

DRUGS USED IN HYPERTHYROIDISM

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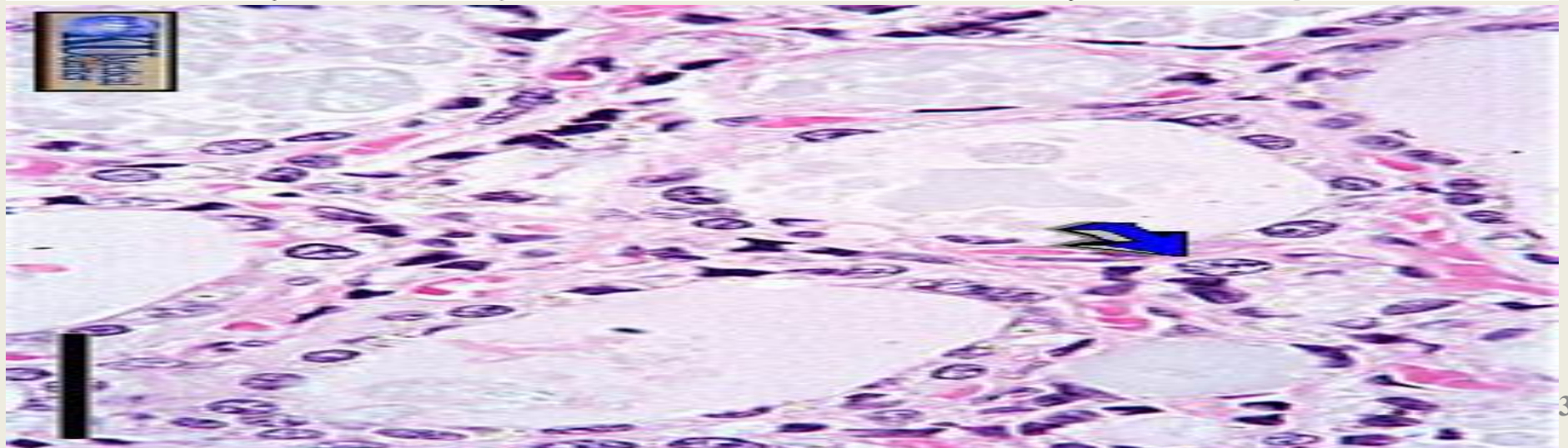
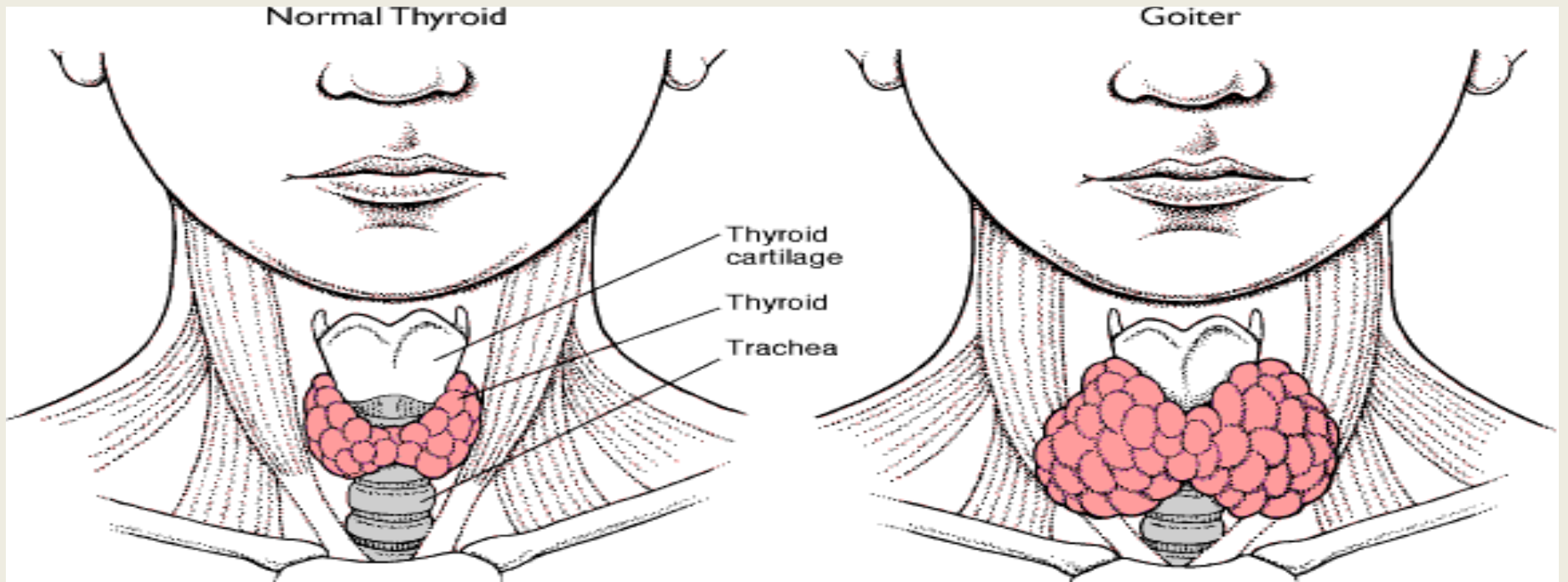
Slides were adapted from prof. AlMotrfi and prof. Bassiouni

