DRUGS USED IN HYPERTHYROIDISM

Prof. Abdulrahman Almotrefi

Prof. Yieldez Bassiouni

Learning objectives

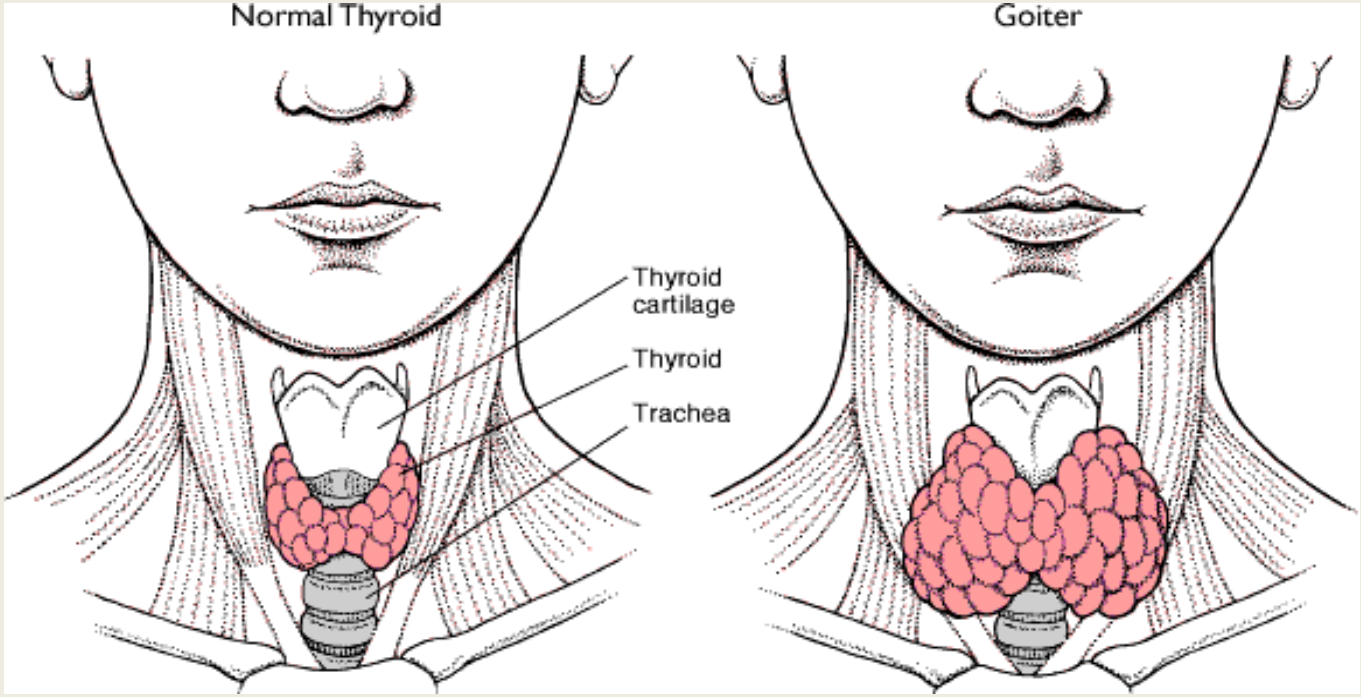
By the end of this lecture, students should be able to:

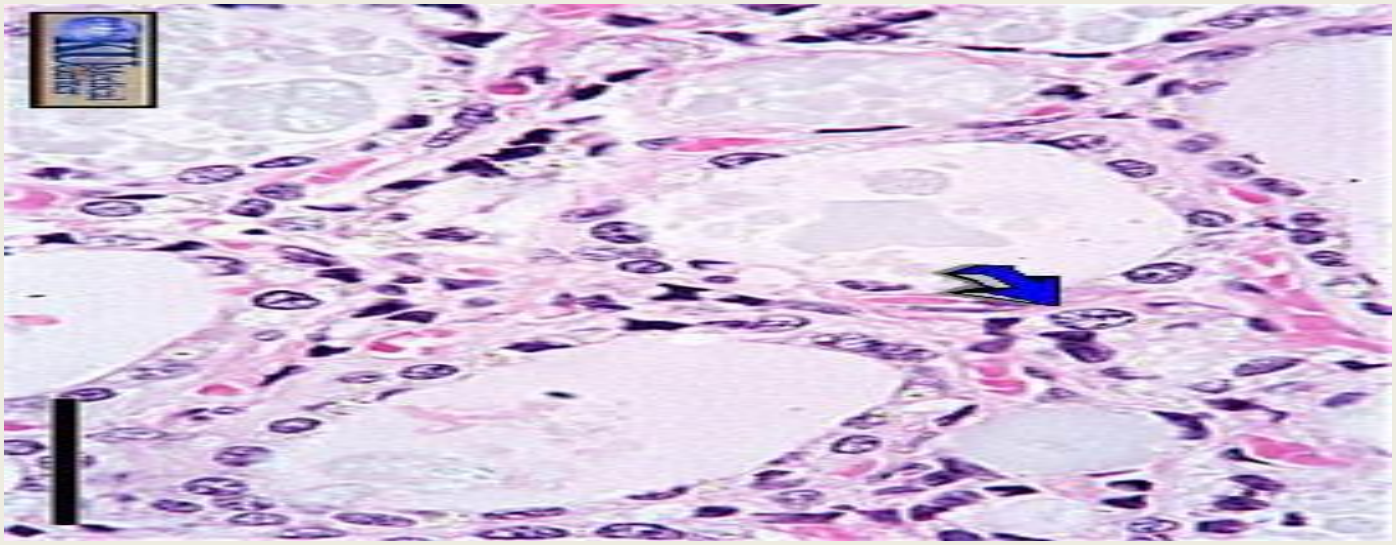
- **Describe different classes of drugs used in hyperthyroidism and their mechanism of action**

