

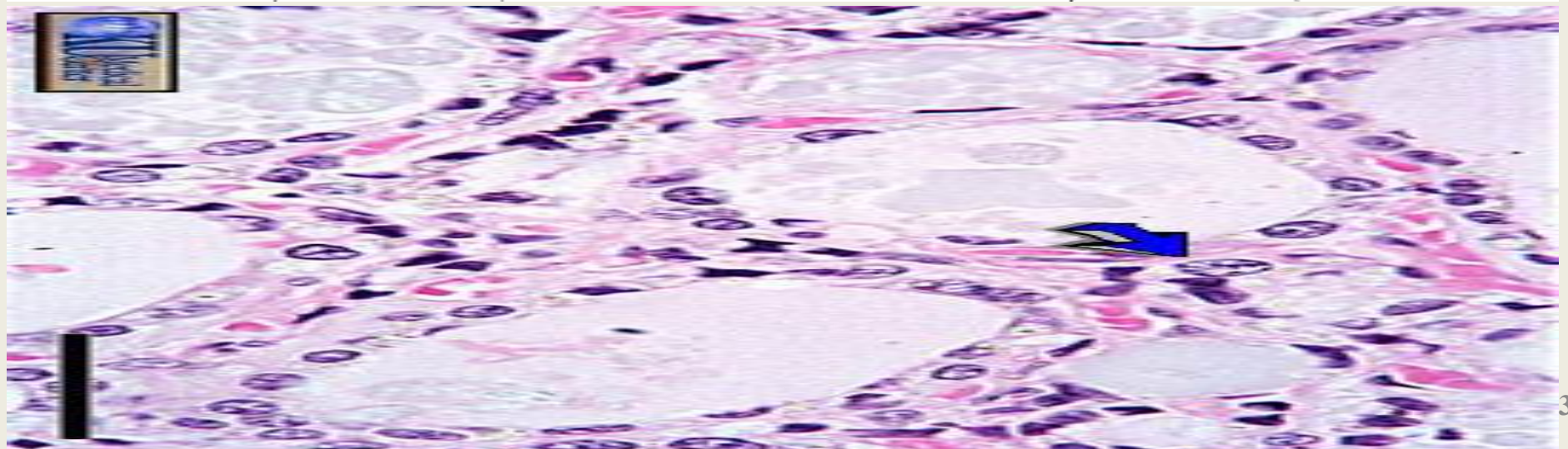
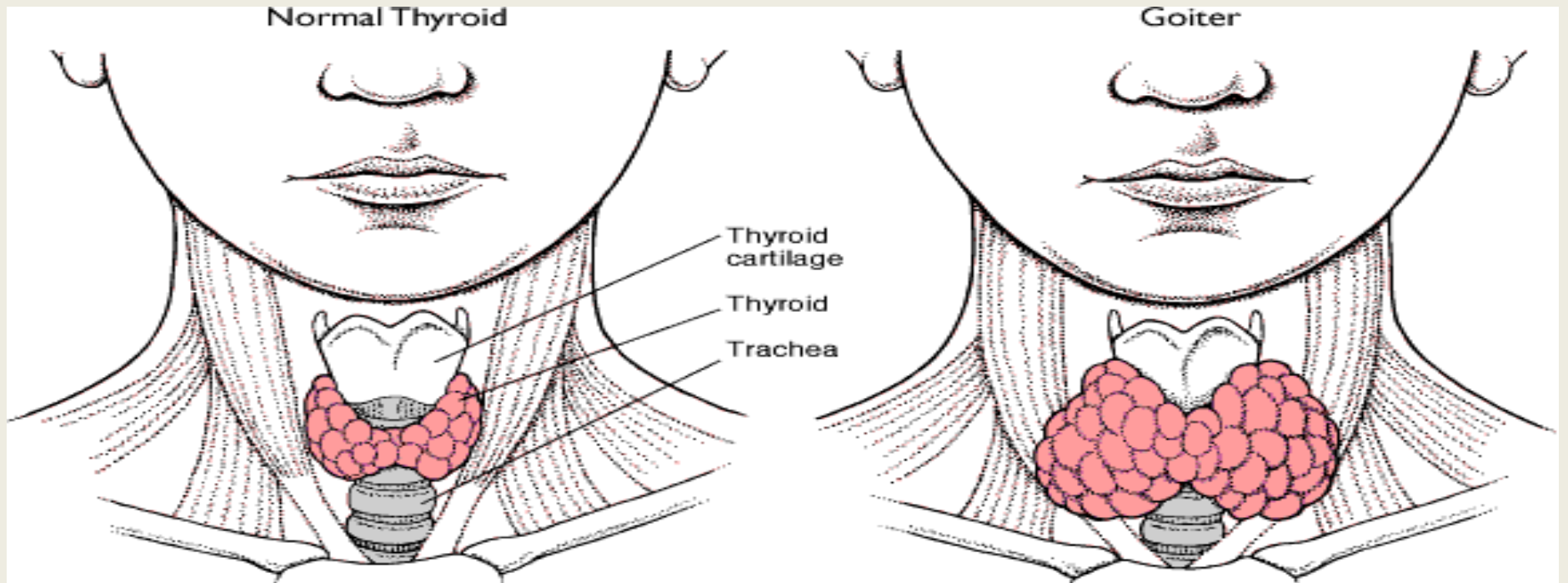
# **DRUGS USED IN HYPERTHYROIDISM**

# Learning objectives

By the end of this lecture, students should be able to:

- **Describe** different classes of drugs used in hyperthyroidism and their mechanism of action
- **Understand** their pharmacological effects, clinical uses and adverse effects
- **Recognize** treatment of special cases such as hyperthyroidism during pregnancy, Graves' disease and thyroid storm

# Thyroid Gland



# Thyroid function

- **Normal amount** of thyroid hormones are essential for **normal growth and development** by maintaining the level of energy metabolism in the tissue.
- Either too little or too much thyroid hormones will bring disorders to the body.