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**

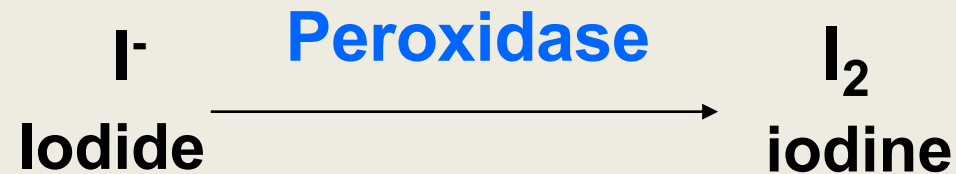
Thyroid function

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
 - iodized bread
 - dairy products
 - shellfish
- Minimum requirement: 75 micrograms/day

Iodine Metabolism

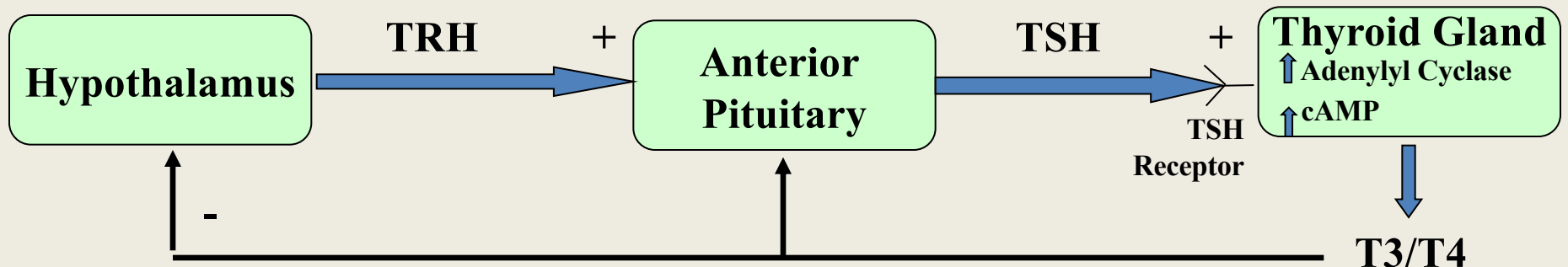
- Dietary iodine is **absorbed in the GI tract**, then taken up by the thyroid gland (or removed from the body by the kidneys)
- Iodide taken up by the thyroid gland is **oxidized** by peroxidase in the lumen of the follicle:



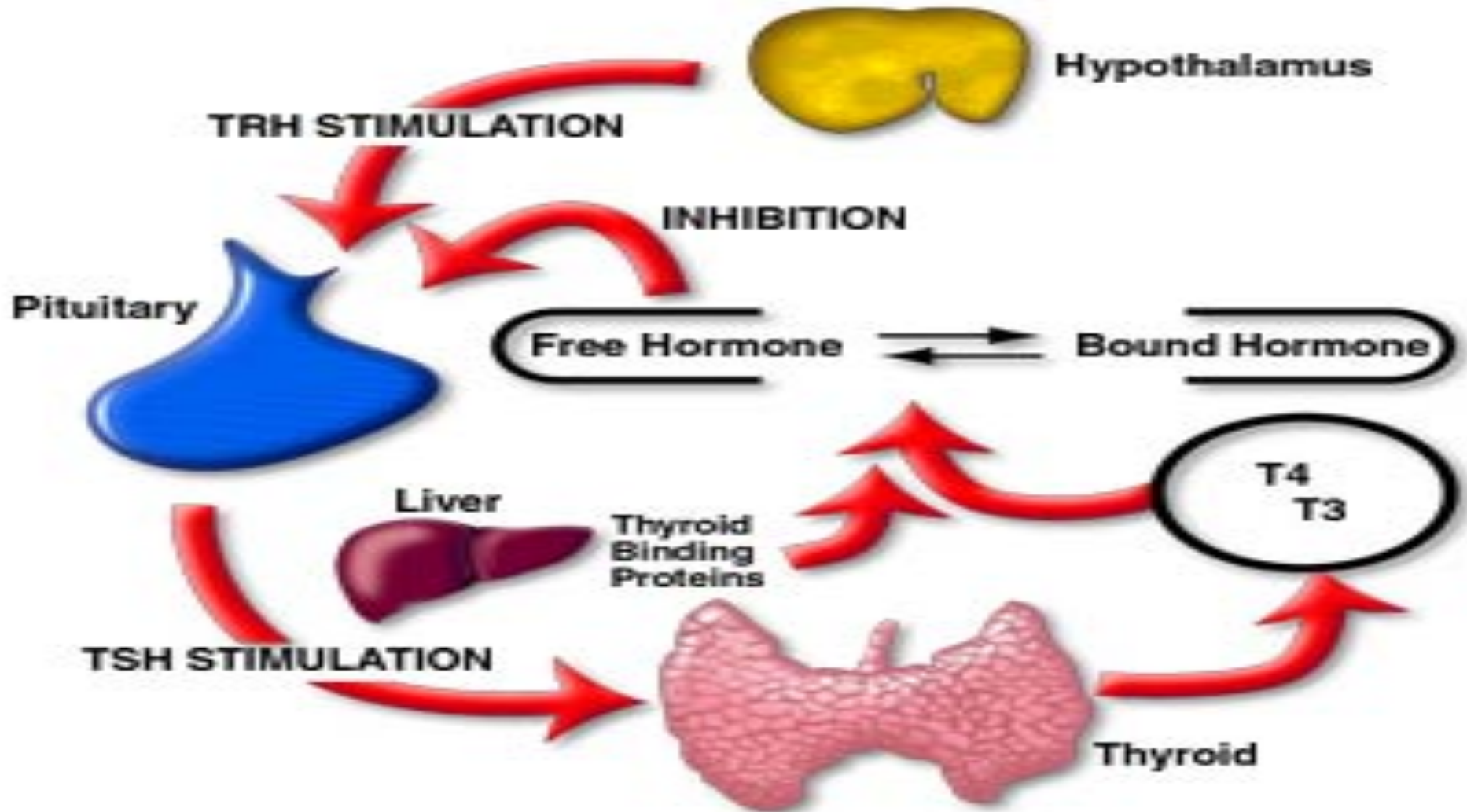
- Oxidized iodine can then be used in production of thyroid hormones

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



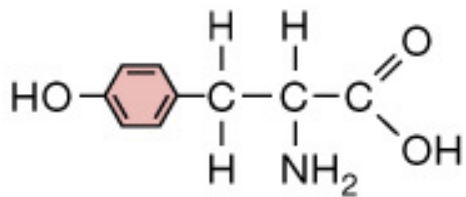
TRH (Thyrotropin Releasing Hormone)

TSH (Thyroid Stimulating Hormone or Thyrotropin)

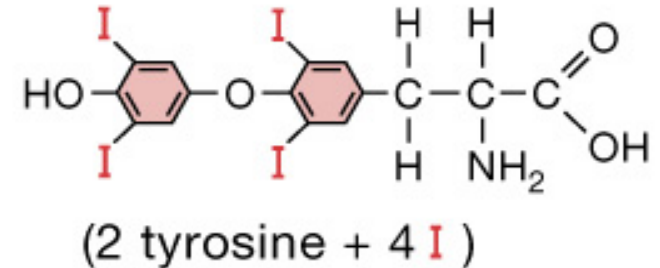
Thyroid Hormones

- There are two biologically active thyroid hormones:
 - **Tetraiodothyronine** (T4; thyroxine)
 - **Triiodothyronine** (T3)

