity for T4 is ~10-fold greater than for T3.
- Transthyretin also carries some T4.
- Albumin carries small amounts of T4 and T3.
- TBG, transthyretin and albumin are made

Importance of free versus protein-bound hormone

- Only free T4 and free T3 are biologically active and regulated by feedback loops.
- Therefore conditions that alter TBG levels alter total T4 and T3, but do not alter free T4 and free T3.
- Pregnancy
- Acute hepatitis
- Chronic liver failure

PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

- Metabolic rate and heat production:
  - ↑ metabolic activities
  - ↑ O_2 consumption to most metabolically active tissues
  - BMR can ↑ by 60 – 100%
  - Since ↑ metabolism results in ↑ heat production → thyroid hormone effects is calorigenic
- Intermediary metabolism:
  - Modulates rates of many specific reactions involved in metabolism

Sympathomimetic effect-

- Sympathomimetic: any action similar to one produced by the sympathetic nervous system
- Thyroid hormone ↑ target cell responsiveness to catecholamines

The cardiovascular system:

- ↑ the heart's responsiveness to circulating catecholamines.
- ↑ heart rate and force of contraction → ↑ CO
- In response to the heat load → peripheral vasodilation to eliminate generation of extra

TABLE 1 ■ Physiologic Effects of Thyroid Hormones[1,4,7]

System	Effects
Cardiovascular	Increases heart rate Increases the force of cardiac contractions Increases cardiac output as a result of the previous two effects Promotes peripheral vasodilation
Central nervous	Essential for normal brain development, such as cerebellar growth and nerve myelination Necessary for normal intellectual development in infants Necessary for emotional stability in adults
Gastrointestinal	Increases appetite Increases secretion of "digestive juices" Increases gastric motility
Hematopoietic	Influences erythropoiesis
Metabolic	Profoundly affects oxidative metabolism Increases oxygen consumption in all tissues except the brain, gonads, and spleen Promotes heat production Influences synthesis and degradation of carbohydrate, fat, and protein
Respiratory	Influences lung development Necessary for surfactant production Increases rate and depth of respirations
Skeletal	Indirectly promotes growth formation by actions on the pituitary gland Acts synergistically with growth hormone and other growth factors that promote bone formation Directly affects skeletal maturation **Necessary** for progression of tooth development and eruption
Skin	Necessary for growth and maturation of the epidermis and hair follicles

Laboratory Evaluation and Imaging Studies of Thyroid Function

- Serum T4
- Serum T3
- TSH
- Anti-thyroid antibodies
- Thyroid stimulating Immunoglobulins
- Thyroid uptake and scan
- Thyroid Ultra sound

Serum Thyroxine (T4)

- Measure free T4, not total T4
- Only free T4 is biologically active
  - Conditions that alter TBG alter total T4 but not free T4
  - Pregnancy raises total T4
  - Chronic liver failure lowers total T4

•High in hyperthyroidism

- Low in hypothyroidism

Serum Triiodothyronine (T3)

- High in hyperthyroidism
- •Low in hypothyroidism
- But generally not worth measuring in hypothyroidism because T3 is less sensitive and less specific than the decrease in free T4

- •Measurement of free T3 is preferable to total T3.

Serum Thyrotropin (Thyroid Stimulating Hormone; TSH)

- TSH is LOW in hyperthyroidism
- TSH is HIGH in hypothyroidism

- TSH is the most sensitive screening test for hyperthyroidism and primary hypothyroidism
- TSH within the normal range excludes these diagnoses

Antithyroid Antibodies

- Antimicrosomal antibodies (***thyroid peroxidase antibodies)***
- •Anti-thyroglobulin antibodies
- •Present in ~95% of Hashimoto's and ~60% of Graves' patients at the time of diagnosis
- •Usually not very helpful in making a diagnosis or guiding therapy

