

# **Thyroid Disease:**

**Pathophysiology, Hypothyroidism,  
Hyperthyroidism, Thyroid Nodules**



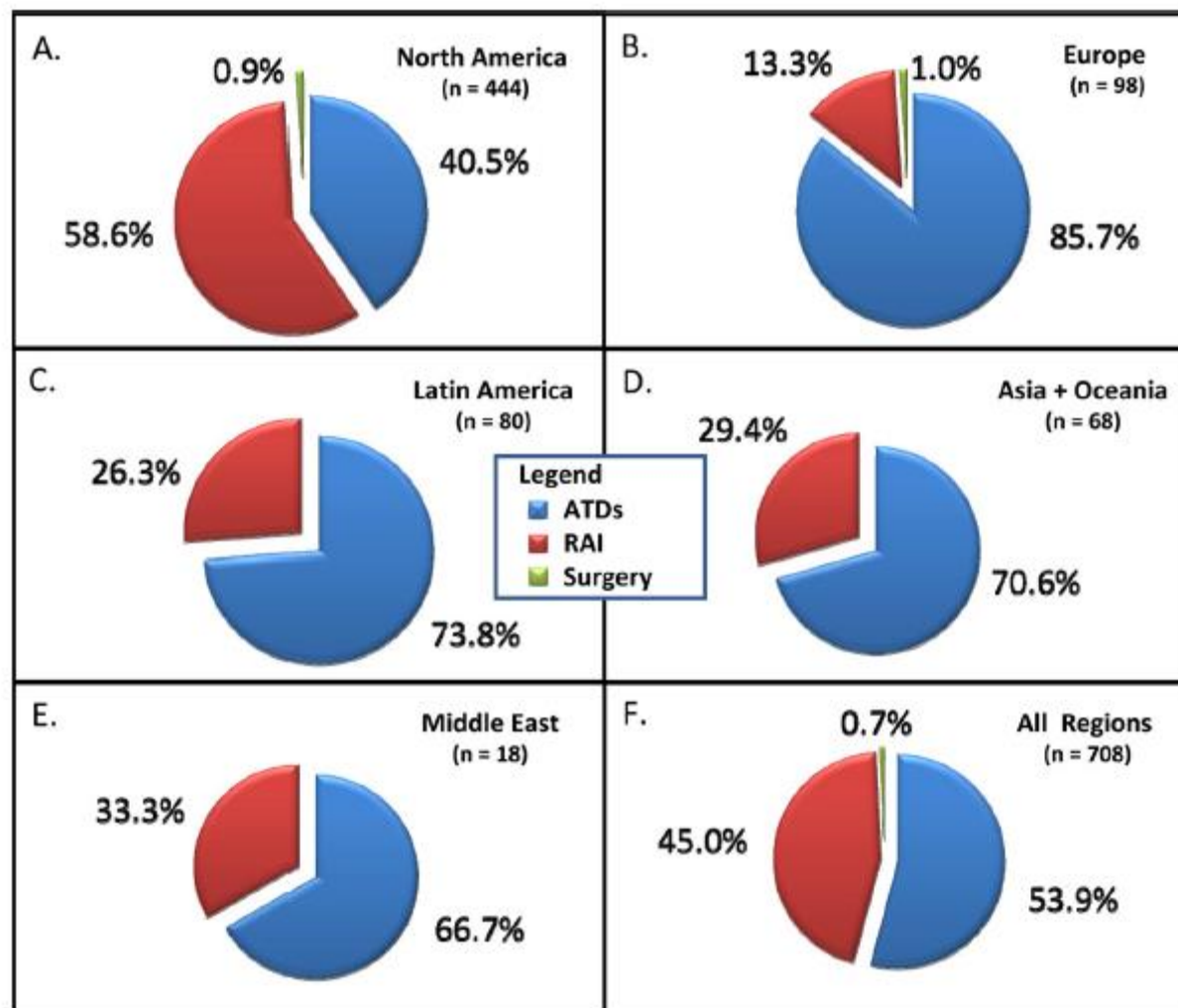
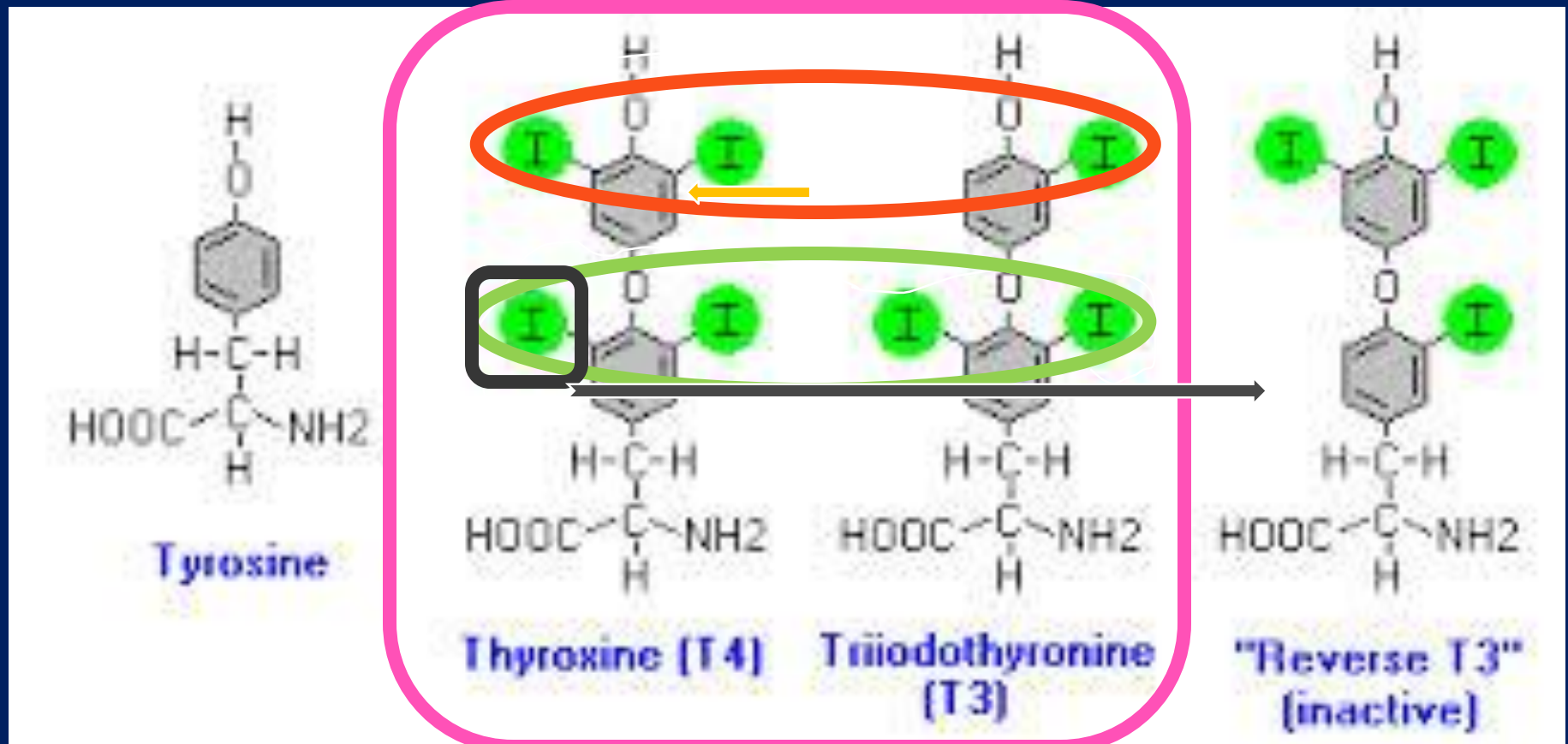
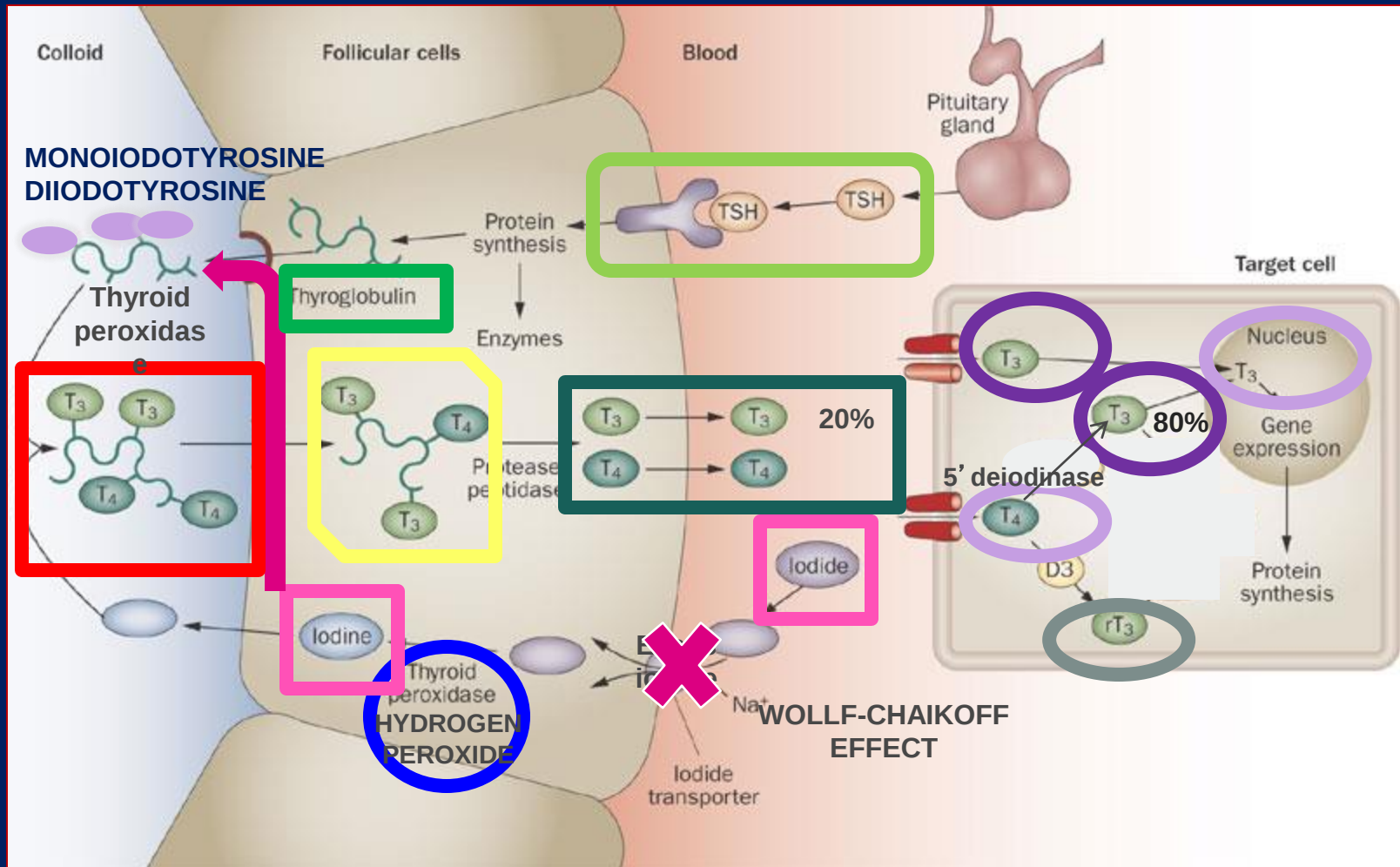