# Thyroid function

## Important functions are:

- **Growth & development, especially in the embryo & brain**
- **Thermoregulation: increase basal metabolic rate (BMR)**
- **Helps maintain metabolic energy balance**
- **CVS: increase HR & cardiac output which increase oxygen demand**

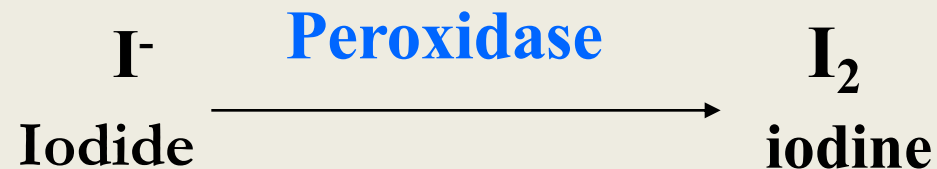
# Thyroid function

## Iodine Importance:

- Thyroid hormones are unique biological molecules in that they incorporate iodine in their structure
- Adequate iodine intake (diet, water) is required for normal thyroid hormone production
- Major sources of iodine:
  - iodized salt
  - iodated bread
  - dairy products
  - shellfish
- Minimum requirement: 75 micrograms/day

# Iodine Metabolism

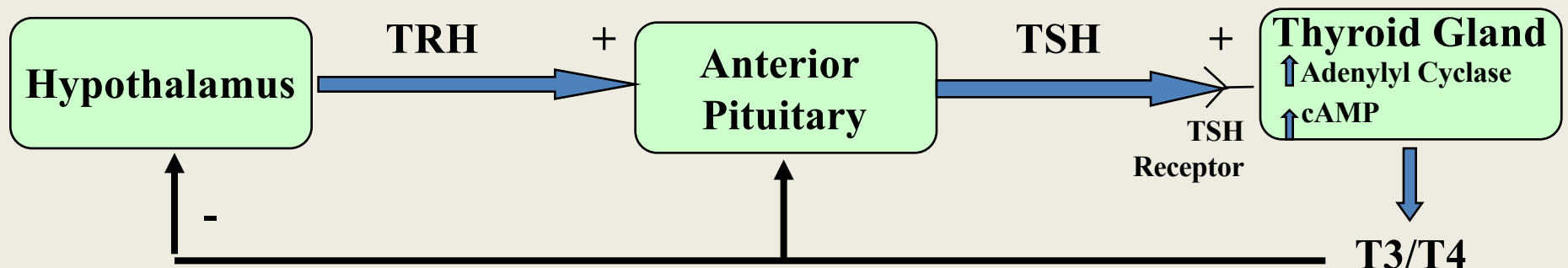
- Dietary iodine is **absorbed in the GI tract**, then taken up by the thyroid gland (or removed from the body by the kidneys)
- Iodide taken up by the thyroid gland is **oxidized** by peroxidase in the lumen of the follicle:



- Oxidized iodine can then be used in the production of thyroid hormones

# Thyroid Regulation

- Hypothalamus secretes **Thyrotropin-Releasing Hormone (TRH)** which stimulates synthesis & release of thyrotropin (**Thyroid Stimulating Hormone** or TSH) by the anterior pituitary
- TSH then stimulates the thyroid gland to uptake iodine, synthesize & release T4 & T3
- T4 & T3 levels feedback to both hypothalamus & pituitary affecting the release of TRH & TSH