Thyroid Stimulating Immunoglobulins

- Is present in Graves' disease

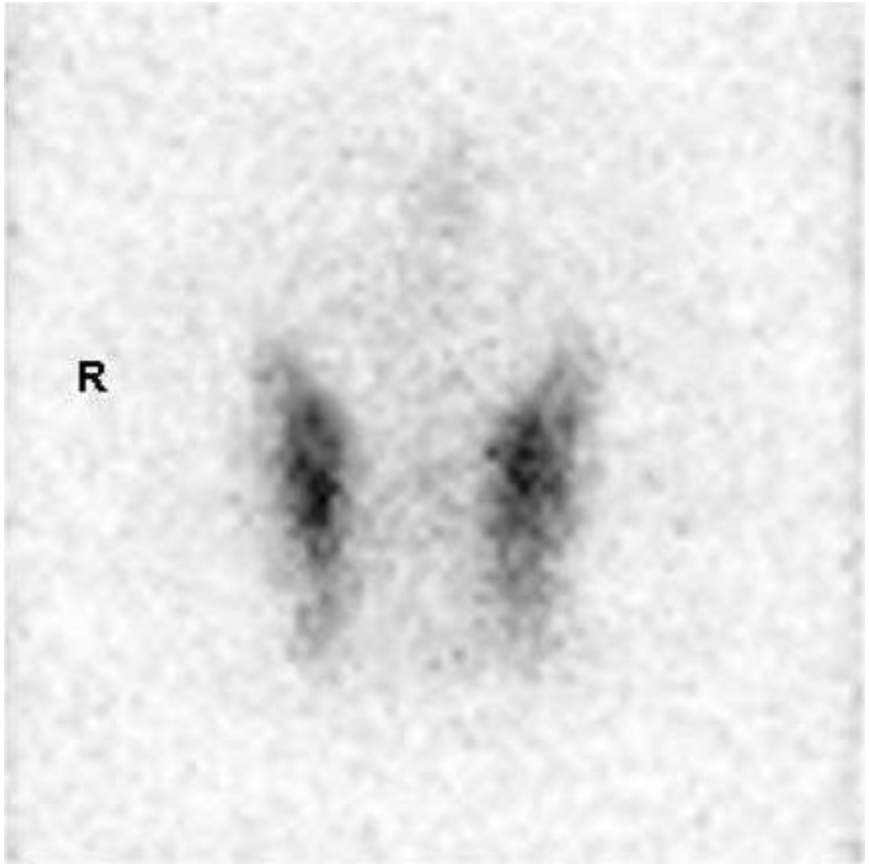
Imaging studies

- Thyroid uptake and scan
- •Thyroid US
- •Neck CT

Thyroid uptake and scan

- I-123
- I-131
- Technetium 99

- *Radiotracer:
- Injectable IV: Technetium (15 min later: scan)
- Oral: 131 I and 123 I;(24 h later: scan/uptake)
- Scan: structure
- Uptake: function
- Obtain pregnancy test before the test



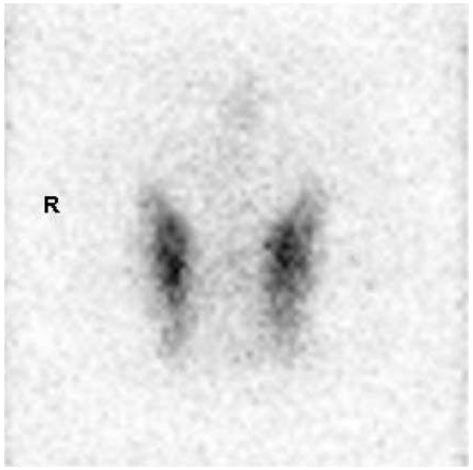
Radioiodine Uptake

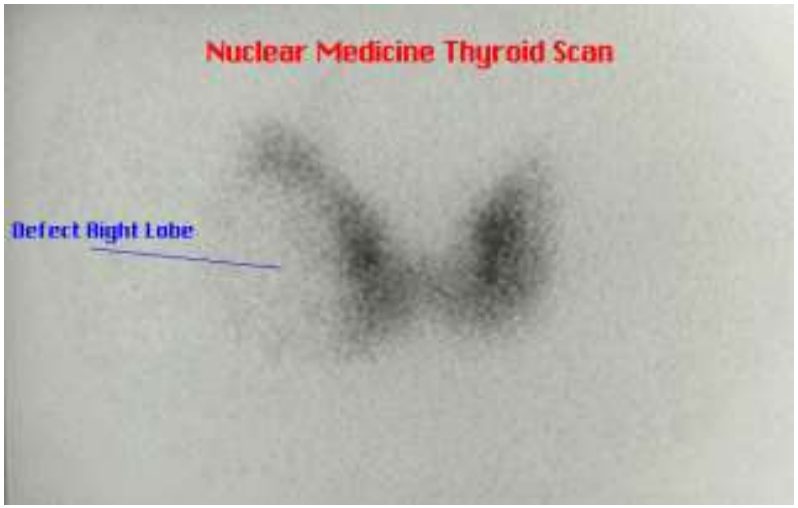
- Used to evaluate the cause of hyperthyroidism
- High if the thyroid is hyper-functioning, e.g. Graves' disease
- Low if thyroid hormone is leaking out of damaged thyroid cells (subacute thyroiditis) or the patient is taking excess exogenous thyroid hormone

- Expressed as a *NUMBER(e.g., 35%)*
- Used to calculate the dose of I-131 to treat hyper-functioning thyroid tissue or cancer.