FIG. 3. International differences in the selection of primary treatment modality for the index case of uncomplicated GD.

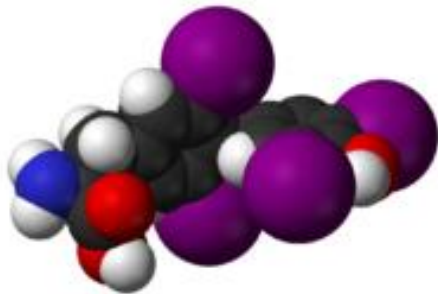
**T4 and T3 are biologically active but  
T3 much more so , rT3 does nothing**



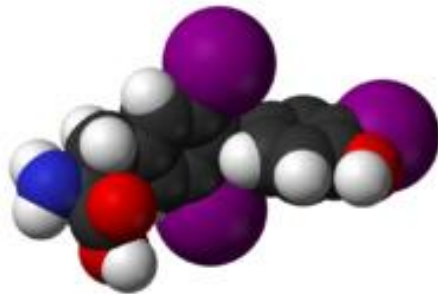
# Thyroid Hormone Synthesis Occurs in Thyroid Follicles



# Majority Thyroid Hormone Circulates Bound to Binding Globulins Which Serve a Storage and Buffer Function

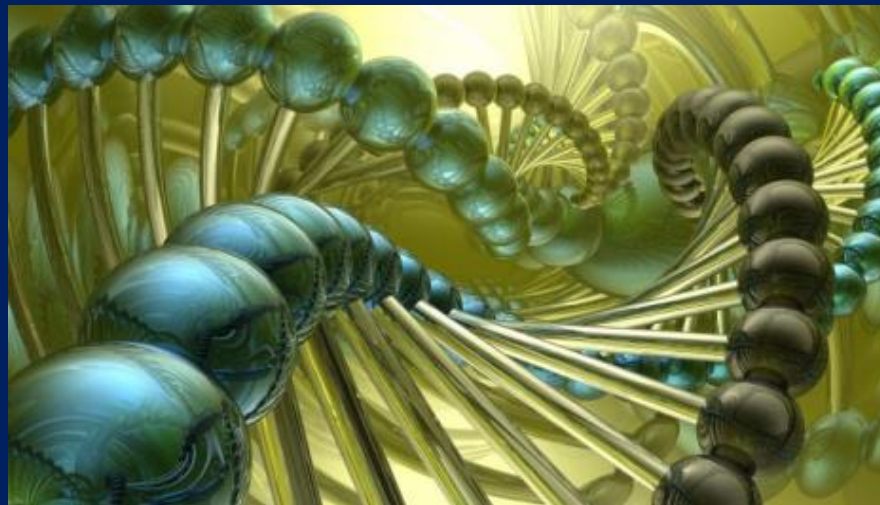


Thyroxine (T4)



Triiodothyronine (T3)

**ONLY FREE  
HORMONES  
ACTIVE**

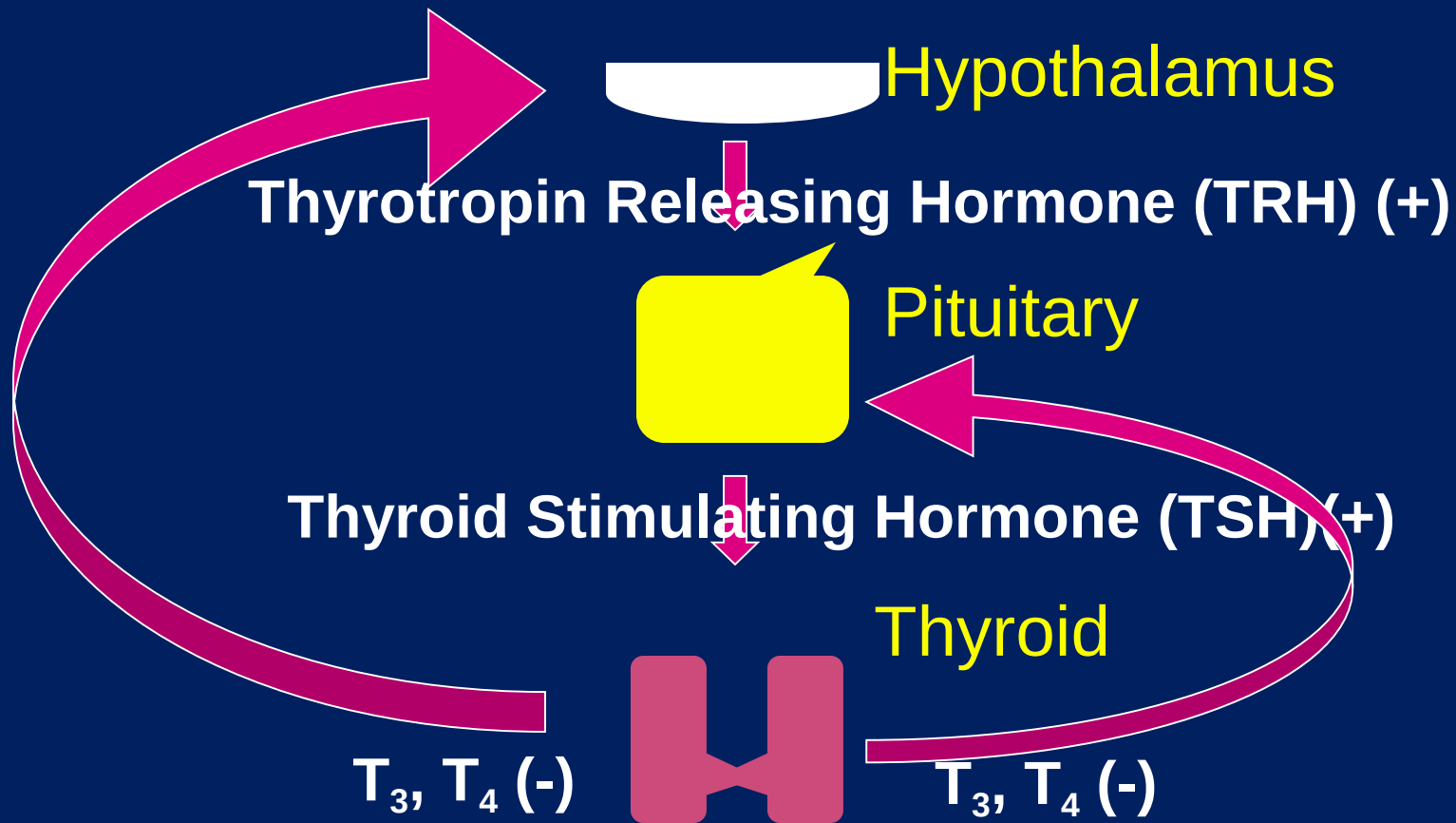


Thyroxine Binding Globulin

**Transthyretin,  
albumin and  
lipoproteins**

**Congenital -  $\uparrow\downarrow$   
High estrogen-  $\uparrow$   
Liver failure-  $\downarrow$**

# Hypothalamic Pituitary Thyroid Axis

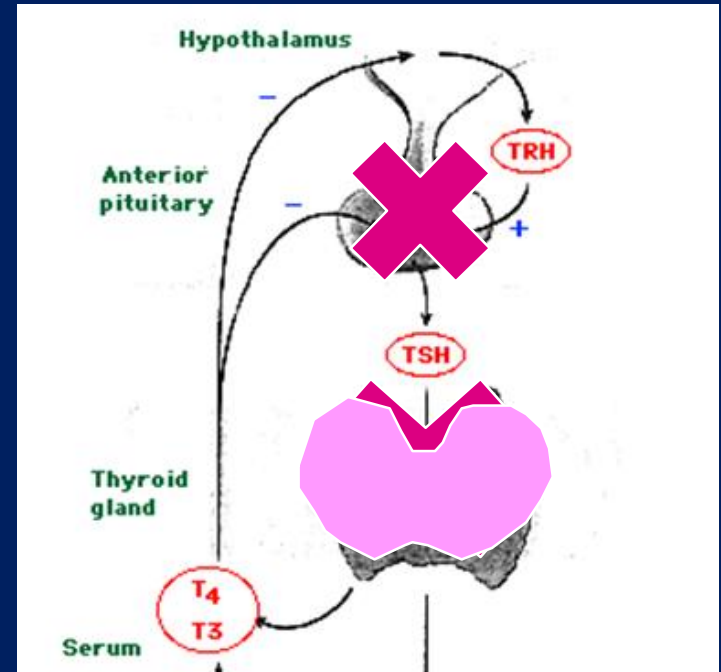


# Hypothyroidism

□ Definition: Deficiency of thyroid hormone

□ Causes:

- » Primary (TSH high) ~95%
  - Pituitary disease
  - Hypothalamic disease
- » Thyroid Hormone Resistance (rare)



□ Relatively common:

- » 2% adult women, 0.2% adult men
- » >60 y/o: 6% adult women; 2% adult men
- » May be higher in select groups

# Clinical Features: Hypothyroidism

## □ Constitutional Symptoms:

- » cold intolerance
- » fatigue, lethargy
- » hoarseness

## □ Integument:

- » thickened/yellowed, Dry, non-pitting edema (=“Myxedema”) of hands/feet/periorbital region, alopecia.