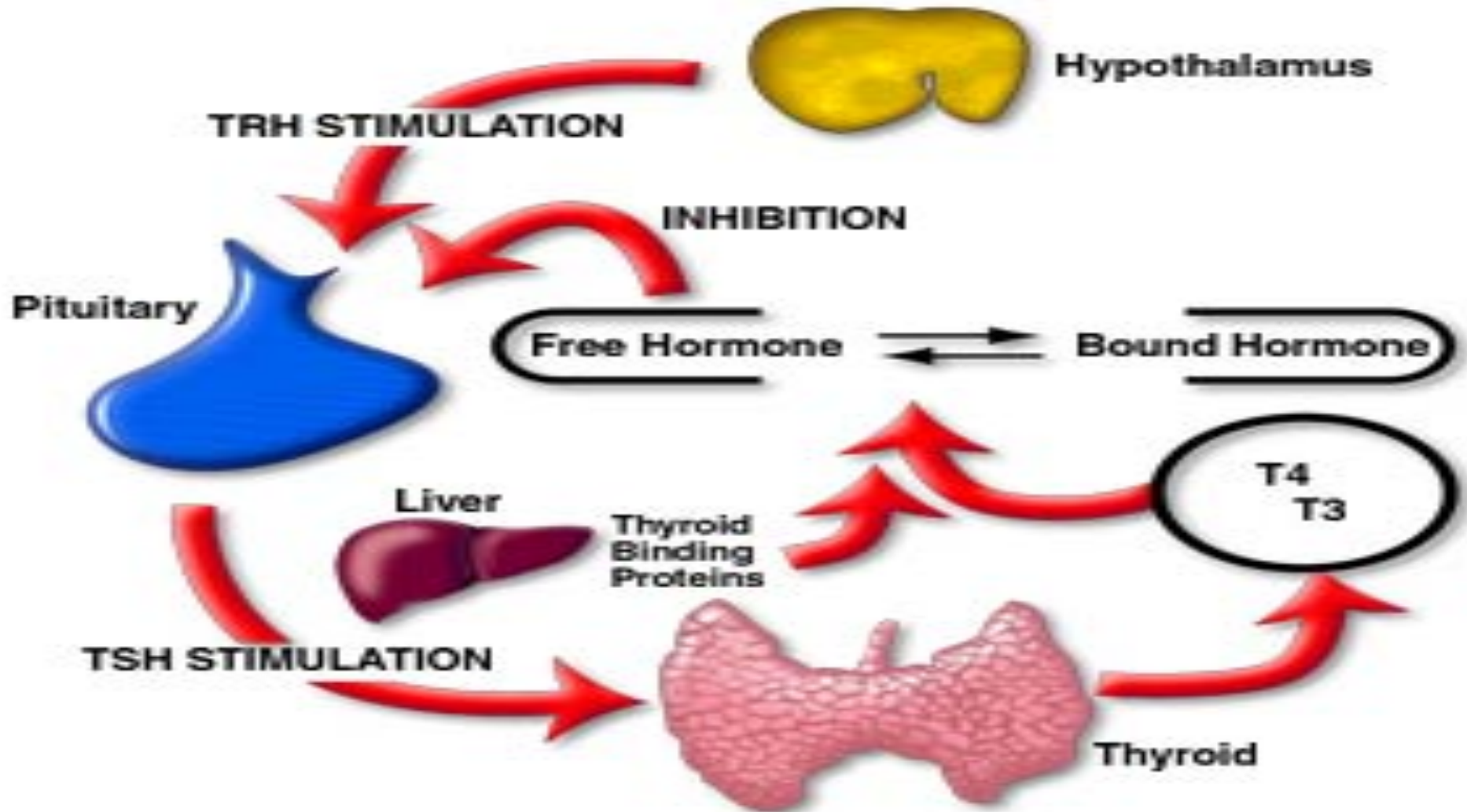




# Thyroid Regulation

- **TSH** release is influenced by hypothalamic **TRH**, and by thyroid hormones themselves.
- **Thyroid hormones** exert negative feedback on TSH release at the level of the anterior pituitary.
  - Inhibition of **TSH synthesis**
  - Decrease in **pituitary receptors for TRH**

# Thyroid Regulation



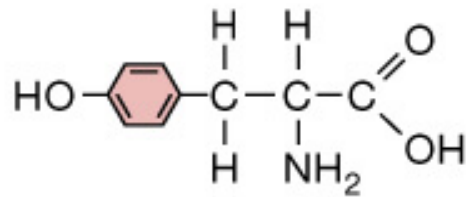
**TRH** (Thyrotropin Releasing Hormone)

**TSH** (Thyroid Stimulating Hormone or Thyrotropin)

# Thyroid Hormones

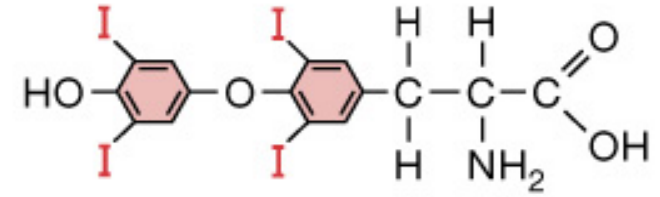
- There are two biologically active thyroid hormones:
  - **Tetraiodothyronine** (T<sub>4</sub>; thyroxine)
  - **Triiodothyronine** (T<sub>3</sub>)

**Tyrosine**



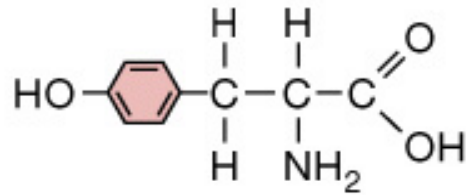
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**Thyroxine (T<sub>4</sub>)**



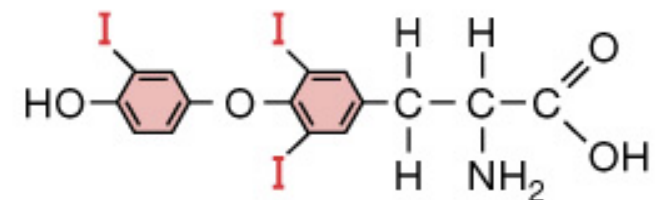
(2 tyrosine + 4 I)

