DRUGS USED IN HYPERTHYROIDISM

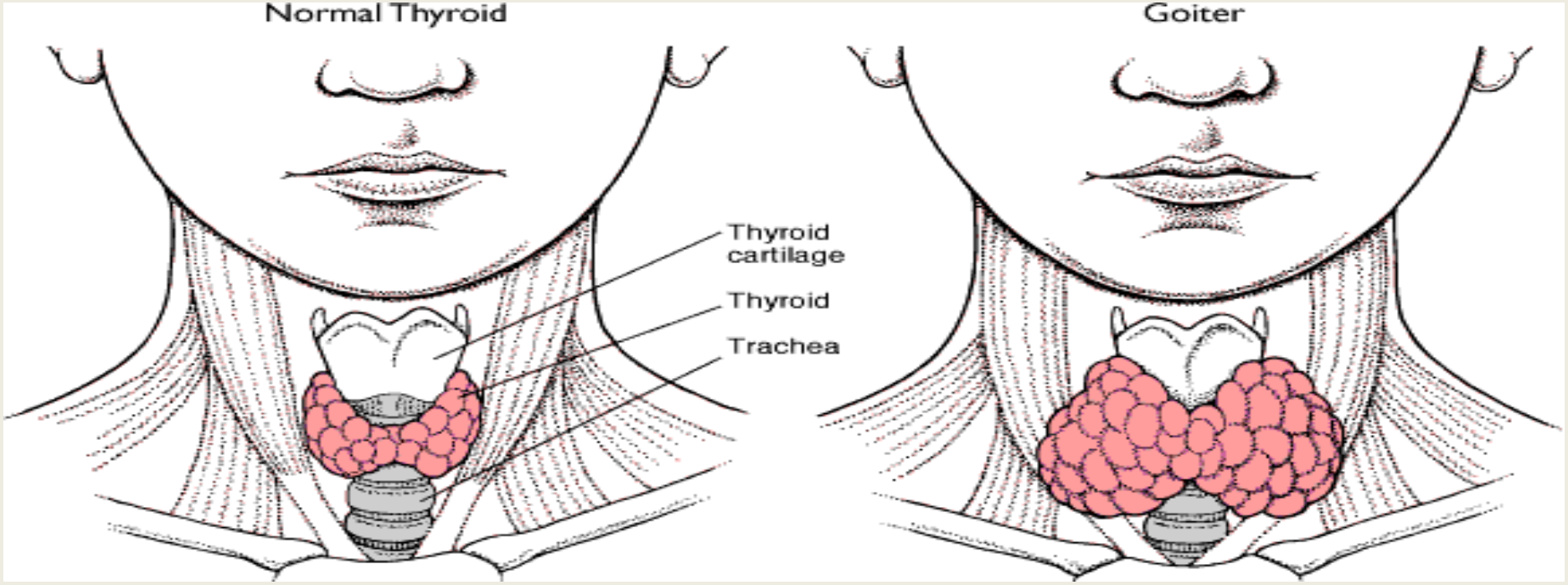
Slides were adapted from prof. AlMotrfi and prof. Bassiouni