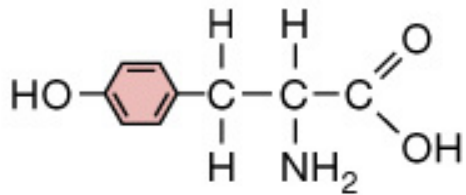
Tyrosine



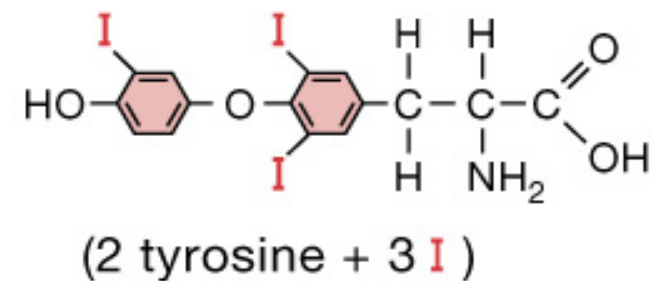
Thyroxine (T4)

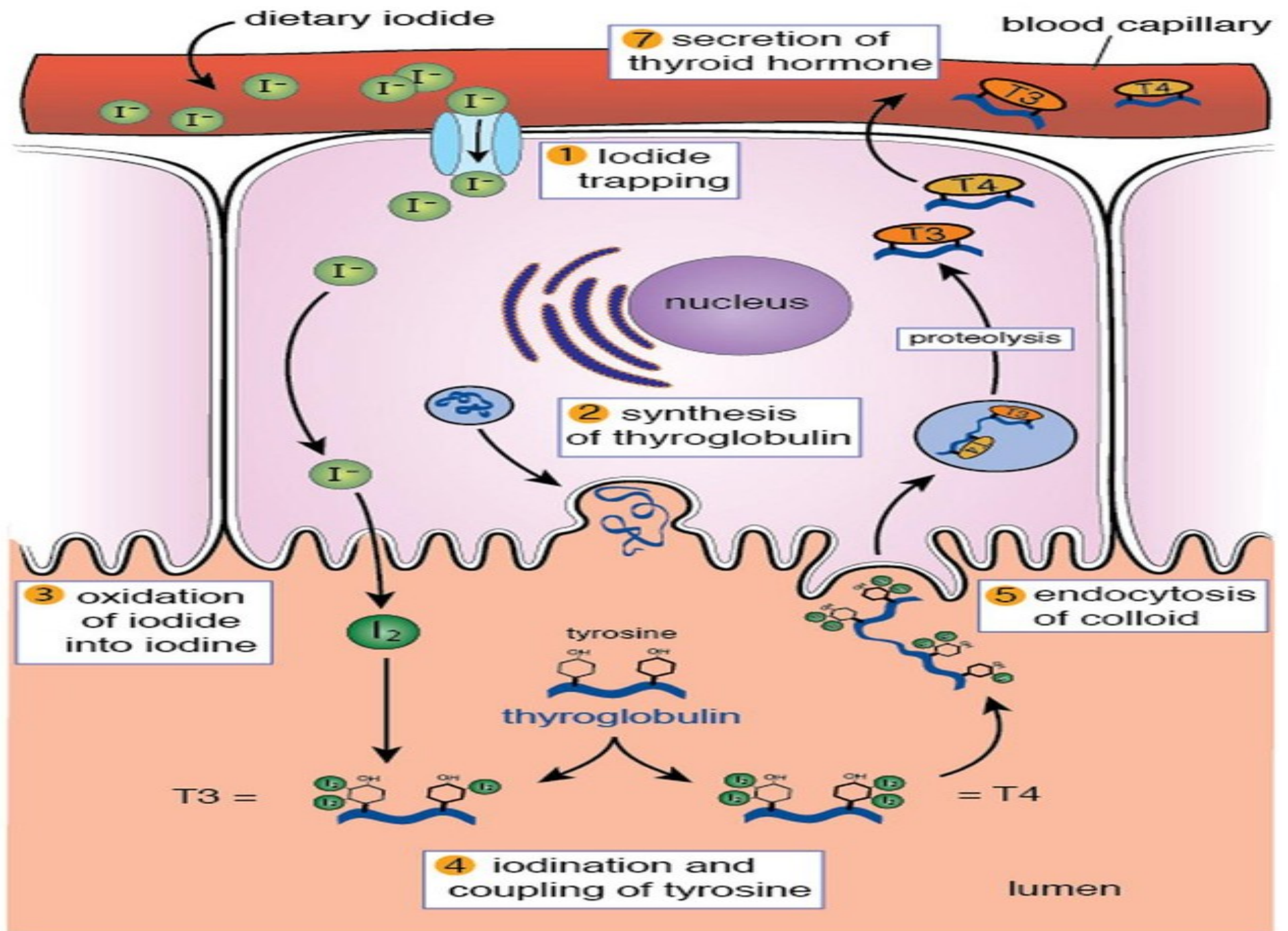


Tyrosine



Triiodothyronine (T3)