## □ Cardiovascular:

- » ↓ contractility, ↓ rate, ↓ cardiac output, pericardial/pleural effusions, ↑ peripheral vascular resistance. CHF rare.

# Clinical Features: Hypothyroidism

## ❑ Gastrointestinal:

- » ↓ appetite, constipation, weight gain (5-10% increase)

## ❑ Gynecologic:

- » menorrhagia, menstrual irregularities

## ❑ Musculoskeletal:

- » myalgias, arthralgias

## ❑ Hematologic:

- » anemia

## ❑ Neurologic:

- » delayed relaxation phase of DTRs, difficulty concentrating, poor Memory, somnolence, depression, headache, paresthesias

# Myxedema



Robbins' Pathology Online



# Causes of Hypothyroidism

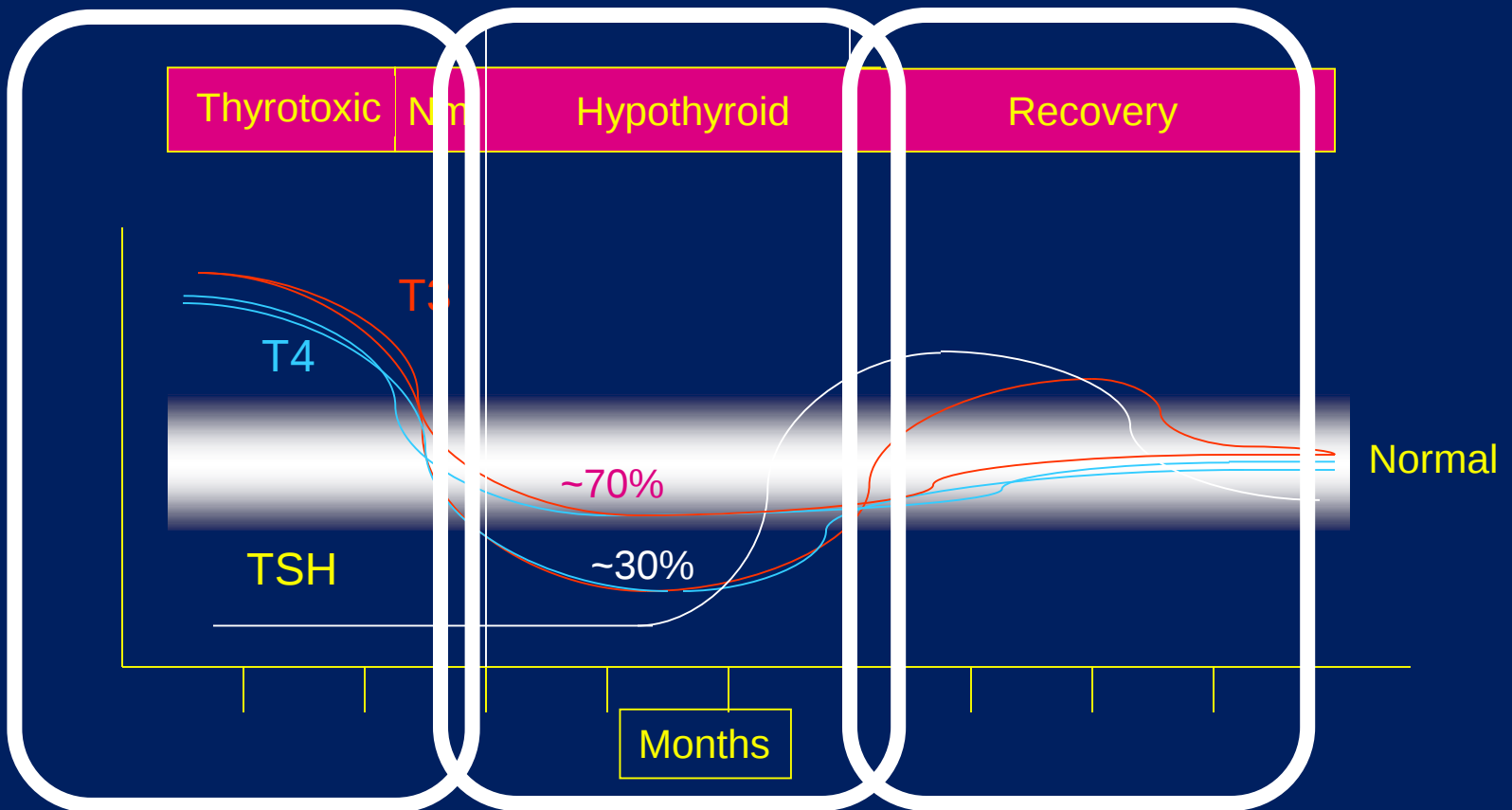
## ❑ Primary Hypothyroidism

- » Iodine deficiency
- » Iatrogenic-surgery, radioablation
- » Autoimmune thyroid destruction
- » Drugs interfering with hormone synthesis
- » Infiltrative disease
  - hemochromatosis, sarcoidosis, neoplastic disease
- » Congenital thyroid agenesis or defects in hormone synthesis

# Hashimotos Thyroiditis

- ❑ Most common type of thyroid disease
- ❑ Genetic predisposition followed by environmental insult.
  - » Lymphocytic infiltrate, fibrosis
  - » Autoantibodies (thyroglobulin and peroxidase)
  - » Gland variable findings
  - » Hypothyroidism usually develops

# Effect of Silent/Subacute Thyroiditis on Thyroid Function Tests



Modified from Nickolai, T.F., Werner & Ingbar's The Thyroid, Chapter 36, Braverman & Utiger, ed., 6th Edition, 1991.