**Tyrosine**

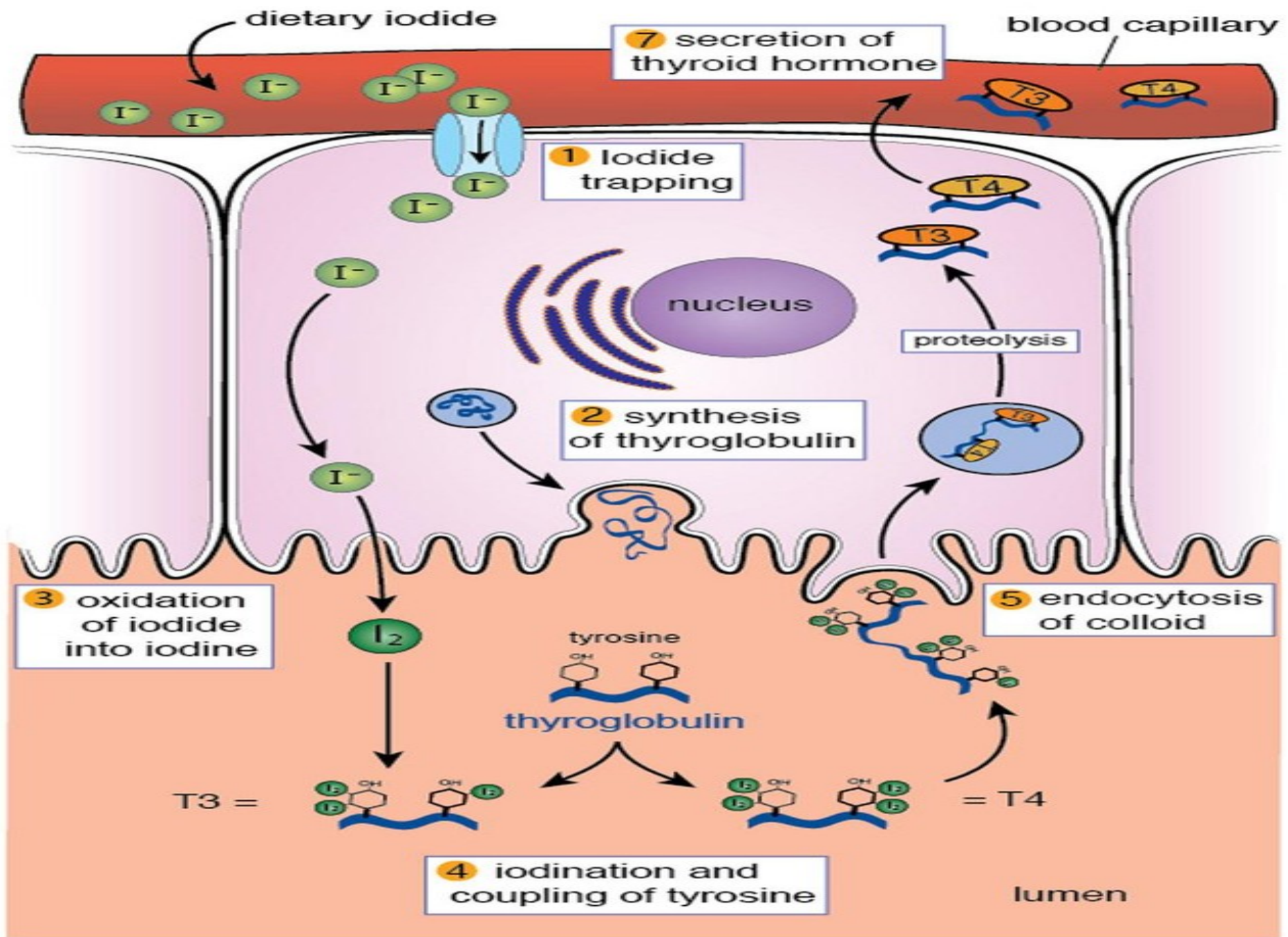


I

**Triiodothyronine (T<sub>3</sub>)**



(2 tyrosine + 3 I)



# Thyroid Hormones Synthesis

1. Iodide trapping: uptake of iodide by the thyroid gland
2. Oxidation of iodide: (to its active form)  
**thyroid peroxidase (key enzyme of the synthesis)**
3. Iodine organification : the iodination of tyrosyl groups of thyroglobulin into monoiodotyrosine (MIT),  
and diiodotyrosine (DIT).
4. Formation of T4 and T3 from MIT and DIT :  
**thyroid peroxidase (TPO)**

# Thyroid Hormones Disorders

## **THYROTOXICOSIS :**

**Is the term for all disorders with increased levels of circulating thyroid hormones**

## **HYPERTHYROIDISM :**

**Refers to disorders in which the thyroid gland secretes increased amounts of hormones**

## **HYPOTHYROIDISM:**

**Refers to disorders in which the thyroid gland secretes decreased amounts of hormones**

## **Thyroid neoplasia**

**Benign enlargement or malignancies of the gland**

**THYROTOXICOSIS is :**

**Hypermetabolic state caused by thyroid hormone excess at the tissue level**

**While HYPERTHYROIDISM is :**

**Increased thyroid hormones synthesis and secretion**

- All patients with hyperthyroidism have thyrotoxicosis**
- Not all patients with thyrotoxicosis have hyperthyroidism**