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 excess thyroid hormone 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

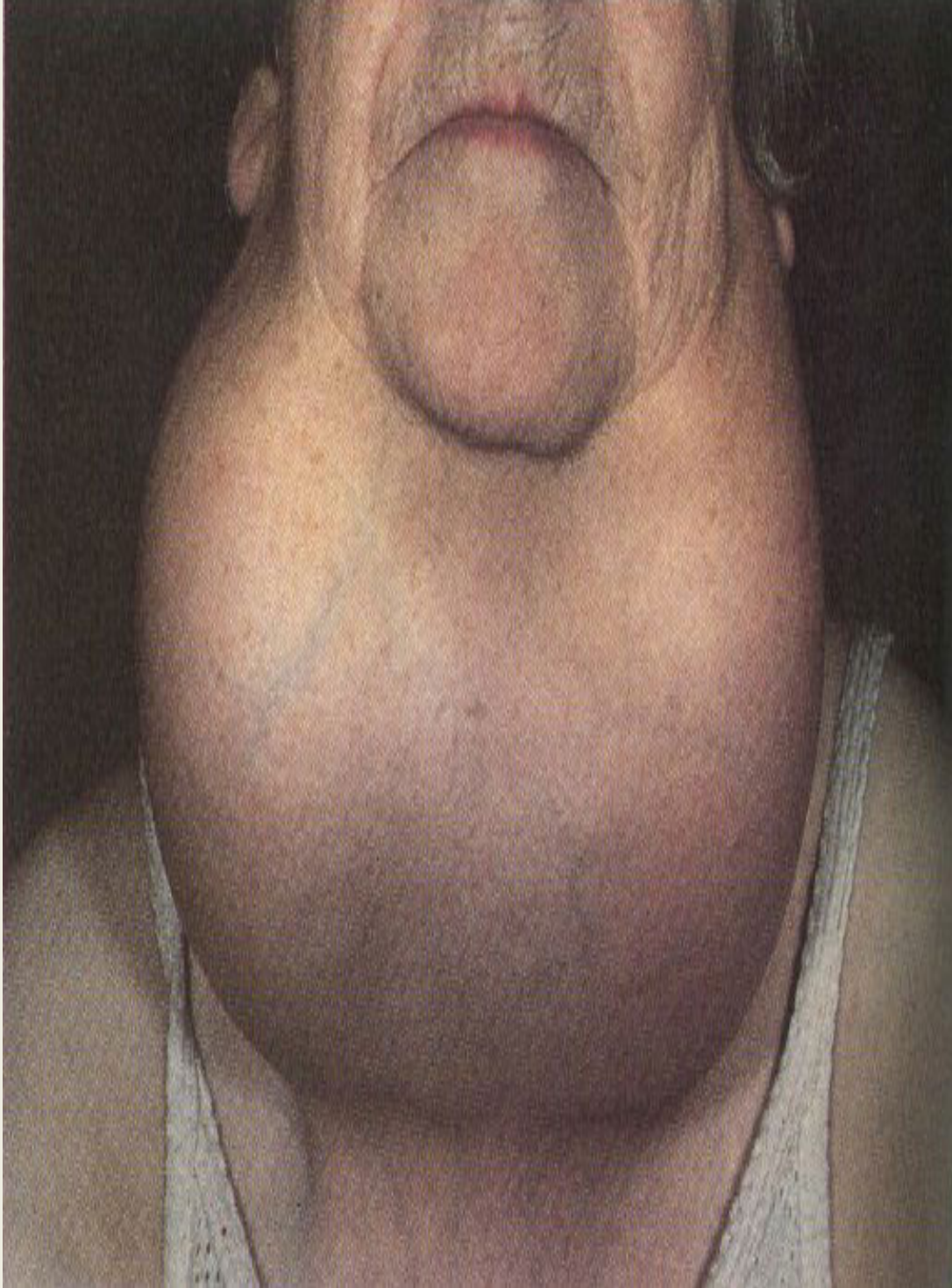
- Graves' disease (60-80%)
- Multinodular goitre (14%)
- Adenomas / carcinomas