# Laboratory Diagnosis: Hypothyroidism

## Primary Hypothyroidism:

Subclinical Hypothyroidism

Mild Hypothyroidism

Overt Hypothyroidism

TSH

Free T4

T3

↑

N

N

↑

N/↓

N/↓

↑

↓

N/↓

Secondary Hypothyroidism

↓/N

↓

N/↓



# Treatment of Hypothyroidism

**Replace with levo-thyroxine (L-T4)**

**(Example Brands: Synthroid®, Levoxyl®,  
Levothroid®, Unithroid®)**

**Monitor thyroid function tests every 6-8  
weeks until steady dose is achieved;  
goal is to normalize TSH in most cases**

**Therapy with T3 (cytomel) or other thyroid  
preparations is rarely indicated.**

# Myxedema Coma

- ❑ Severe untreated hypothyroidism
- ❑ Hypothermia, hypoglycemia, shock, hypoventilation, ileus
- ❑ 50% mortality
- ❑ Treat with IV levothyroxine, steroids

# Myxedema Coma-a clinical diagnosis at the end of a hypothyroid continuum

## Precipitating Factors:

- Severe Illness
  - Infection, Atherosclerotic Event
- Surgery
- Sedative Drugs, Anesthetics

## Signs:

- Bradycardia
- Hypotension
- Hypothermia
- Hypoventilation
- Stupor, Coma
- Delayed deep tendon reflexes
- Dry, puffy skin

## Emergent Treatment:

Treat underlying disorder

Thyroid hormone dose is controversial:

Usually loading dose IV to saturate receptors  
Monitor cardiac rhythm, EKG; supportive care  
Avoid T3 if possible due to risk of myocardial ischemia

Hydrocortisone 100 mg IV q 8°

# Hyperthyroidism: Clinical Features

## » Cardiac

- Sinus Tachycardia/Atrial Fibrillation
- Congestive heart failure (high-output)
- Angina
- Increased pulse pressure

## » Musculoskeletal

- Tremor
- Proximal Muscle Weakness (Myopathy)

## » Neurologic/Psychiatric

- Anxiety, Hyperactivity, Mania
- Disorientation, Coma
- Rarely, seizures/convulsions

# Causes of Hyperthyroidism

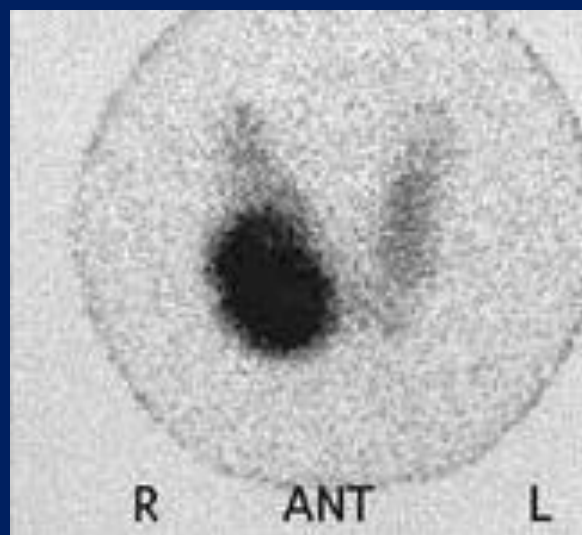
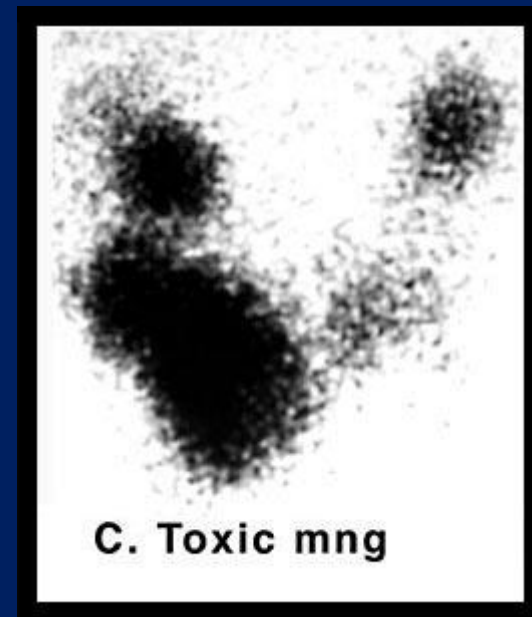
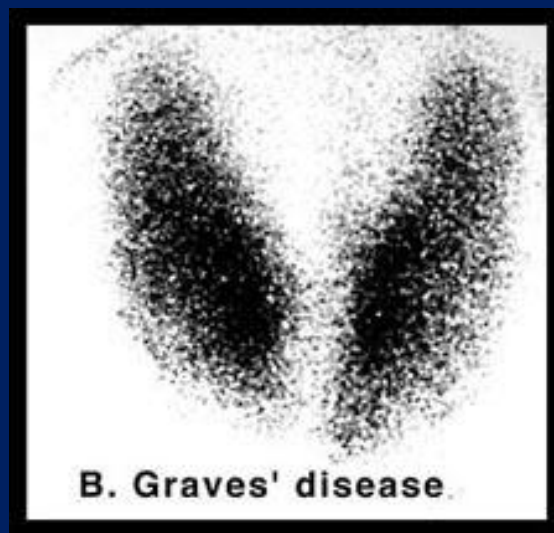
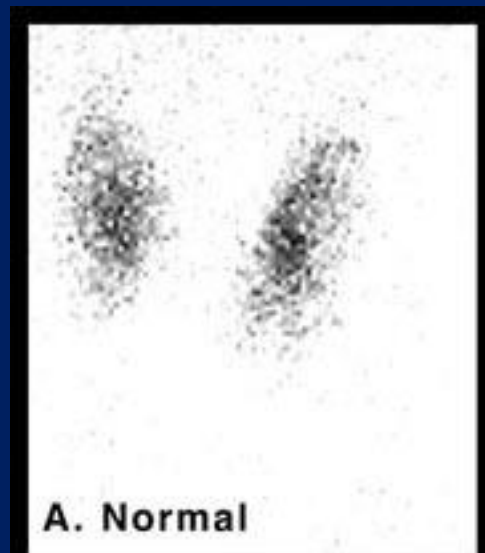
- Toxic Diffuse Goiter (Grave's)      ~70%
- Multinodular Goiter      ~20%
- Toxic Adenoma (nodule)      ~ 5%
- Non Goitrous causes:
  - » Thyroiditis
  - » Thyroid hormone use
  - » Uncommon/Rare disorders
- Molar Pregnancy