Thyroid Scan (nuclear medicine)

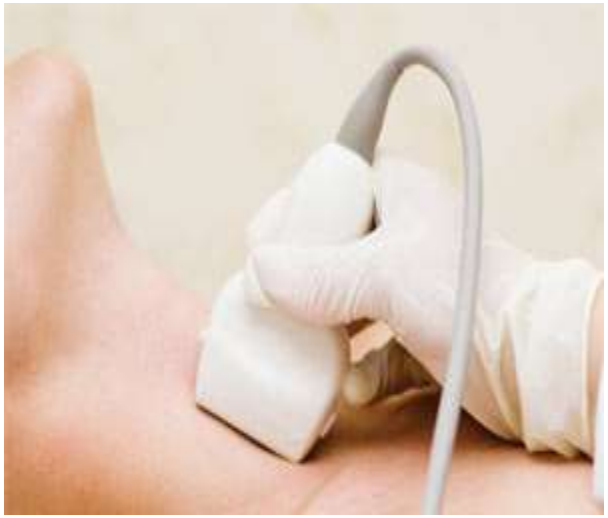
- Primary use is to determine whether palpated nodules are functional or non-functional.
- “Hot” nodules concentrate the radionuclide and are essentially always benign.
- “Cold” nodules are usually benign but are sometimes malignant.
- The majority, perhaps 90%, of palpable nodules are cold.

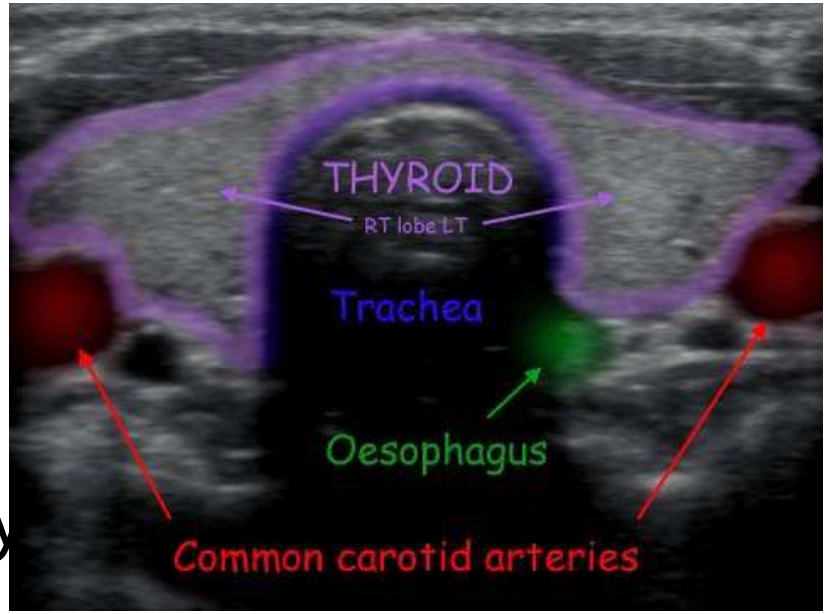




Thyroid Ultra Sonography

- Painless, quick, no contrast material, no radiation
- Can be used in pregnancy, while on L-thyroxine therapy, after exogenous iodine exposure
- Can detect thyroid nodules as small as 2-3 mm and provide guidance for FNA biopsy





Indications for thyroid US

- Goiter
- If thyroid gland is normal on physical exam:
- External radiation during childhood
- History of familial thyroid cancer
- Lymph node metastases
- Prior to parathyroid surgery

Diseases Of Thyroid Gland

- **DIVIDED INTO:**

HYPOTHYROIDISM (Gland destruction)

- Under-production of thyroid hormones

Myxoedema (Gull Disease)

Cretinism

Thyroiditis

HYPERTHYROIDISM (thyrotoxicosis)

- Over-production of thyroid hormone
  - Grave's Disease
  - Thyrotoxicosis

GOITER- Diffuse and multi-nodular

NEOPLASTIC PROCESSES

- Beningn
- Malignant

Hypothyroidism

Resulting from reduced circulating level of T3 and T4

Causes of Hypothyroidism

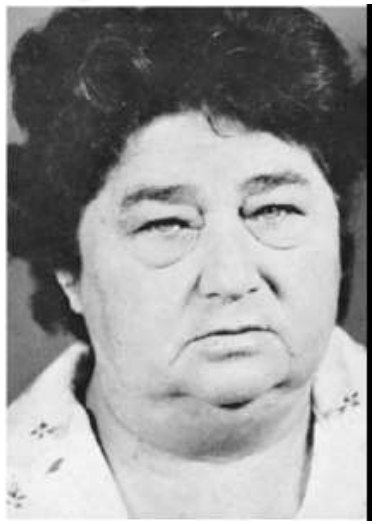
- **Primary**

  1. Dietary Iodide deficiency
  2. Iodine defficiency
  3. Autoimmune (Hashimoto´s Thyroiditis)
  4. Drugs: amiodarone, lithium, thiocyanates, phenylbutazone, sulfonylureas
  5. Iatrogenic- Surgical removal of the thyroid gland and radiation treatment
  6. Congenital (1 in 3000 to 4000)
  7. Infiltrative disorders

- **Secondary**
  - Pituitary gland destruction
  - Isolated TSH deficiency
  - Bexarotene(anti cancer drug) treatment
  - Hypothalamic disorders

- Hypothyroidism appears in 3 forms-
- 1. Myxoedema (Gull Disease)
- 2. Cretinism
- 3. Thyroiditis

Myxoedema (Gull Disease)