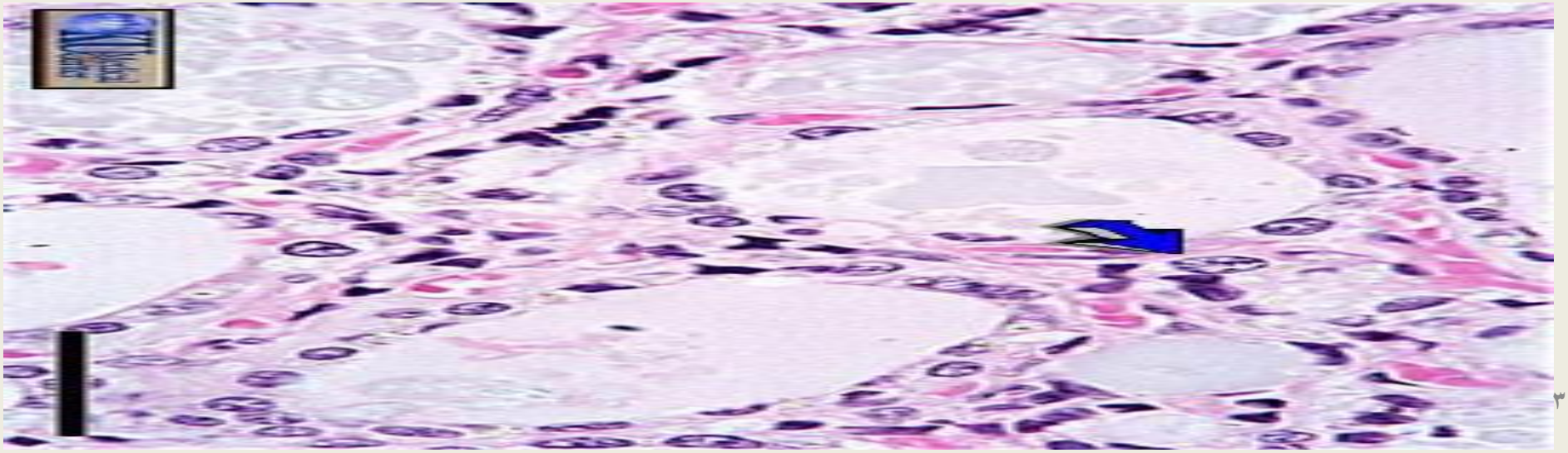
Learning objectives

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**

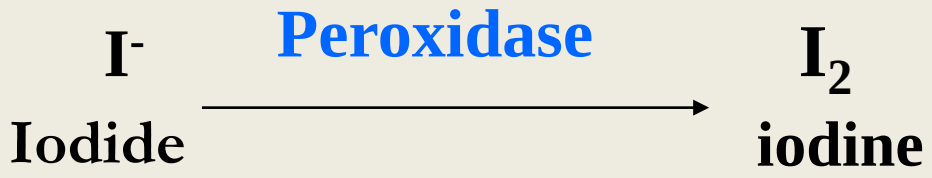
Thyroid function

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

Iodine Metabolism

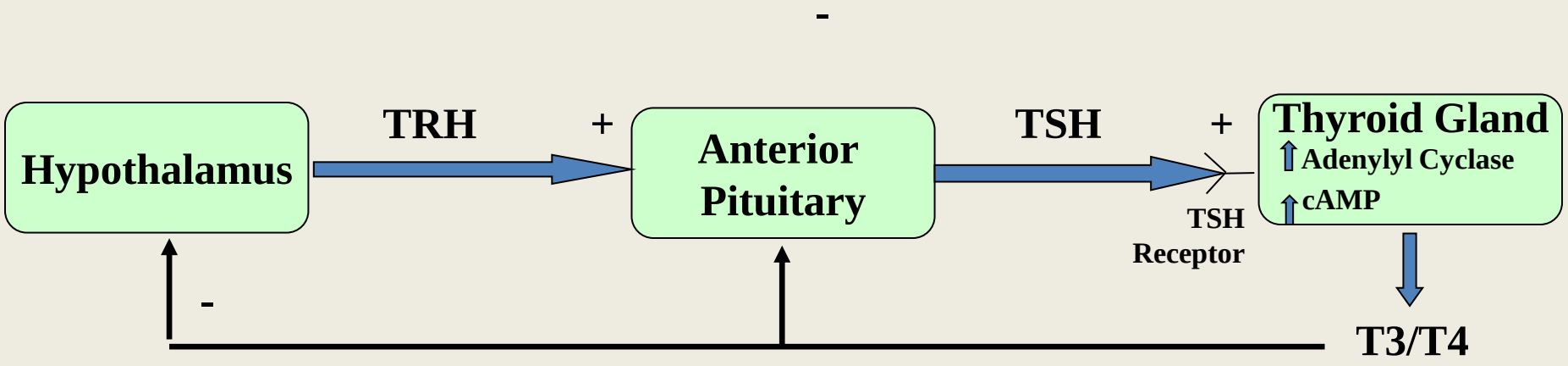
- **Dietary iodine is absorbed in the GI tract, then taken up by the thyroid gland (or removed from the body by the kidneys)**
- **Iodide taken up by the thyroid gland is oxidized by peroxidase in the lumen of the follicle:**



- **Oxidized iodine can then be used in 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