# Causes of thyrotoxicosis

## With high RAIU

- Graves' disease (60-80%)
- Multinodular goitre (14%)
- Adenomas / carcinomas

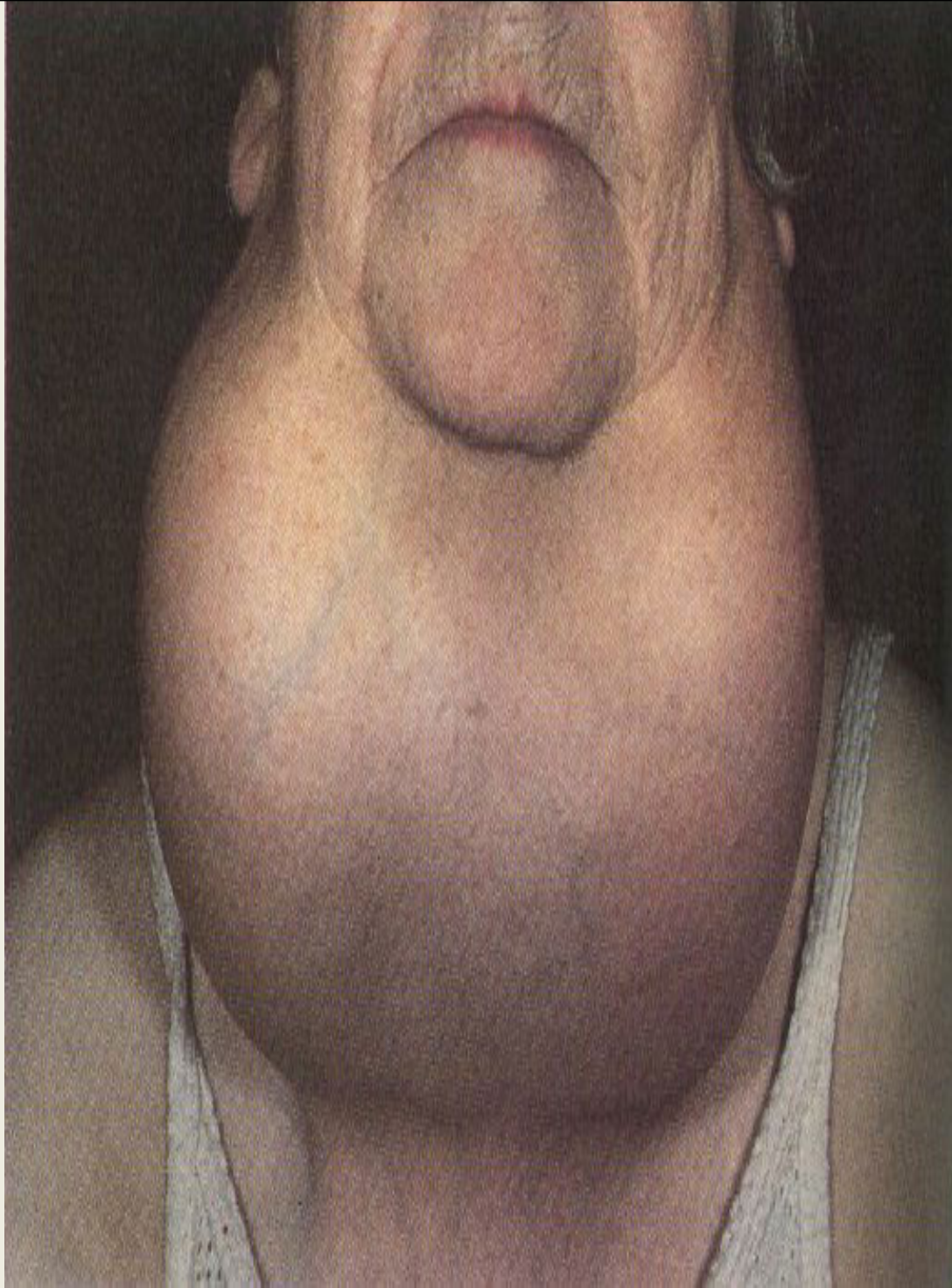
## With low RAIU

- Thyroiditis
- Iodine-induced thyrotoxicosis:
  - Drugs (e.g. Amiodarone)
  - Radiographic contrast media



# **Features of Graves' Disease (Diffuse Toxic Goiter)**

- Caused by thyroid stimulating immunoglobulins that stimulate TSH receptor, resulting in sustained thyroid over activity**
- Mainly in young adults aged 20 to 50**
- 5 times more frequent in women**
- Swelling and soft tissues of hands and feet**
- Clubbing of fingers and toes**
- Half of cases have Exophthalmos (not seen with - other causes of hyperthyroidism)**
- 5% have pretibial myxedema (thyroid dermopathy)**



F. Netter  
M.D.  
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SEVERE  
PROGRESSIVE  
EXOPHTHALMOS

TESTING FOR  
RESILIENCY



**Pretibial  
myxedema**

# **Features of Toxic Multi-nodular Goiter**

- **Second most common cause of hyperthyroidism**
- **Most cases in women in 5th to 7th decades**
- **Often have long standing goiter**
- **Symptoms usually develop slowly**