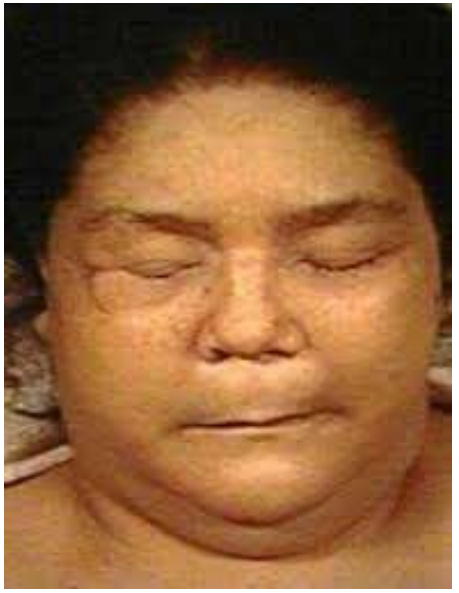


- **hypothyroidism developing in adults,**

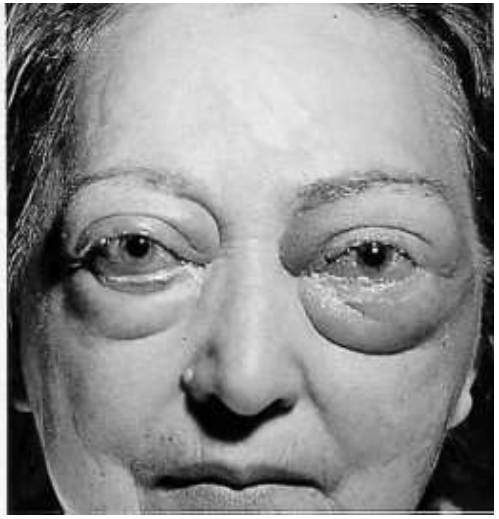
deposition of excess mucoprotein in skin of forearm,

Leg, feet

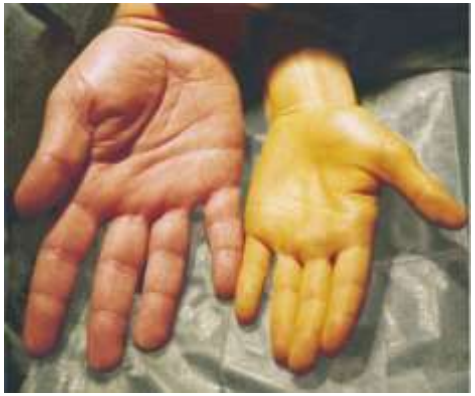
- **Features-**
  - Enlargement of thyroid gland (Goiter)
  - Lack of interest in daily household chores.
  - slowing of physical and mental activity
  - generalized fatigue, dull look
  - apathy
  - overweight
  - ↓ CO
    - shortness of breath
    - ↓ exercise capacity
  - ↓ Sympathetic activity
    - constipation
    - ↓ sweating



- **Skin**-dry, thicken, yellow(carotinemia), cool (↓ blood flow)
- edema, puffy face, periorbital swelling.
- Ptosis (drooping of upper eyelid)
- coarse hair
- broadening of facial features
- enlarged tongue
- deepening of voice (telephonic voice)

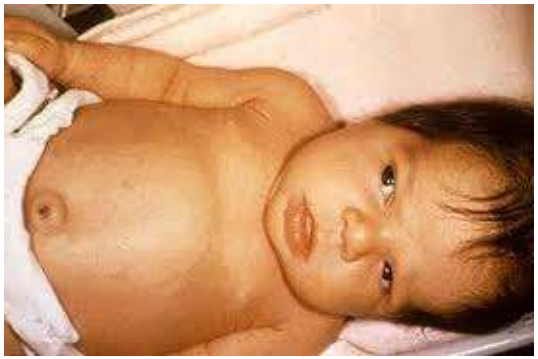


- **Calorigenic action-** BMR decreases to 30-40%
- cold-intolerant
- **Bone marrow-** anemia (normocytic, normochromic)
- Menstrual irregularities
- **Carbohydrate metabolism-** Low blood sugar
- **Lipid metabolism-** Increased serum Cholesterols, TGs, phospholipids



- **CNS**- Myxedematous madness (psychosis)
- Knee jerk reaction time increased
- Memory loss

Cretinism



- hypothyroidism developing

in infancy/early childhood, due to maternal iodine deficiency.

- Listless, somnolent, apathetic to play, devoid of initiatives.

- **Features-**
- Severe mental retardation (imbeciles-IQ-25-49)
- Occurs in iodine deficient areas of world (i.e. Himalayas, China, Africa)

- **Clinical-**
- Impaired skeletal development
- Impaired CNS development
- Inadequate maternal thyroid hormone prior to fetal thyroid gland formation → severe mental retardation
- Often deaf and mute
- Dwarfism and stunted growth
- Thick, coars, dry skin
- Protruded abdomen (pot belly-Splanchnomegaly) and enlarged tongue
- Failure of sexual developments
- Delayed milestones-
  - Length of the child fails to increase
  - Dentition is delayed
  - Delayed sitting up and head holding
  - Delayed walking
  - Delayed closure of ant fontanels
  - Delayed standing up and speech

- On the left, a euthyroid 6 year old girl at the 50th height percentile (105 cm).
- On the right, a 17 year old girl with a height of 100 cm, mental retardation, myxedema and a TSH of 288 (normal 0.3-5.5).