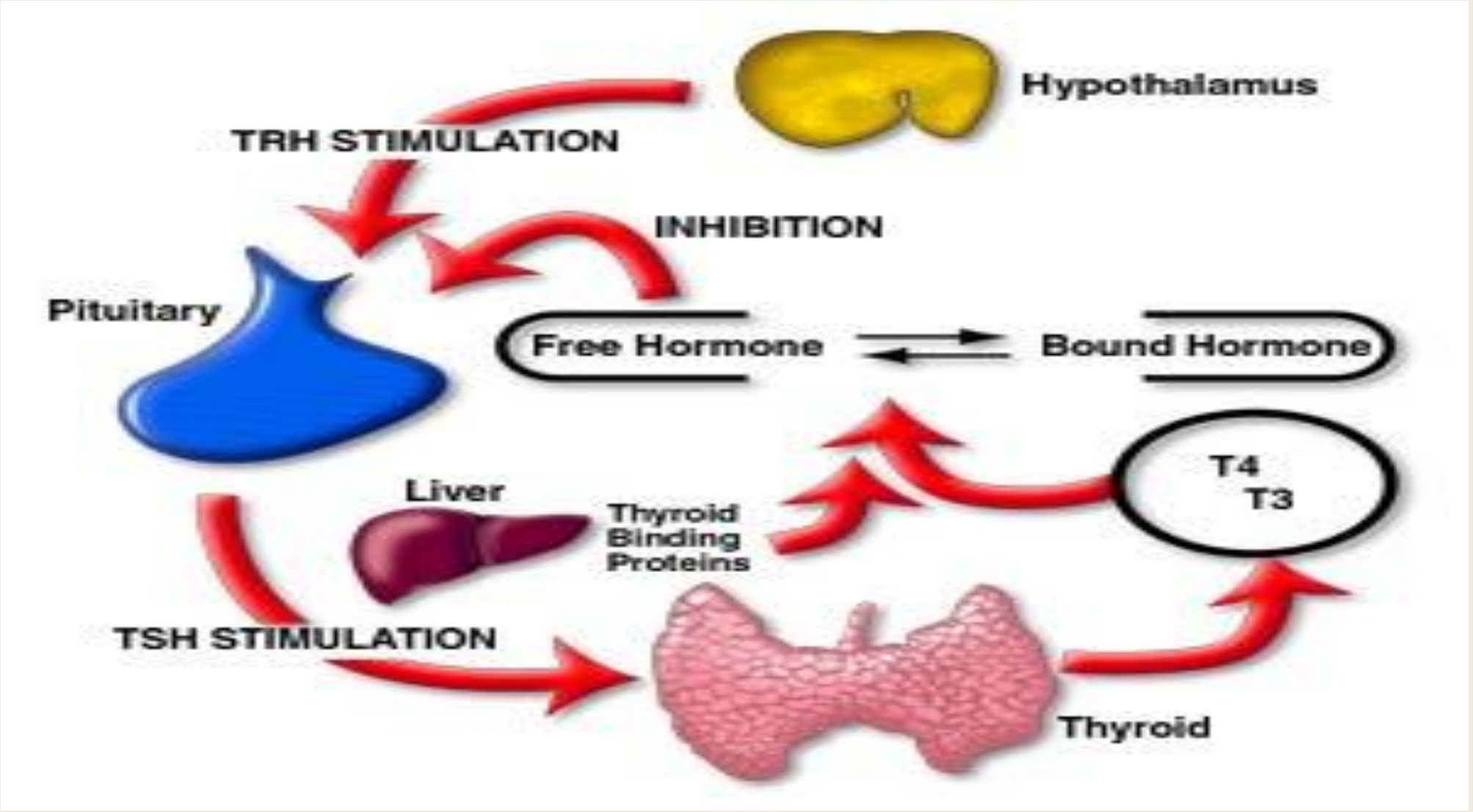


Thyroid Regulation

- **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**

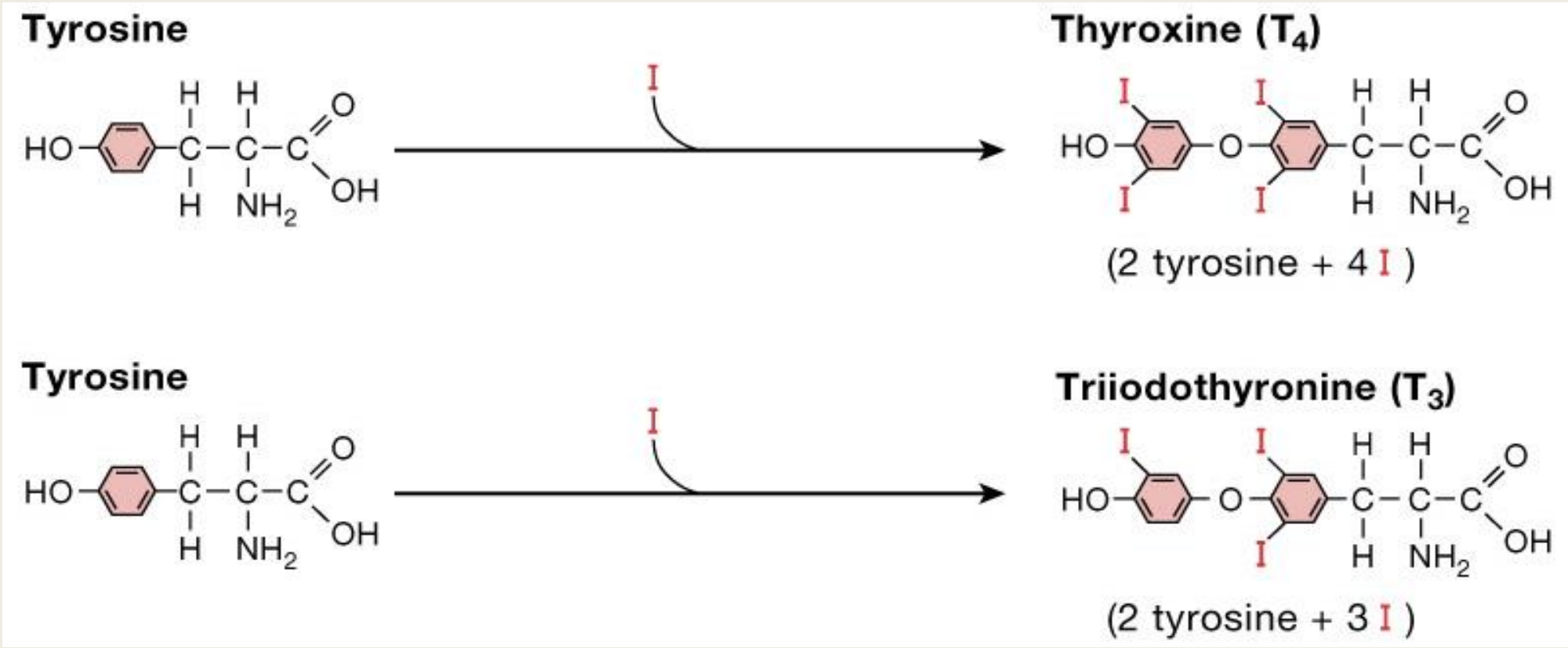
Thyroid Regulation

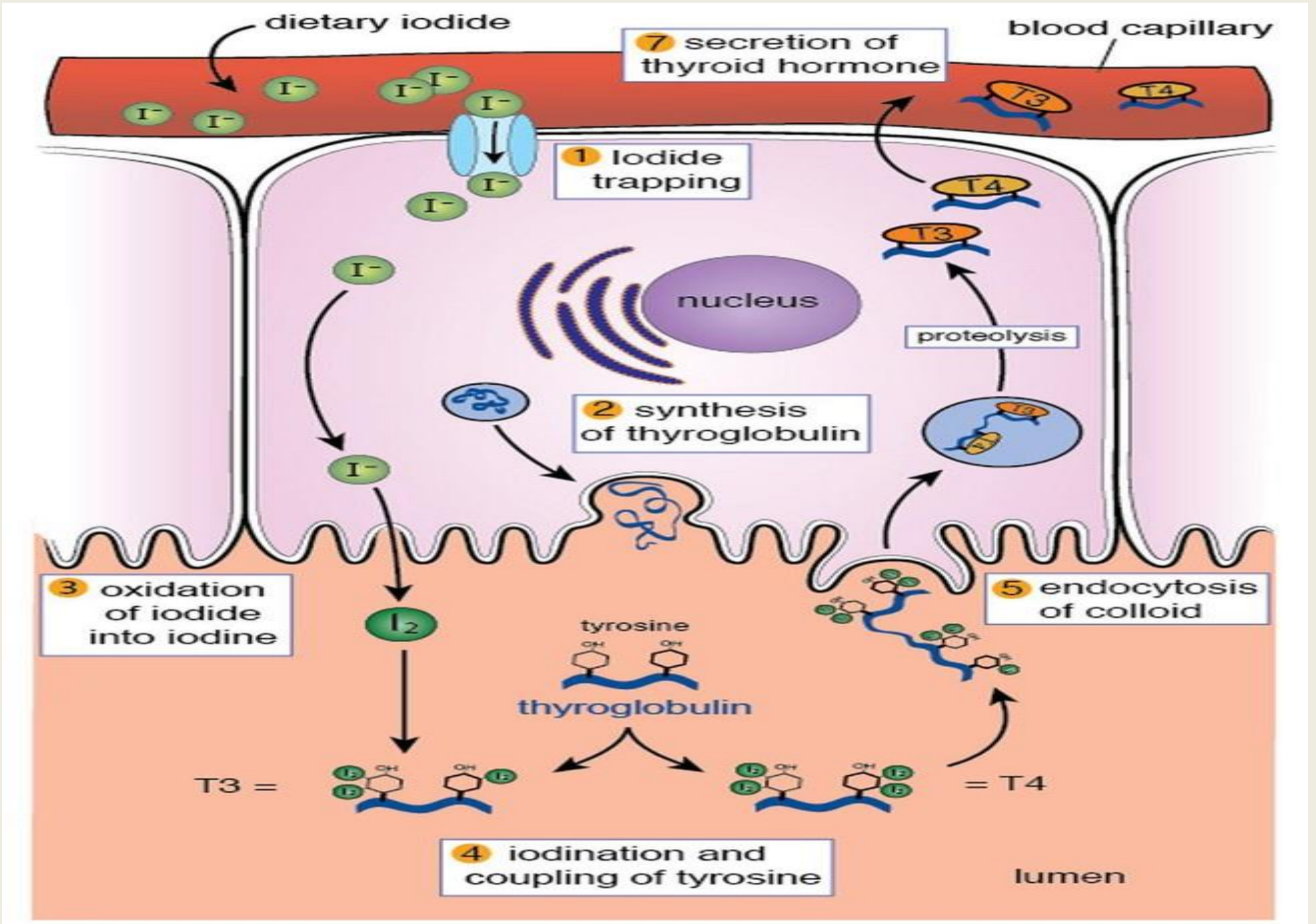


TRH (Thyrotropin Releasing Hormone)
TSH (Thyroid Stimulating Hormone or Thyrotropin)

Thyroid Hormones

- There are two biologically active thyroid hormones:
  - **Tetra**iodothyronine (T4; thyroxine)
  - **Tri**iodothyronine (T3)




dietary iodide
blood capillary
7 secretion of thyroid hormone
1 Iodide trapping
nucleus
proteolysis
2 synthesis of thyroglobulin
3 oxidation of iodide into iodine
5 endocytosis of colloid
tyrosine
thyroglobulin
T3 =
= T4
4 iodination and coupling of tyrosine
lumen