# THYROTOXICOSIS

## Symptoms:

- Irritability
- Dysphoria
- Heat intolerance & sweating
- Palpitations
- Fatigue & weakness
- Weight loss
- Diarrhea

## Signs:

- Arrhythmias
- Thyroid enlargement
- Warm, moist skin
- Exophthalmus
- Pretibial myxedema

# Treatment of Hyperthyroidism

- ***Thioamides ( antithyroid drugs)***
- **Iodides**
- **Radioactive iodine**
- **Beta blockers**
- **Surgery**

# THIOAMIDES

- **Propylthiouracil ( PTU )**

- **Methimazole**

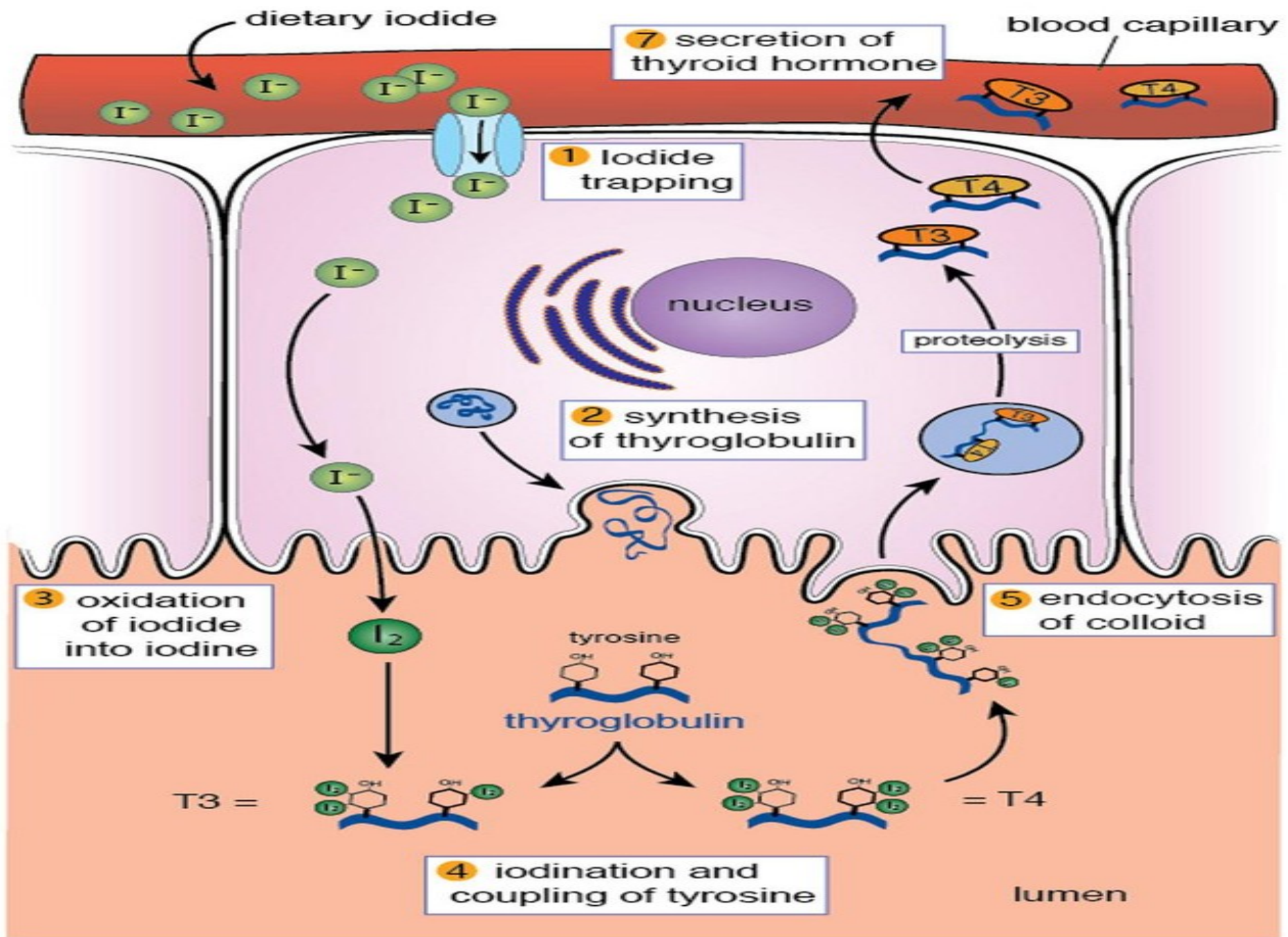
- **Carbimazole**

( prodrug converted to the active metabolite methimazole)

# Mechanism of Action

- Inhibit synthesis of thyroid hormones by inhibiting the peroxidase enzyme that catalyzes the iodination of tyrosine residues
- Propylthiouracil ( but not methimazole ) blocks the conversion of T4 to T3 in peripheral tissues