# Diagnosis of Hyperthyroidism

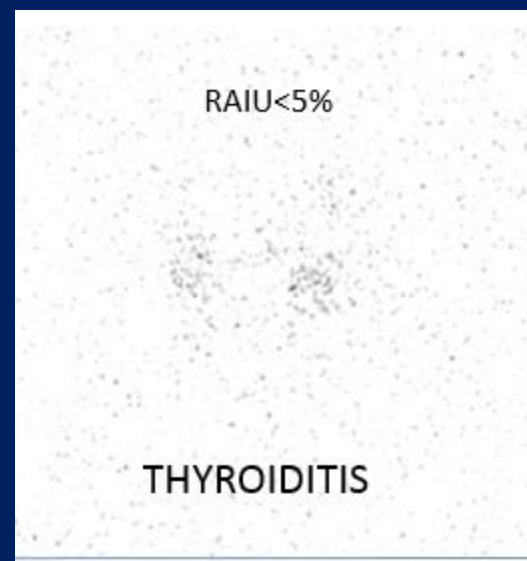
- Physical Examination
- Laboratory Tests:
  - » Common:
    - Thyroid Stimulating Hormone (TSH)
    - Free T4
    - T4 Panel (Total T4, %TUptake, Free T4 Index)
  - » Less Common:
    - Total T3 (Free T3)
  - » Infrequently:
    - TSI, Thyroid antibodies

# Laboratory Diagnosis: Hyperthyroidism

|                                                            | <u>TSH</u> | <u>T4</u> | <u>Free T4</u> | <u>T3</u> |
|------------------------------------------------------------|------------|-----------|----------------|-----------|
| Primary:                                                   |            |           |                |           |
| Subclinical Hyperthyroidism                                | ↓          | N         | N              | N         |
| Hyperthyroidism                                            | ↓          | ↑         | ↑              | ↑         |
| T3 thyrotoxicosis                                          | ↓          | N         | N              | ↑         |
| Secondary Hyperthyroidism<br>(TSH Secreting Adenoma-Rare!) | ↑          | ↑         | ↑              | ↑         |



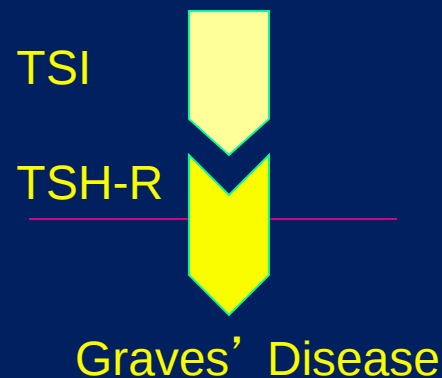
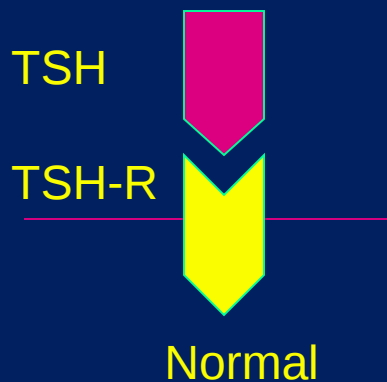
Toxic  
adenoma



# Graves' Disease (Toxic Diffuse Goiter)

Pathophysiology: Autoimmune Disease

Thyroid stimulating immunoglobulins (TSI) activate the TSH receptor in thyroid cells



# Graves' Disease (Toxic Diffuse Goiter)

## Clinical Features of Graves' Disease:

- » Diffusely enlarged, non-tender goiter, usually symmetric, sometimes associated with thyroid bruit or thrill
- » Graves' Ophthalmopathy (~30%)
- » Graves' Dermopathy (~2%)
- » Acropachy (1-2%)

# Graves' Disease (Toxic Diffuse Goiter)

- Laboratory Tests
  - » No laboratory test is specific for Grave's Disease
  - » RAIU elevated (4 and/or 24 hour uptake %)
  - » Thyroid Scintigraphy: diffuse increased uptake
  - » Thyroid Stimulating Immunoglobulins (TSI) fairly specific, somewhat sensitive, but not usually indicated



# Graves' Disease (Toxic Diffuse Goiter)

Clinical Features of Graves' Disease:



Wartofsky, Harrison's Textbook of Medicine Online, 2004

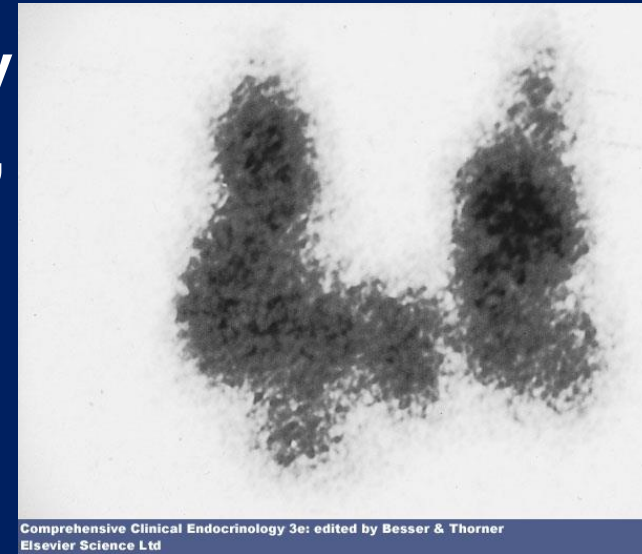




# Toxic Multinodular Goiter

- **Pathogenesis**

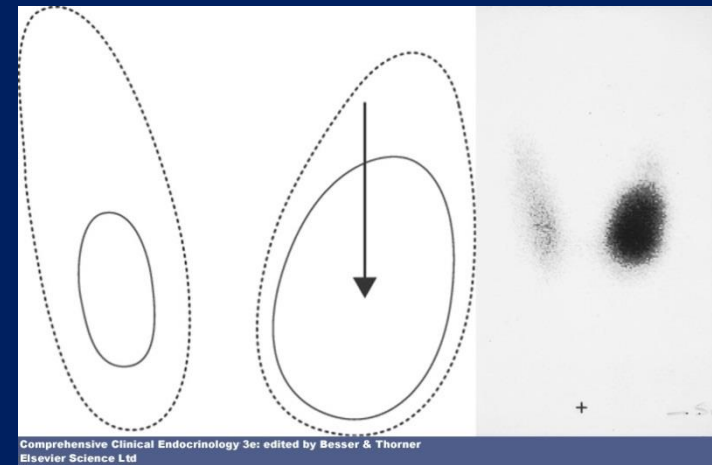
- » Final phase of evolution of goiter over time
- » Nodules gradually acquire autonomy
- » Influenced by growth factors, iodine, and genetic/hereditary factors
- » May also be a role of the immune system
- » Monoclonal expansion of follicles in many, but not all cases
- » Some mutations have been identified in the TSH receptor, or cytogenetic abnormalities observed