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

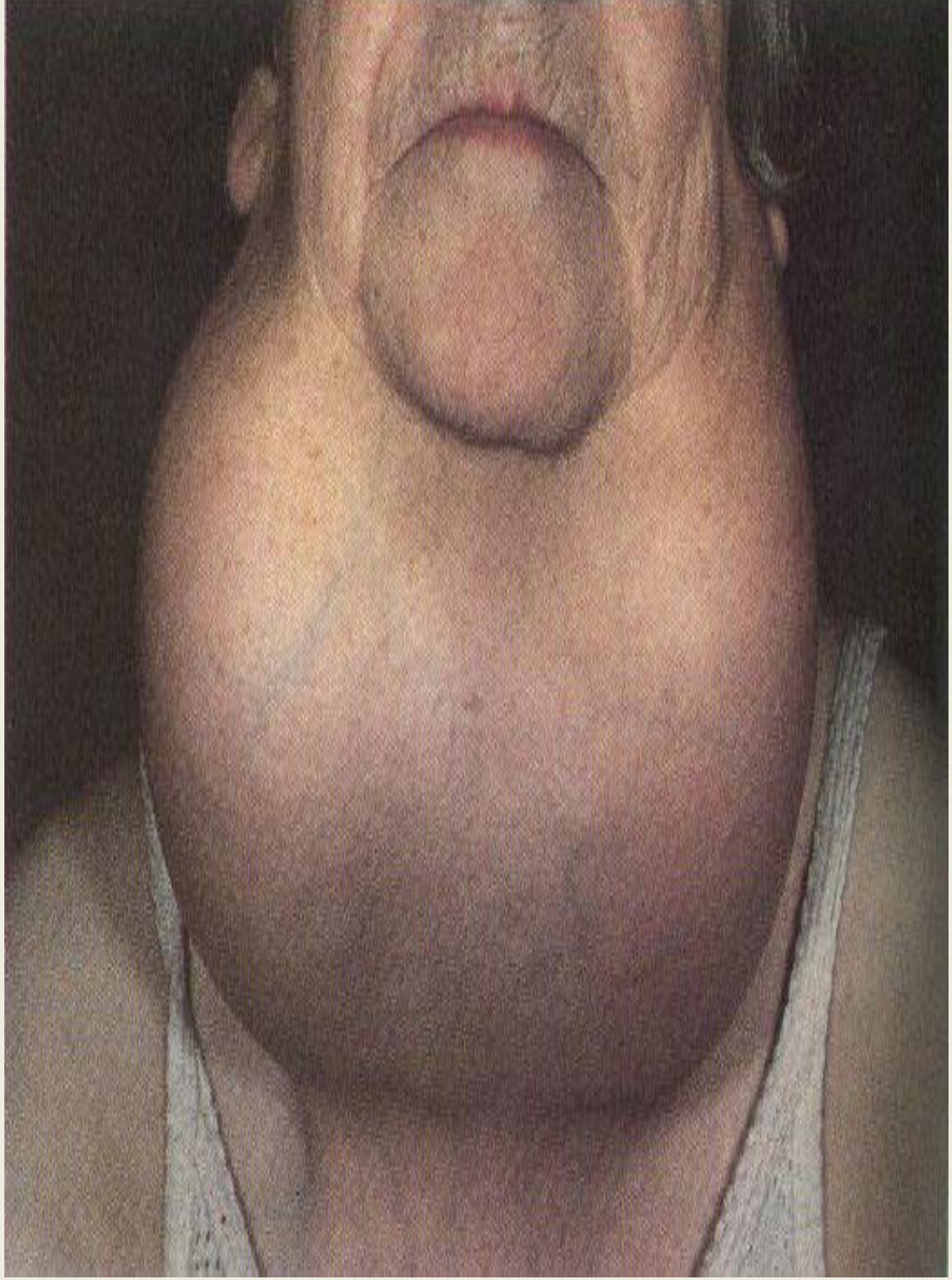
With low RAIU

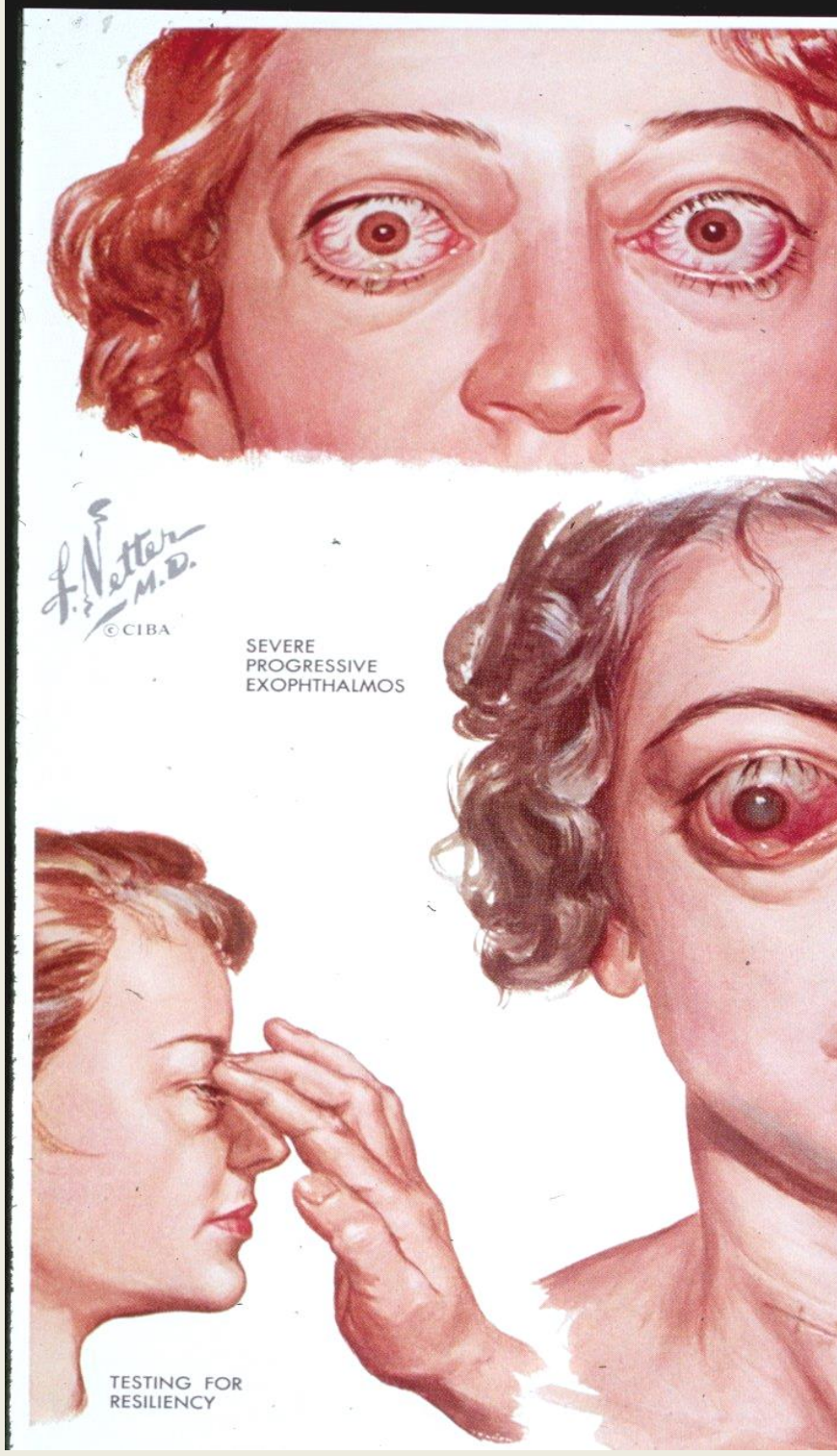
- Thyroiditis
- Iodine-induced thyrotoxicosis:
    - Drugs (e.g. Amiodarone)