# Pharmacokinetic comparison between Propylthiouracil and Methimazole

	Propylthiouracil	Methimazole
<b>Absorption</b>	Rapidly absorbed	Rapidly absorbed
<b>Protein binding</b>	80-90%	Most of the drug is free
<b>Accumulation</b>	in thyroid	in thyroid
<b>Excretion</b>	Kidneys as inactive metabolite within 24 hrs	Excretion slow, 60-70% of drug is recovered in urine in 48 hrs

# Pharmacokinetic comparison between Propylthiouracil and Methimazole

	<b>Propylthiouracil</b>	<b>Methimazole</b>
<b>Half life</b>	1.5 hrs ( short )	6 hrs ( long )
<b>Administration</b>	Every 6-8 hours	Every 8 hours
<b>Pregnancy</b>	<p><b>Crosses placenta</b></p> <p><b>Recommended in pregnancy ( Crossing placenta is less readily as it is highly protein bound )</b></p>	<p><b>Concentrated in Thyroid &amp; crosses placenta</b></p> <p><b>Not recommended in pregnancy</b></p>
<b>Breast feeding</b>	<p><b>Less secreted in breast milk</b></p> <p><b>Recommended</b></p>	<p><b>secreted</b></p> <p><b>Not recommended</b></p>

# Adverse Effects Thioamides

<b>Adverse Effect</b>	<b>Frequency</b>	<b>comments</b>
<b>Skin reactions</b>	4–6%	<b>Urticarial or macular reactions</b>
<b>Arthralgia</b>	1–5%	
<b>Polyarthrititis</b>	1–2%	<b>So-called anti-thyroid arthritis</b>
<b>GIT effects</b>	1–5%	<b>gastric distress and nausea</b>

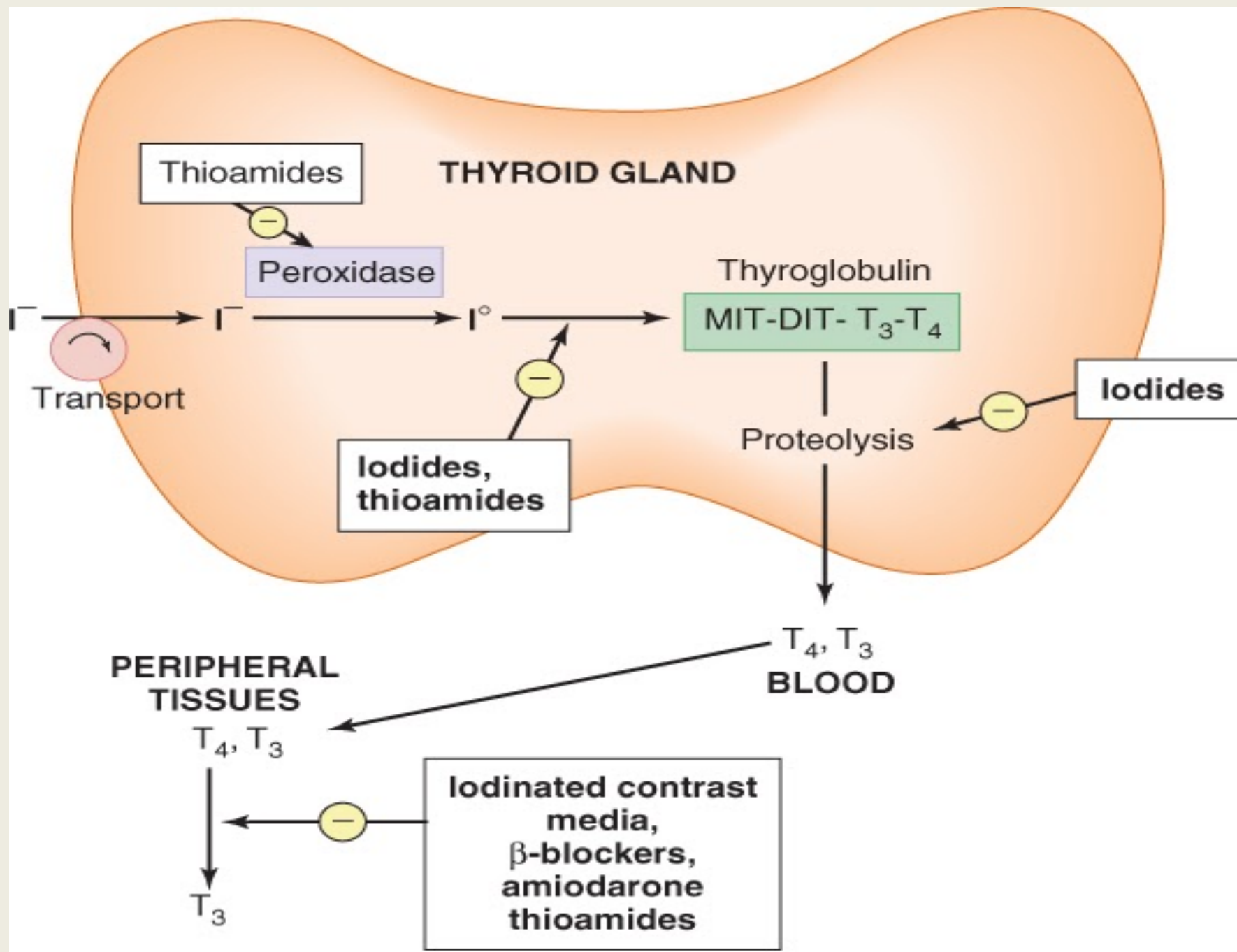
## Adverse Effects (cont.)