- (Werner & Ingbar's The Thyroid, 8th Edition, page 744.)

Lab Findings-

- Increased TSH
- Decreased free T4
- Decreased FT3

- Anti-TPO and anti-Tg Abs (Hashimoto’s)

Hypothyroidism: Therapy

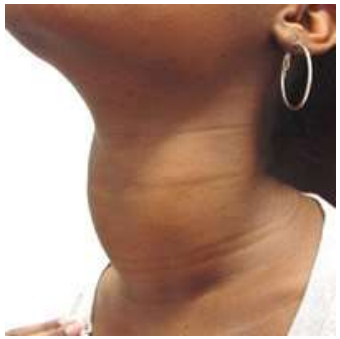
- L-Thyroxine (levothyroxine; T4)
- Goals-
- Alleviate symptoms
- Normalize TSH

Thyroiditis

Inflammation of thyroid

Types:

- **a) Hashimoto thyroiditis**
- 1) gradual thyroid failure due to autoimmune destruction of thyroid
- 2) 45-65 yrs
- 3) 10:1 female predominance
- 4) major cause of non endemic goiter in children
- 5) genetic component- patients with Turner syndrome have ↑ circulating anti-thyroid Ab



- **Clinical:**

- **1)** progressive depletion of thyroid epithelial cells
- **2)** replaced with mononuclear cells and fibrosis
- **3)** comes to clinical attention as painless enlargement of thyroid with some degree of hypothyroidism
- **4)** hypothyroidism progresses slowly
- **5)** can be preceded by “hashitoxicosis” (transient hyperthyroidism caused by inflammation associated with Hashimoto's thyroiditis)
- **6)** patients at risk in developing other autoimmune diseases
- **7)** no cancer risk

- **b) Subacute (granulomatous) thyroiditis**
- **[“ De Quervain thyroiditis”]**

- **i)** occurs less often than Hashimoto
- **ii)** 30-50 yrs
- **iii)** female preponderance 5:1
- **iv)** caused by viral infection (Coxsackie virus, mumps and adenoviruses)
- **v)** history of upper respiratory infection just prior to onset of thyroiditis
- **vi)** seasonal incidence (summer peak)
- **vii)** acute or gradual
- **viii)** painful presentation, radiating to jaw, throat, ears: especially when swallowing

- **ix)** inflammation and hyperthyroidism are transient
- **x)** self limited disease

- **c) Subacute lymphocytic (painless) thyroiditis**
- **i)** uncommon
- **ii)** hyperthyroid presentation
- **-** may present with any of signs of hyperthyroidism (no opthalmopathy, as in Graves disease)

- **d) Riedel thyroiditis**
- **i)** fibrosis of thyroid and neighboring structures
- **ii)** presents as hard and fixed thyroid which clinically is similar to CA

Congenital Hypothyroidism

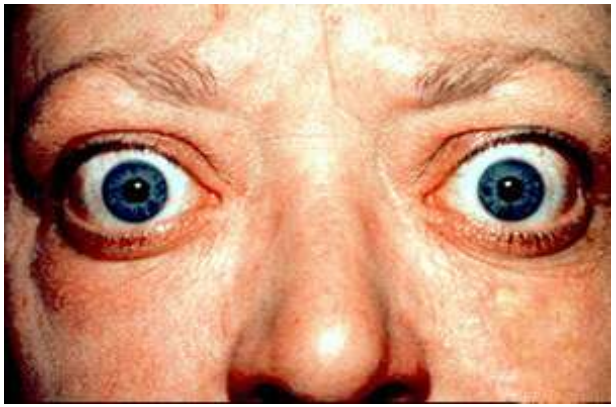
- **Prevalence:** 1 in 3000 to 4000 newborns
- **Cause:** Dysgenesis 85%
- **Treatment:**
  - Supplemental treatment With Levothyroxine is “essential” for a normal C.N.S. Development and prevention of mental retardation

Hyperthyroidism

- It is a condition resulting from increased level of circulating FT4 and FT3

- **Cause-**
- Thyrotoxicosis
- **Causes of Thyrotoxicosis:**
  - Primary Hyperthyroidism
    1) Grave´s disease(Exopthalmic Goiter)
    2) Toxic Multinodular Goiter
    3) Toxic adenoma
    4) Functioning thyroid carcinoma metastases
    5) Activating mutation of TSH receptor
    6) Drugs: Iodine excess