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**
- Clubbing of fingers and toes**
- Half of cases have Exophthalmos (not seen with - other causes of hyperthyroidism)**
- 5% have pretibial myxedema (thyroid dermopathy)**





**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)**

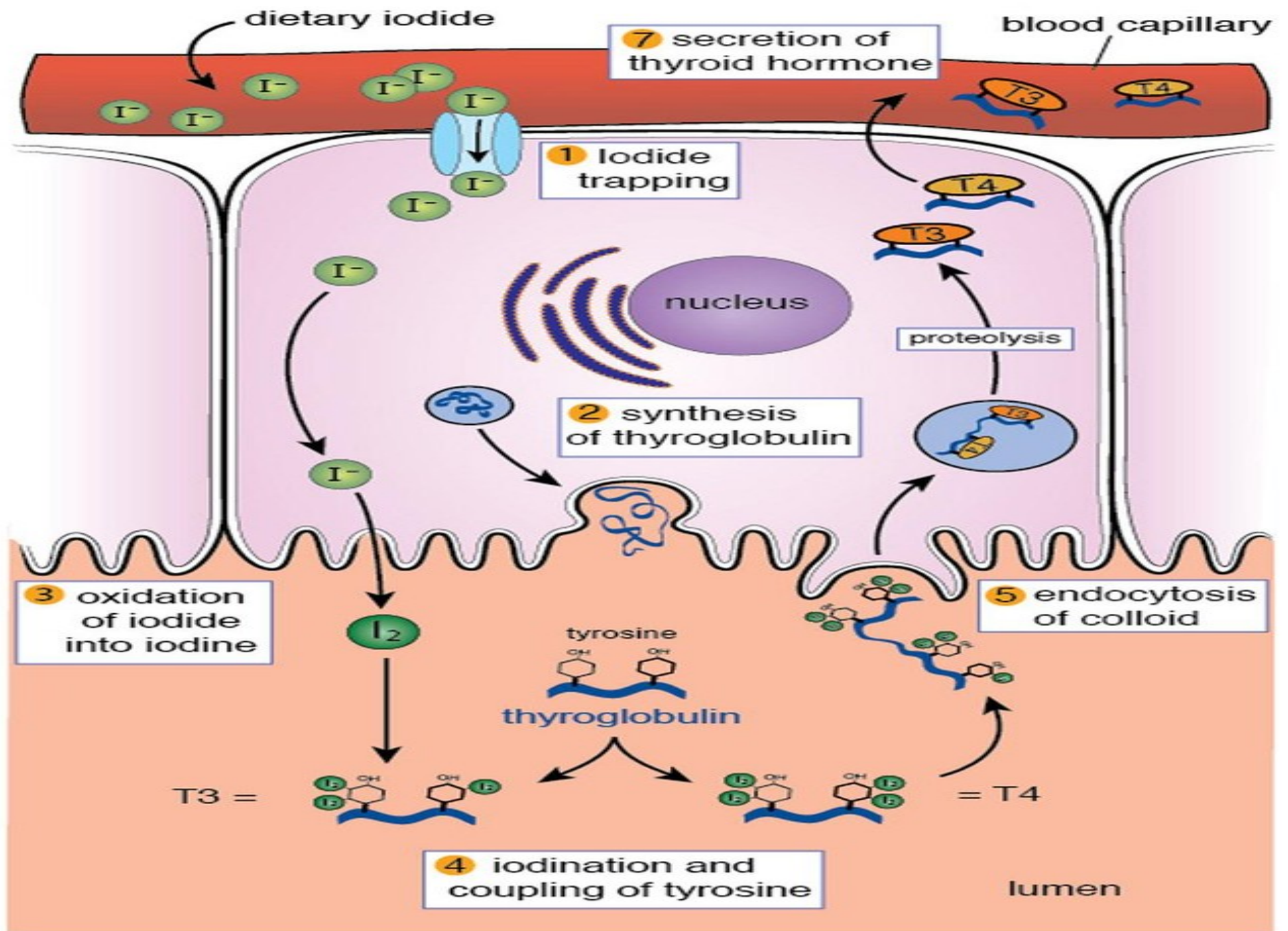
- **Methimazole**

- **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
Absorption	Rapidly absorbed	Rapidly absorbed
Protein binding	80-90%	Most of the drug is free
Accumulation	in thyroid	in thyroid
Excretion	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