    - Radiografic contrast media

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)

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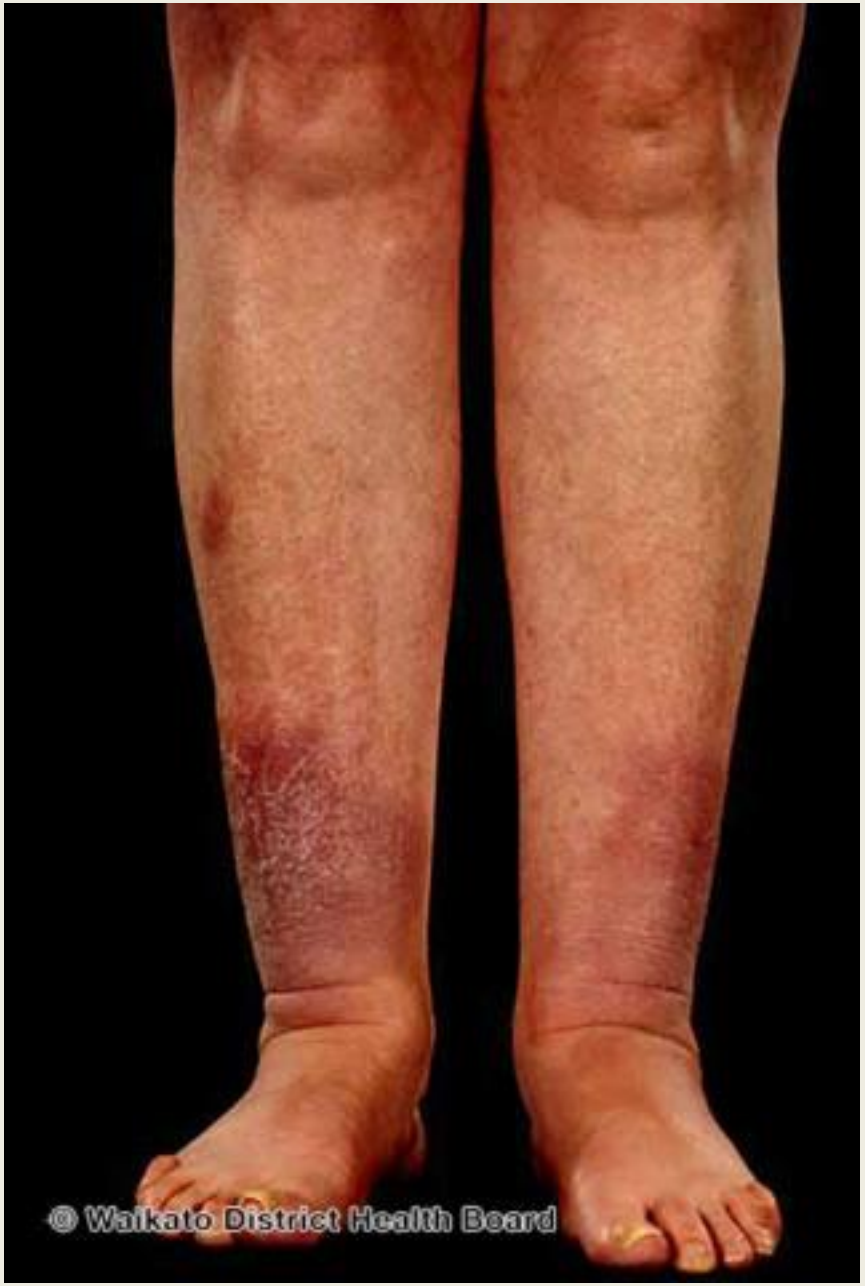
SEVERE
PROGRESSIVE
EXOPHTHALMOS
TESTING FOR
RESILIENCY