Graves disease

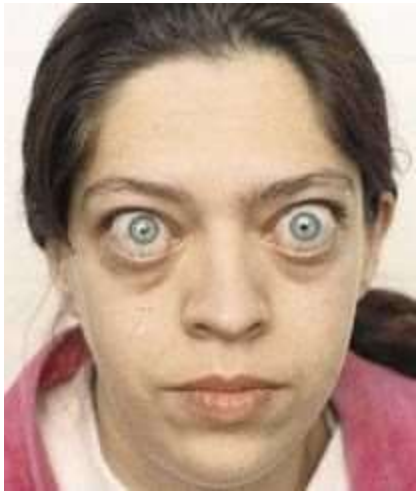


- Most common cause of endogenous hyperthyroidism
- **Characteristics:**
- a) hyperthyroidism
- i) diffuse enlargement of thyroid
- ii) lymphocytic infiltration
- b) infiltrative ophthalmopathy
- i) with resultant exophthalmos
- c) localized infiltrative dermopathy
- i) “pretibial myxedema”

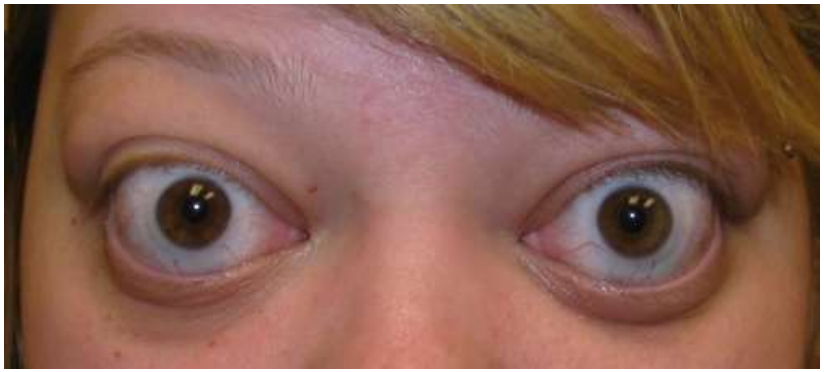
- peak incidence 20-40
- female preponderance (7:1)
- familial link
-
- **Pathogenesis:**
- a) autoimmune disorder
- b)Thyroid stimulating Ab (Long acting thyroid stimulator)→ action like TSH
- c)LATS protectors- prevent inactivation of LATS

- LATS combine with receptors on thyroid cells plasma membrane and displace TSH from its binding sites.
- Act via cAMP to cause prolonged action.
- Leads to-
- Increased formation and release of T3,T4
- Increased growth of thyroid gland

Features



- **Exopthalmos-**
- Protrusion of the eye ball with visibility of sclera between lower lid and cornea.
- Due to-
- retro-orbital connective tissue and ocular muscles are increased
- i) inflammatory edema (cytokines induced)
- ii) T-cell infiltration
- iii) fatty infiltration
- iv) mucopolysaccharide and water accumulation
- v) these cause eye to bulge outward



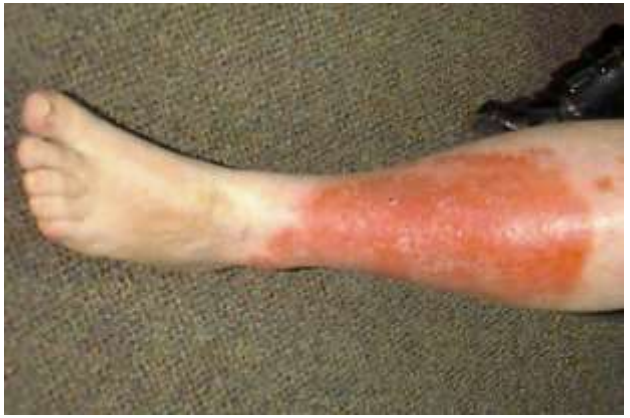
- **Lid retraction-**
- Visibility of sclera

between upper lid and cornea

- Due to overstimulation of levator palpebrae superiosis

- **Calorigenic action-**
- BMR ↑ 30%-100%
- Heat intolerance
- Weight loss (thyrotoxic myopathy)
- Lactation ↑
- Scanty periods
- Vitamine B & C deficiency
- **CVS-** tachycardia, high output cardiac failure
- **Thyroid diabetes**
- Decreased serum lipid levels

- **CNS**- overexcitibility, tremors,irritability,nervousness
- Smooth, moist, warm skin
- Flushing of face and hands
- Overgrown nails (**acropachy**), which may lift off the nail bed (**onycholysis**)
- Fine soft thinned scalp hair
- Generalized itching (**pruritus**)
- Increased skin pigmentation
- "**Pretibial myxedema**"



Thyrotoxicosis

- **Symptoms:**
  - Hyperactivity
  - Irritability
  - Dysphoria
  - Heat intolerance & sweating
  - Palpitations
  - Fatigue & weakness
  - Weight loss with increased appetite
  - Diarrhea
  - Polyuria
  - Sexual dysfunction

- **Signs:**
  - Tachycardia
  - Atrial fibrillation
  - Tremor
  - Goiter
  - Warm, moist skin
  - Muscle weakness, myopathy
  - Lid retraction or lag
  - Gynecomastia
  - * Exophtalmus
  - * Pretibial myxedema