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

Adverse Effects Thioamides

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

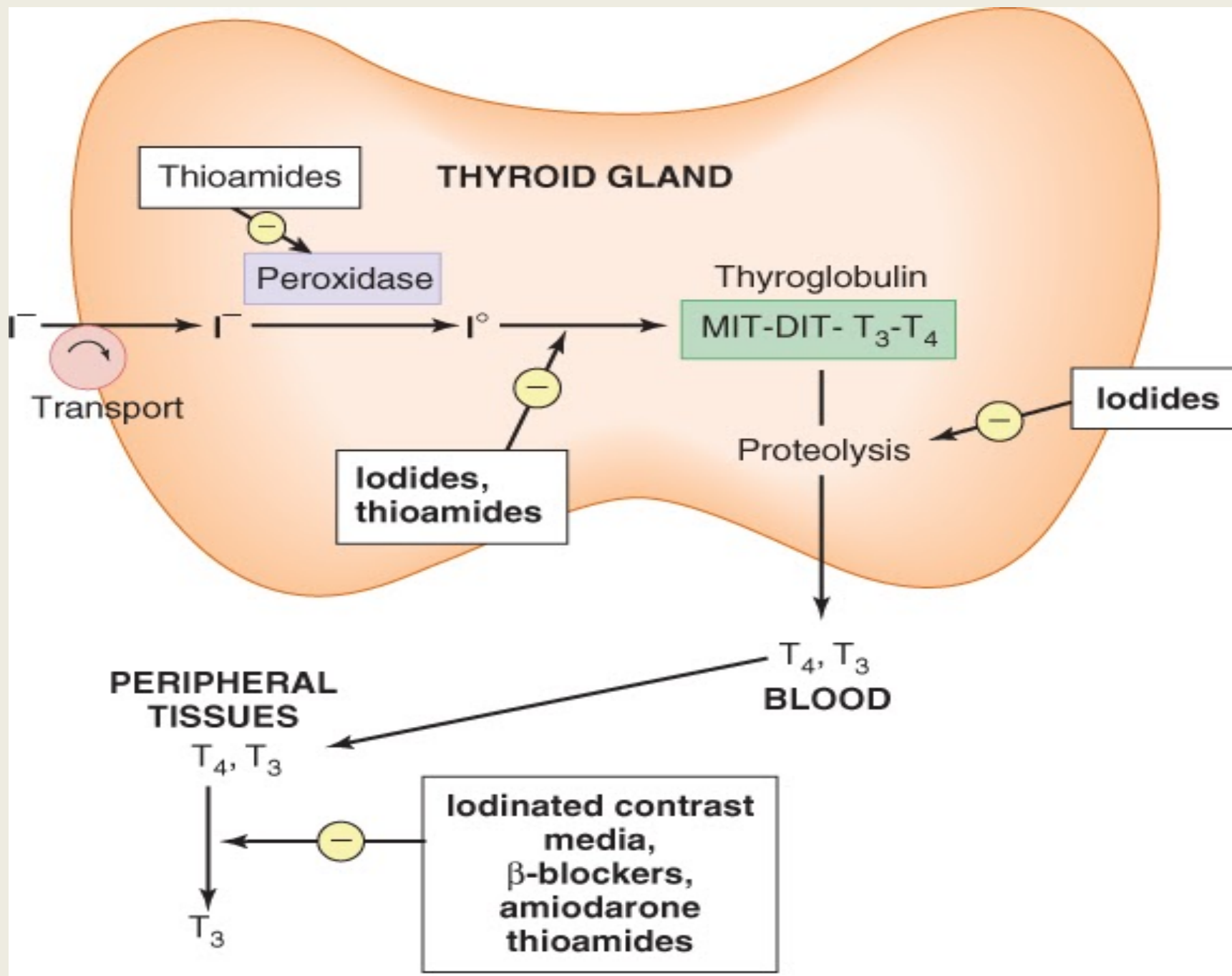
Adverse Effects (cont.)

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

- **Prior to thyroid surgery to decrease vascularity & size of the gland**
- **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}I isotope (therapeutic effect due to emission of β 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}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