- **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**

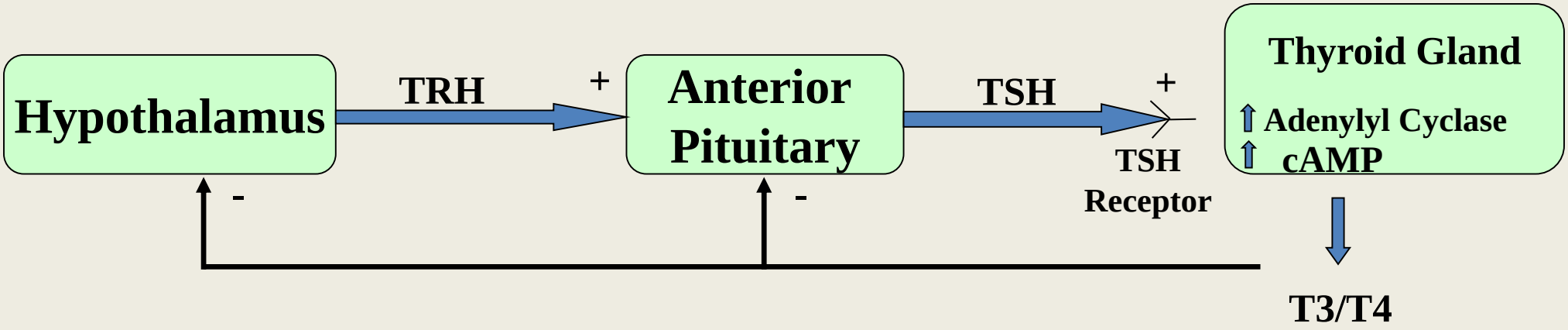
Iodine Metabolism

- 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 peroxide in the lumen of the follicle:

$$I_2 \xrightarrow{H2O2} I^-$$

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

Thyroid Regulation



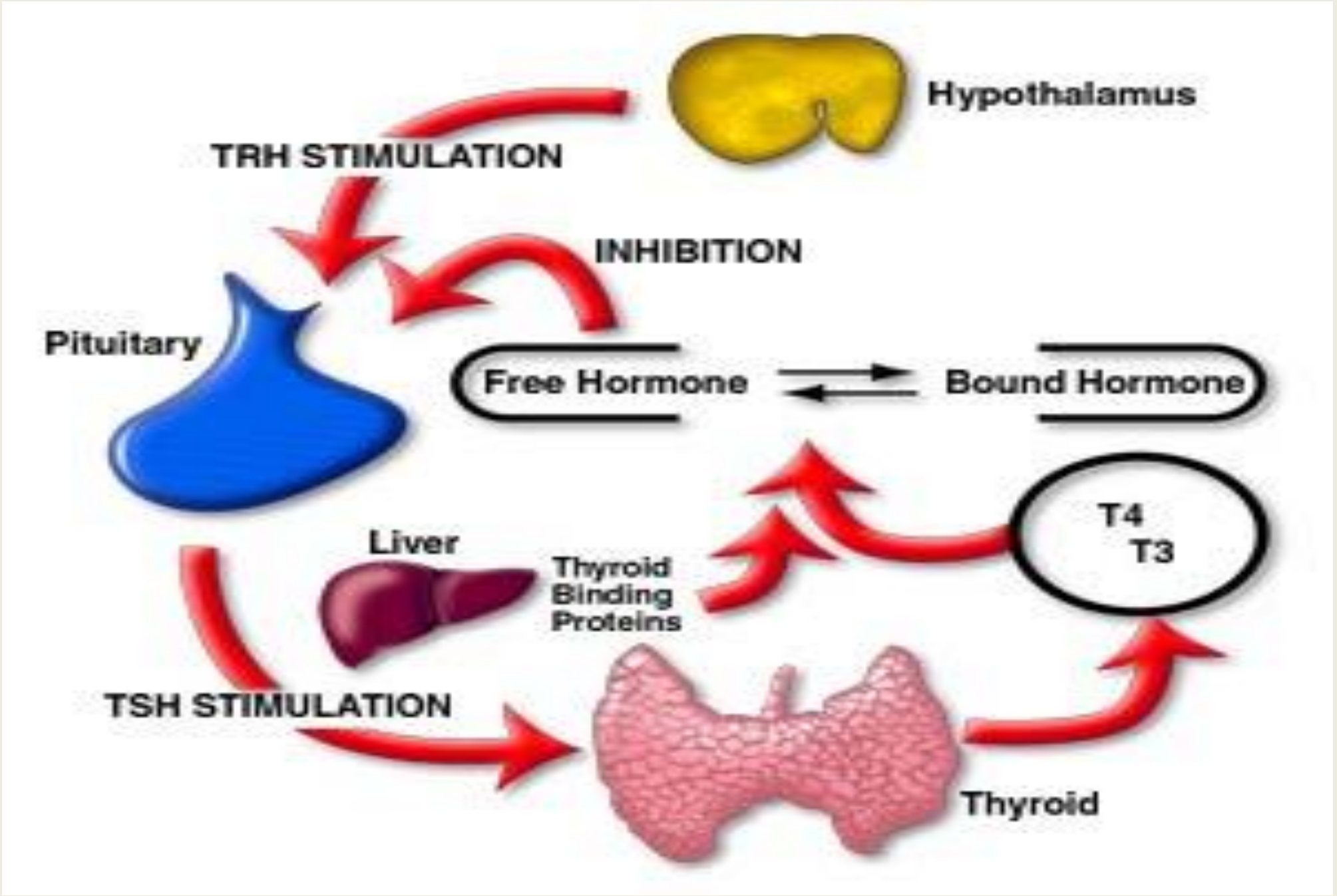
* **TRH** (thyrotropin releasing hormone)
* **TSH** (thyroid stimulating hormone or thyrotropin)