Lab findings-

- Suppressed TSH
- Elevated Free T4
- Elevated Free T3

Treatment:

- **Reducing thyroid hormone synthesis:**
  - Antithyroid drugs (Methimazole, Propylthyouracil)
  - Radioiodine (^{131}I)
  - Subtotal thyroidectomy

- **Reducing Thyroid hormone effects:**
  - Propranolol
  - Glucocorticoids
  - Benzodiazepines

- **Reducing peripheral conversion of T4 to T3**
  - Propylthyouracil
  - Glucocorticoids
  - Iodide

Thyrotoxic crisis or Thyroid storm:

- It´s a life-threatening exacerbation of thyrotoxicosis, acompanied by fever, delirium, seizures, coma, vomiting, diarrhea, jaundice.
- Mortality rate reachs 30% even with treatment

- It´s usually precipitated by acute illness, such as:

  - Stroke, infection,trauma, diabeic ketoacidosis, surgery, radioiodine treatment

Thyroid storm

- i) abrupt onset of severe hyperthyroidism
- ii) febrile, tachycardia
- iii) is a medical emergency
  - death from cardiac arrhythmias

Goiter

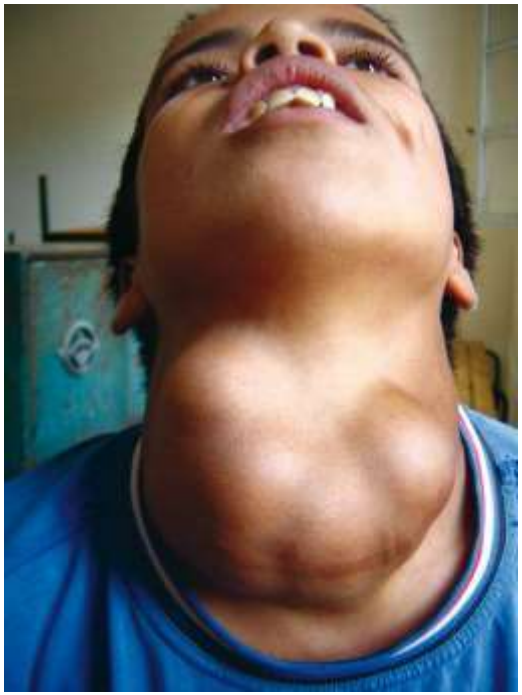
- **Diffuse and multinodular**
- enlargement of the thyroid
- most common manifestation of thyroid disease
- most often caused by dietary iodine deficiency (i.e., impaired synthesis of thyroid hormone)

- **Two types:**
- i) endemic
- ii) sporadic

- **Endemic goiter** (<10% population)
- i) geographic area deficient in iodine
- ii) mountainous areas of world
- - Himalayas, Andes,Alps
- iii) ↑ TSH
- iv) can result from ingestion of certain "**goitrogens**"- cabbage, cauliflower, Brussels,sprouts, turnips, cassava
- Contain Progoitrin/ Progoitrin activator(anti thyroid agent)
- Prevent incorporation of iodine with tyrosine.

- **Sporadic goiter**
- i) less frequent than endemic
- ii) female preponderance
- iii) peak incidence near puberty

- **Multinodular goiter**
- a) recurrent hyperplasia/hypertrophy
- b) all simple nontoxic goiters evolve into multinodular goiters
- c) produce the most extreme thyroid enlargements, often mistaken for neoplasm
- d) asymmetrically enlarged thyroid



- small % of patients may develop a hyperfunctioning thyroid (nodule) resulting in a “toxic multinodular goiter”
- Plummer syndrome is example without dermopathy, nor-ophthalmopathy (as in Graves)
- All goiters may cause “Mass Effects”
  - a) dysphagia
  - b) compression of large vessels
  - c) airway obstruction