Adverse Effect	Frequency	comments
<b>Immunoallergic hepatitis</b>	0.1–0.5%	Almost exclusively in patients taking <b>propylthiouracil</b>
<b>Agranulocytosis</b>	0.1–0.5%	Seen in patients with Graves' disease; occurs within 90 days of treatment
<b>ANCA-positive vasculitis</b> <i>(Anti-neutrophil cytoplasmic antibodies)</i>	Rare	With <b>propylthiouracil</b>
<b>Abnormal sense of taste or smell</b>	Rare	With <b>methimazole</b> only

# **IODINE (Lugol's solution, potassium iodide)**

## **Mechanism of action**

- **Inhibit thyroid hormone synthesis and release**
- **Block the peripheral conversion of T4 to T3**
- **The effect is not sustained ( produce a temporary remission of symptoms )**



# Therapeutic uses

- **Prior to thyroid surgery to decrease vascularity & size of the gland**
- **Following radio active iodine therapy**
- **Thyrotoxicosis**

## Examples

- **Organic iodides as : iopanoic acid or ipodate**
- **Potassium iodide**



# Precautions / toxicity

- Should not be used as a single therapy
- **Should not be used in pregnancy**
- May produce iodism ( Rare, as iodine is not much used now)

## **Iodism Symptoms:**

(skin rash , hypersalivation, oral ulcers, metallic taste, bad breath).

# **RADIOACTIVE IODINE ( RAI )**

- $^{131}\text{I}$  isotope ( therapeutic effect due to emission of  $\beta$  rays )**
- Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels.**
- Clinical improvement may take 2-3 months**
- Half -life 5 days**
- Cross placenta & excreted in breast milk**
- Easy to administer, effective, painless and less expensive**

# Radioactive Iodine ( con.)

- Available as a solution or in capsules
- **Clinical uses :**
  - Hyperthyroidism mainly in old patients (above 40)
  - Graves' disease
  - Patients with toxic nodular goiter
  - As a diagnostic

# Disadvantages

- **High incidence of delayed hypothyroidism**
- **Large doses have cytotoxic actions ( necrosis of the follicular cells followed by fibrosis )**
- **May cause genetic damage**
- **May cause leukemia & neoplasia**

# ADRENOCEPTOR BLOCKING AGENTS

- **Adjunctive therapy to relieve the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.**
- **E.g. Propranolol, Atenolol, Metoprolol**
- **Propranolol is contraindicated in asthmatic patients**

# Thyrotoxicosis during pregnancy

- Better to start therapy before pregnancy with  $^{131}\text{I}$  or subtotal thyroidectomy to avoid acute exacerbation during pregnancy
- During pregnancy radioiodine is contraindicated.
- Propylthiouracil is the drug of choice during pregnancy.

# THYROID STORM

- **A sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life threatening syndrome.**
- **There is hyper metabolism, and excessive adrenergic activity, death may occur due to heart failure and shock.**
- **It is a medical emergency .**

# Management of thyroid storm

- Should be treated in an ICU for close monitoring of vital signs and for access to invasive monitoring and inotropic support
- **Correct electrolyte abnormalities**, Treat cardiac arrhythmia ( if present ) & Aggressively control hyperthermia by applying ice packs
- Promptly administer **antiadrenergic drugs** (e.g. propranolol) to minimize sympathomimetic symptoms



# Management of thyroid storm ( cont..)

- High-dose Propylthiouracil (PTU) is preferred because of its early onset of action ( **risk of severe liver injury and acute liver failure** )
- Administer iodine compounds (Lugol's iodine or potassium iodide) orally or via a nasogastric tube
- Hydrocortisone 50 mg IV every 6 hours to prevent shock.
- Rarely, plasmapheresis has been used to treat thyroid storm

# Management of Hyperthyroidism due to Graves' disease

## Severe Hyperthyroidism



[ markedly elevated serum T4 or T3  
very large goiter, > 4 times normal ]



Definitive therapy with radioiodine preferred in **adults**



Normalization of thyroid function with anti-thyroid drugs before surgery in **elderly patients** and those with heart disease

# Management of Hyperthyroidism due to Graves' disease

## Mild/moderate hyperthyroidism



[ small or moderately enlarged thyroid; children or pregnant or lactating women ]



Primary anti-thyroid drug therapy should be considered



Start methimazole, 5–30 mg/day,  
(PTU preferred in pregnant women)



Monitor thyroid function every 4–6 wk until **euthyroid state** achieved



# Management of Hyperthyroidism due to Graves' disease

## Mild/moderate hyperthyroidism



**Discontinue** drug therapy after 12–18 mo



**Monitor** thyroid function every 2 mo for 6 mo,  
then less frequently



**Relapse**



Definitive radioiodine  
therapy in adults

(Second course of anti-thyroid  
drug therapy in children)



**Remission**



Monitor thyroid function  
every 12 mo indefinitely

# THYROIDECTOMY

- **Sub-total thyroidectomy is the treatment of choice in very large gland or multinodular goiter**

Good Luck