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

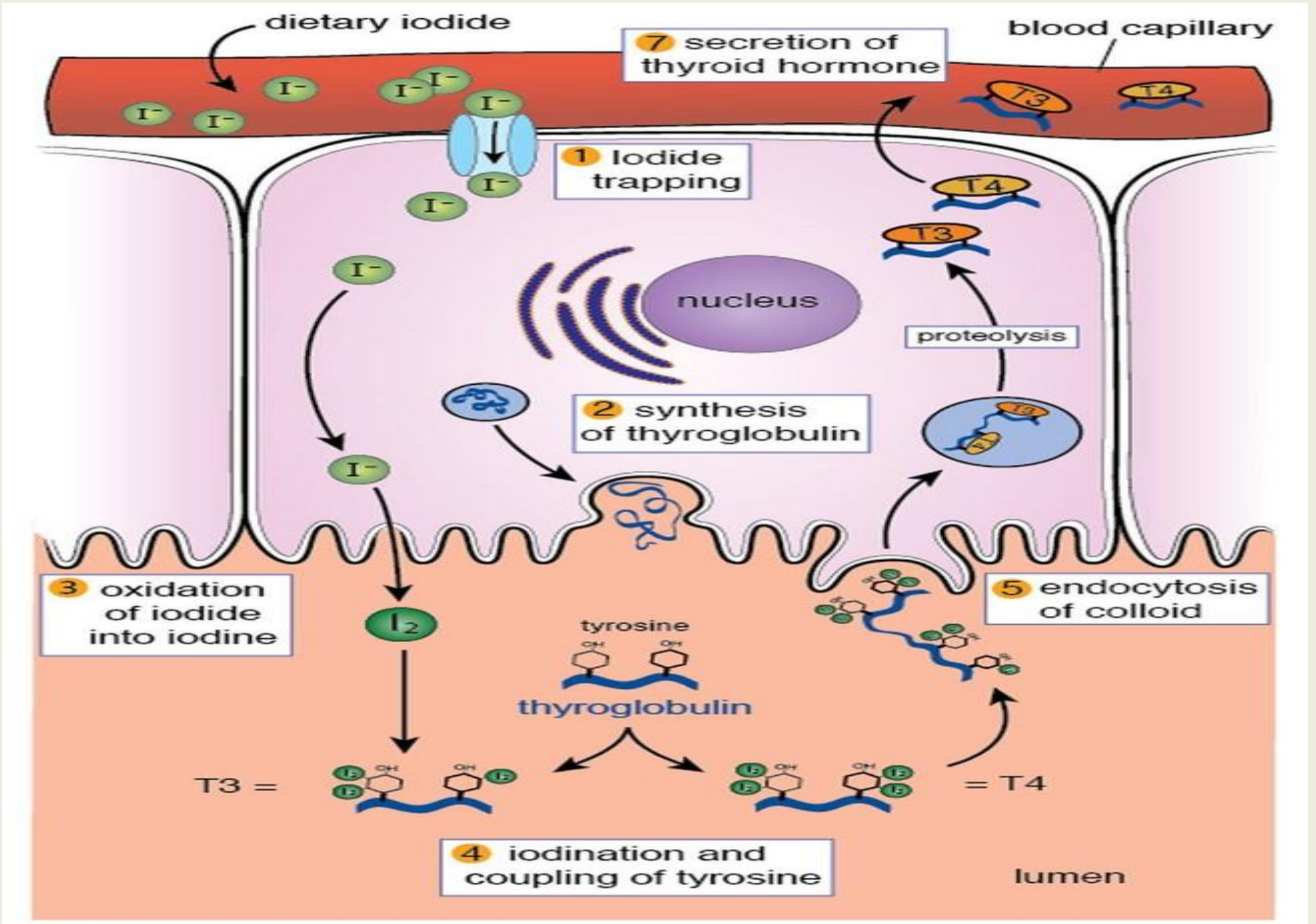
- **Propylthiouracil (PTU)**
- **Methimazole**
- **Carbimazole**