Thyroid Neoplasms

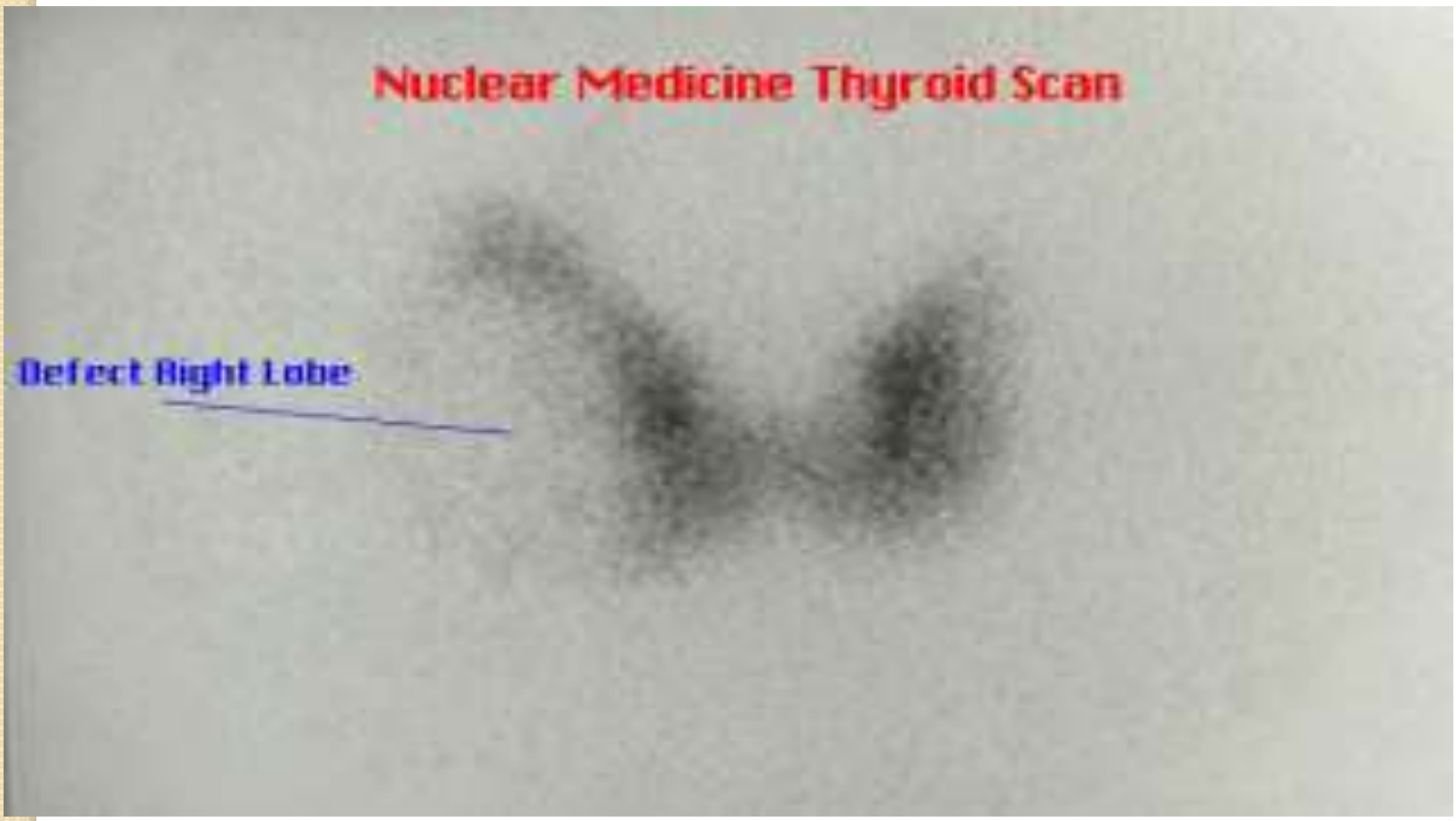
- Adenomas
- discrete solitary masses
- derived from follicular epithelium (i.e., “follicular adenomas”)
-

NOT transform into malignancy

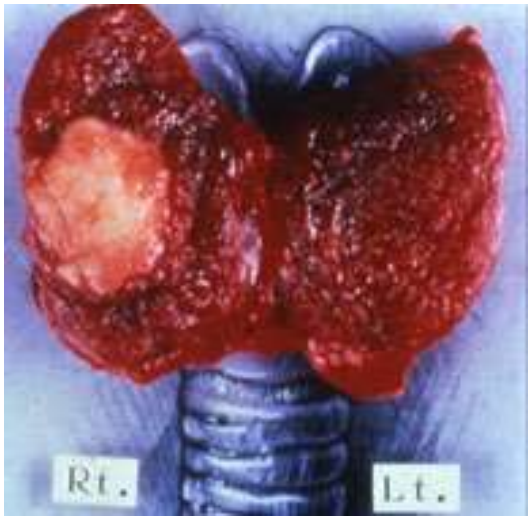
- Usually present as unilateral painless mass
- Take up less radioactive iodine compared to normal thyroid parenchymal cells
- i) “cold” nodules
- ii) ~10% of cold nodules → malignant
- iii) “hot” nodules rarely → malignant
- Biopsy is “gold” standard for diagnosis

- Other benign tumors
- a) cysts
- b) lipomas
- c) hemangiomas
- d) dermoid cysts
- e) teratomas (mainly in infants)

- **Thyroid Cancer typically appears as a "cold nodule". That is to say, it appears as a white area or defect in an otherwise black thyroid. A "cold" area is NOT necessarily cancer. Indeed, most "cold nodules" are benign! Ultrasound, perhaps followed by biopsy, often plays an important role in differentiation**



Thyroid Carcinomas



- most appear in adults
- papillary CA may present in childhood
- female predominance (early and middle adult)
- childhood and late adulthood have equal gender distribution
- Most CA are well differentiated:
- a) papillary CA (~80% of cases)
- b) follicular CA (~15% of cases)
- c) medullary CA (~5% of cases)
- d) anaplastic CA (< 5% of cases)