# Toxic Adenoma (Nodule)

- Pathogenesis

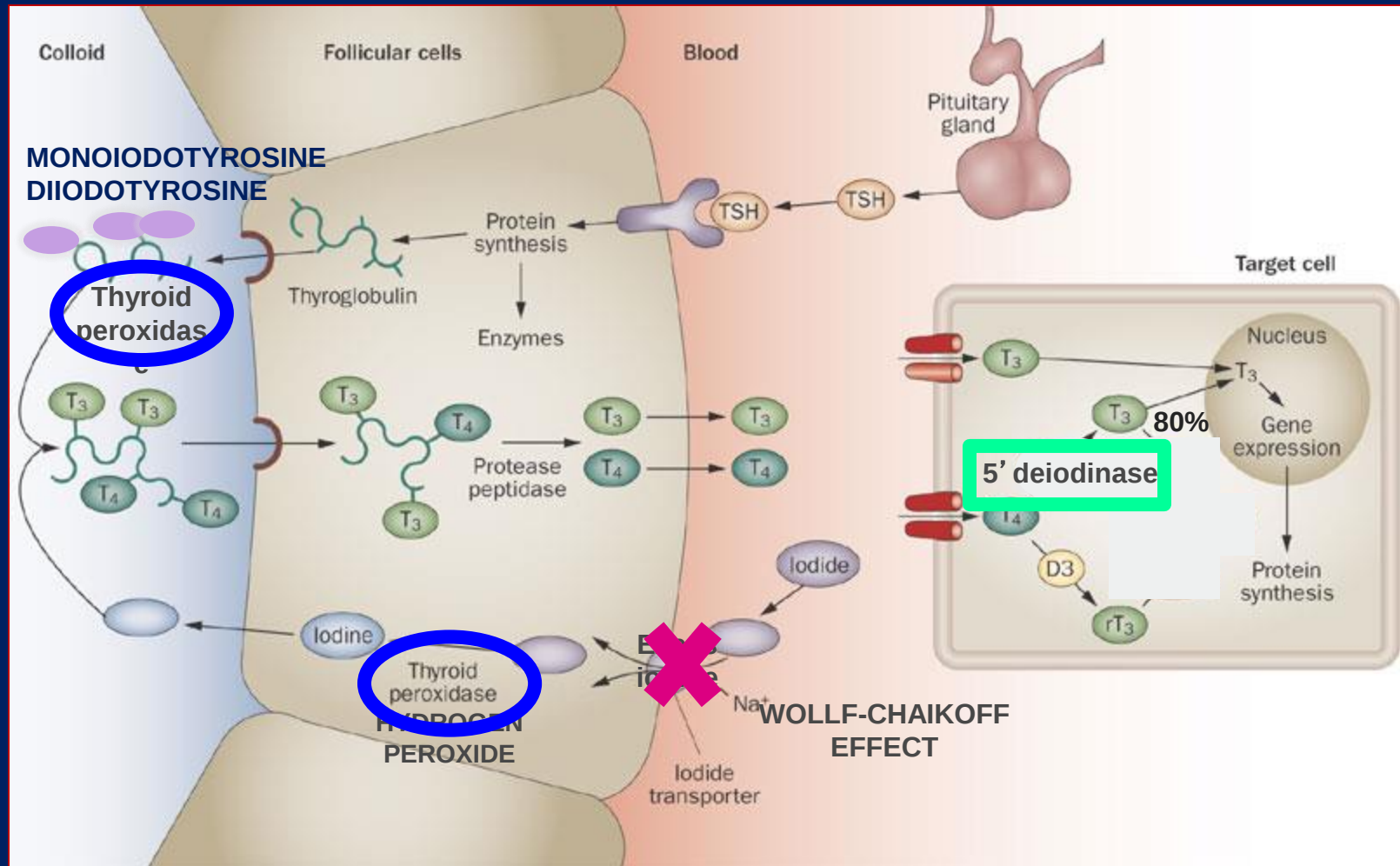
- » Monoclonal expansion of thyroid follicular cells
- » The adenoma escapes regulation by TSH, some studies have found mutations causing constitutive activation of the thyrotropin receptor
- » Almost never malignant
- » May suppress the size of the rest of the gland



# Treatment of Hyperthyroidism

- **Anti-thyroid Drugs**
  - » Methimazole  
(Tapazole®)
  - » Propylthiouracil
- **Radioactive Iodine**
- **Surgery**
- **Ancillary Drugs:**
  - » Beta blockers
  - » Iodine

# PTU and Methimazole Inhibit Thyroid Peroxidase, PTU 5' deiodinase



# Anti-Thyroid Drugs

- Methimazole & Propylthiouracil
- Block production of T4/T3 at several levels
- Take several weeks to reach full therapeutic effectiveness
- Do not affect the size of the goiter, only the level of thyroid hormone production
- Side effects
  - Rare but significant-agranulocytosis, aplastic anemia, hepatotoxicity (PTU), teratogen (methimazole)
  - Methimazole preferred except 1<sup>st</sup> trimester pregnancy

# PTU black box

*WARNING: Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients. Propylthiouracil should be reserved for patients who can not tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism. Because of the risk of fetal abnormalities associated with methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (see Warnings and Precautions).*

Reserved for early pregnancy; thyroid storm; mild intolerance to methimazole in patients not wanting RAI or surgery

# Radioactive Iodine: <sup>131</sup>I

- Safe; no evidence of increased thyroid CA risk
- Effective 70-90% of cases (can re-treat prn).
- Control achieved in several weeks to months.
- Major drawback: *Hypothyroidism*
  - ~ 50% within 3 years, and cumulatively develops at a rate of ~2% per year thereafter.
- Grave's ophthalmopathy may be exacerbated

# Severe Hyperthyroidism- Thyroid Storm

A clinical diagnosis at the end of a hyperthyroid continuum

Emergent Treatment:

- Propylthiouracil (PTU) 300 mg po (pr) q 8<sup>o</sup>

- Iodine (2 hrs after PTU)
  - » SSKI 2 gtt po q 8<sup>o</sup>

- » Fever
- » Mental Status Changes
- » Cardiovascular Collapse

□ Precipitants in hyperthyroid patients:

- » surgery
- » sepsis
- » iodine loads
- » post-partum

- Propranolol (avoid in heart failure) or other beta blocker
- Steroids
- Treat underlying cause(s)