(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**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lumen

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	Crosses placenta Recommended in pregnancy (Crossing placenta is less readily as it is highly protein bound)	Concentrated in Thyroid & crosses placenta Not recommended in pregnancy
Breast feeding	Less secreted in breast milk Recommended	secreted Not recommended

Adverse Effects Thioamides

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

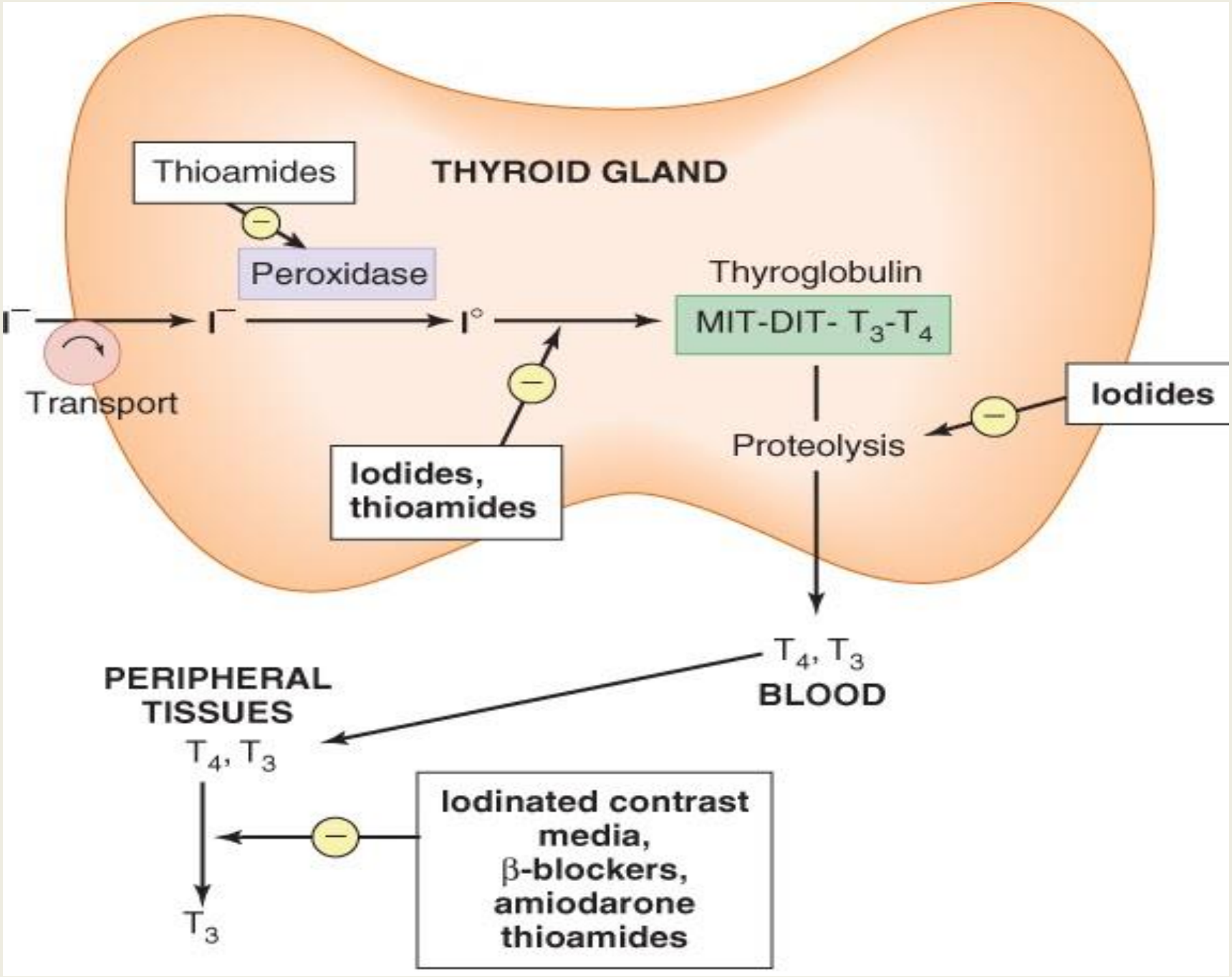
Adverse Effects (cont.)

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 *(Anti-neutrophil cytoplasmic antibodies)*	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)**


Thioamides
THYROID GLAND
Peroxidase
Thyroglobulin
MIT-DIT- T_3-T_4
I^-
I^-
I°
Transport
Iodides, thioamides
Iodides
Proteolysis
T_4, T_3
BLOOD
PERIPHERAL TISSUES
T_4, T_3
Iodinated contrast media, β-blockers, amiodarone thioamides
T_3

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 relief 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 thyriodectomy is the treatment of choice in very large gland or multinodular goiter**

Good Luck