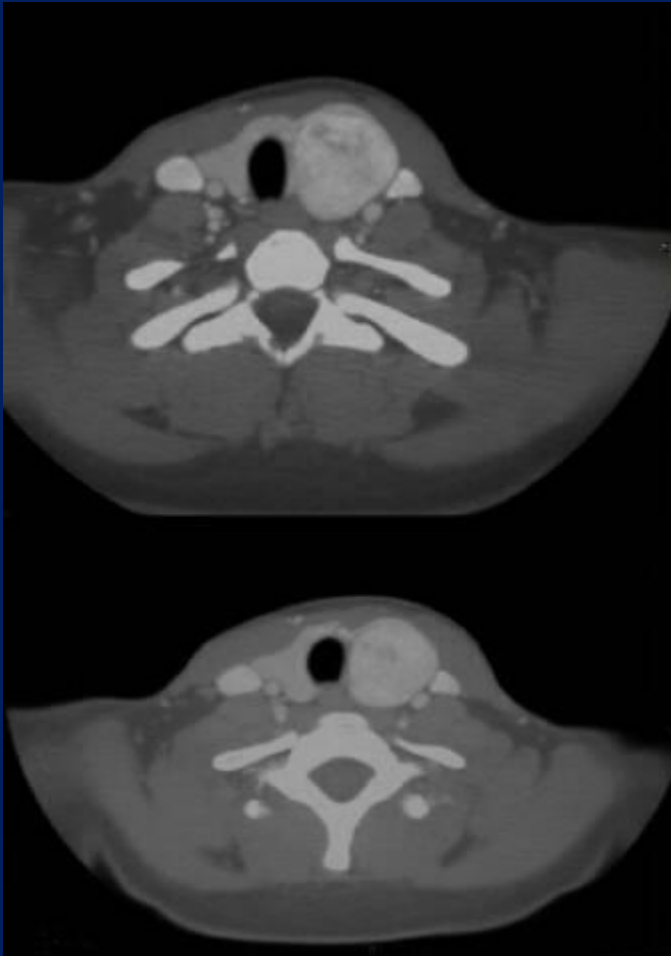
# Thyroid Dysfunction: Summary

## ❓ Hypothyroidism

- » TSH (or T4, if pituitary disease)
- » L-T4 Rx, F/U as appropriate
- » adjust L-T4; normalize TSH in most cases

## ❓ Hyperthyroidism

- » T4, TSH (T3?) establish diagnosis/baseline
- » Auxiliary tests as needed (RAI, ??other)
- » Determine therapy based on cause & pt



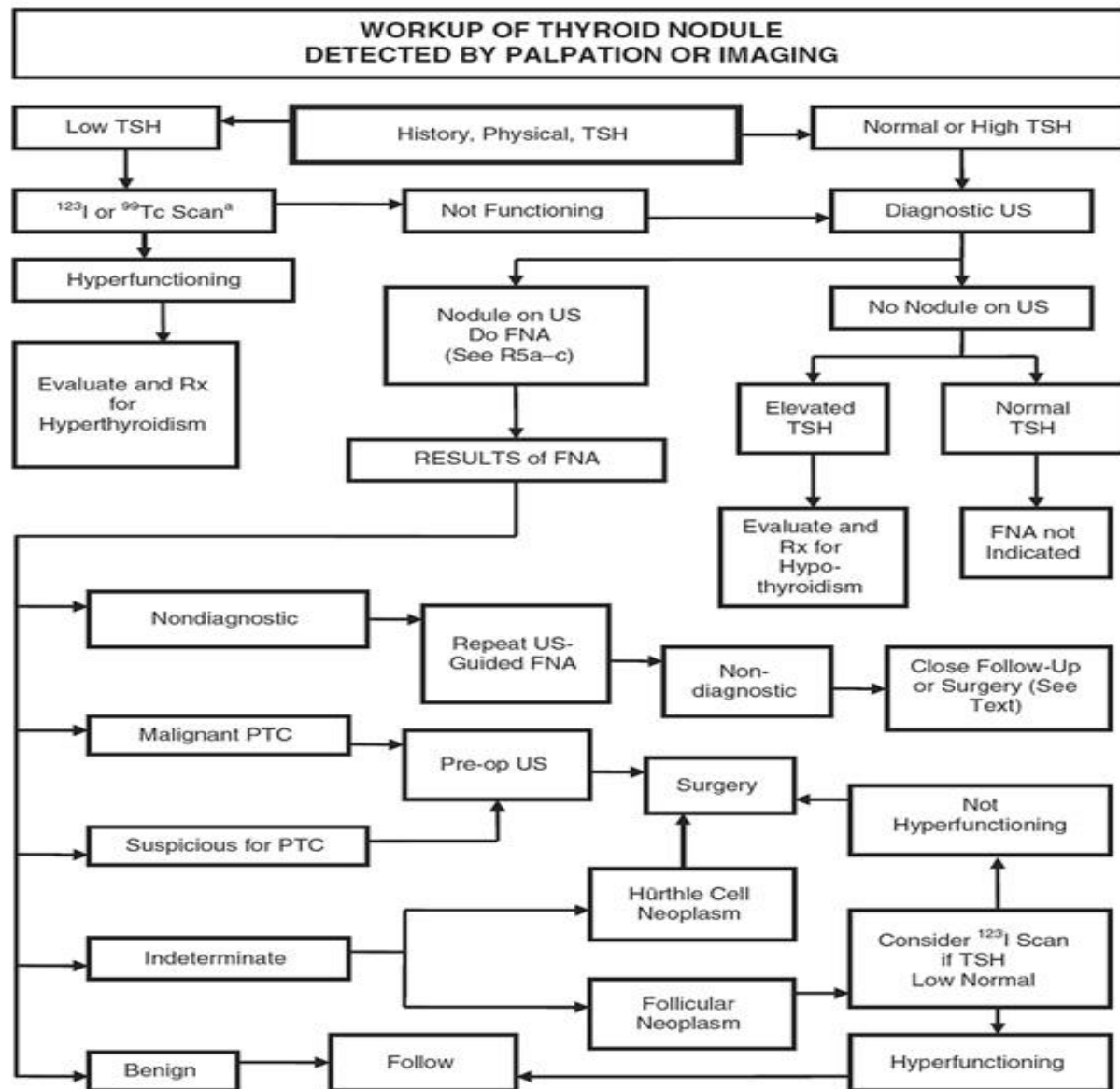


FIG. 1. Algorithm for the evaluation of patients with one or more thyroid nodules.

<sup>a</sup>If the scan does not show uniform distribution of tracer activity, ultrasound may be considered to assess for the presence of a cystic component.

# Initial Evaluation of a Thyroid Nodule Includes a Functional and Anatomical Assessment

**TSH**

**Neck Ultrasound**

**Suppressed TSH: RAI scanning**

**ULTRASOUND  
CHARACTERISTIC**  
CONSIDERATIONS

- High-risk history: History of thyroid cancer in one or more first degree relatives;
- History of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence;
- Size > 1-1.5 CM suspicious or > 1.5-2 cm
- Enlarging
- Suspicious features: microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view.