Thyroid Regulation

- **TSH release is influenced by hypothalamic TRH, and by thyroid hormones themselves.**

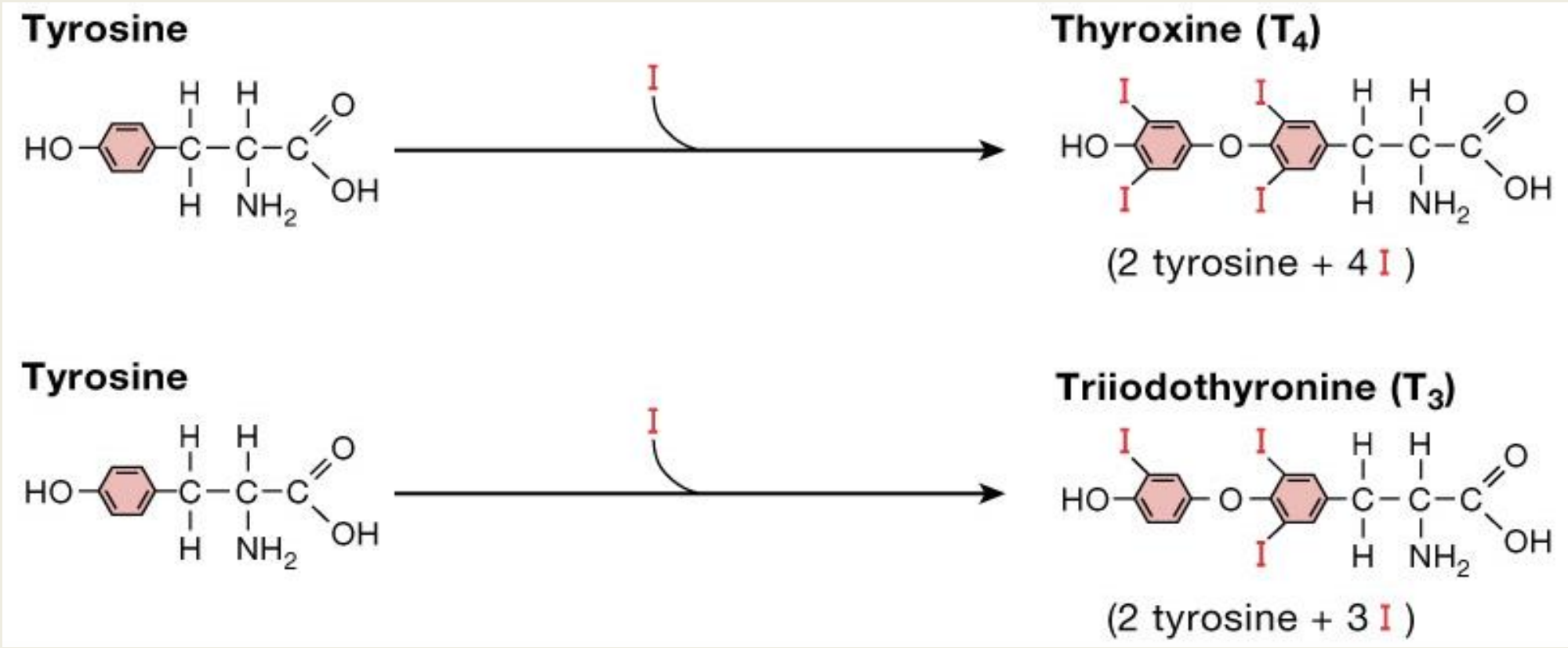
- **Thyroid hormones exert negative feedback on TSH release at the level of the anterior pituitary.**
  - **inhibition of TSH synthesis**
  - **decrease in pituitary receptors for TRH**

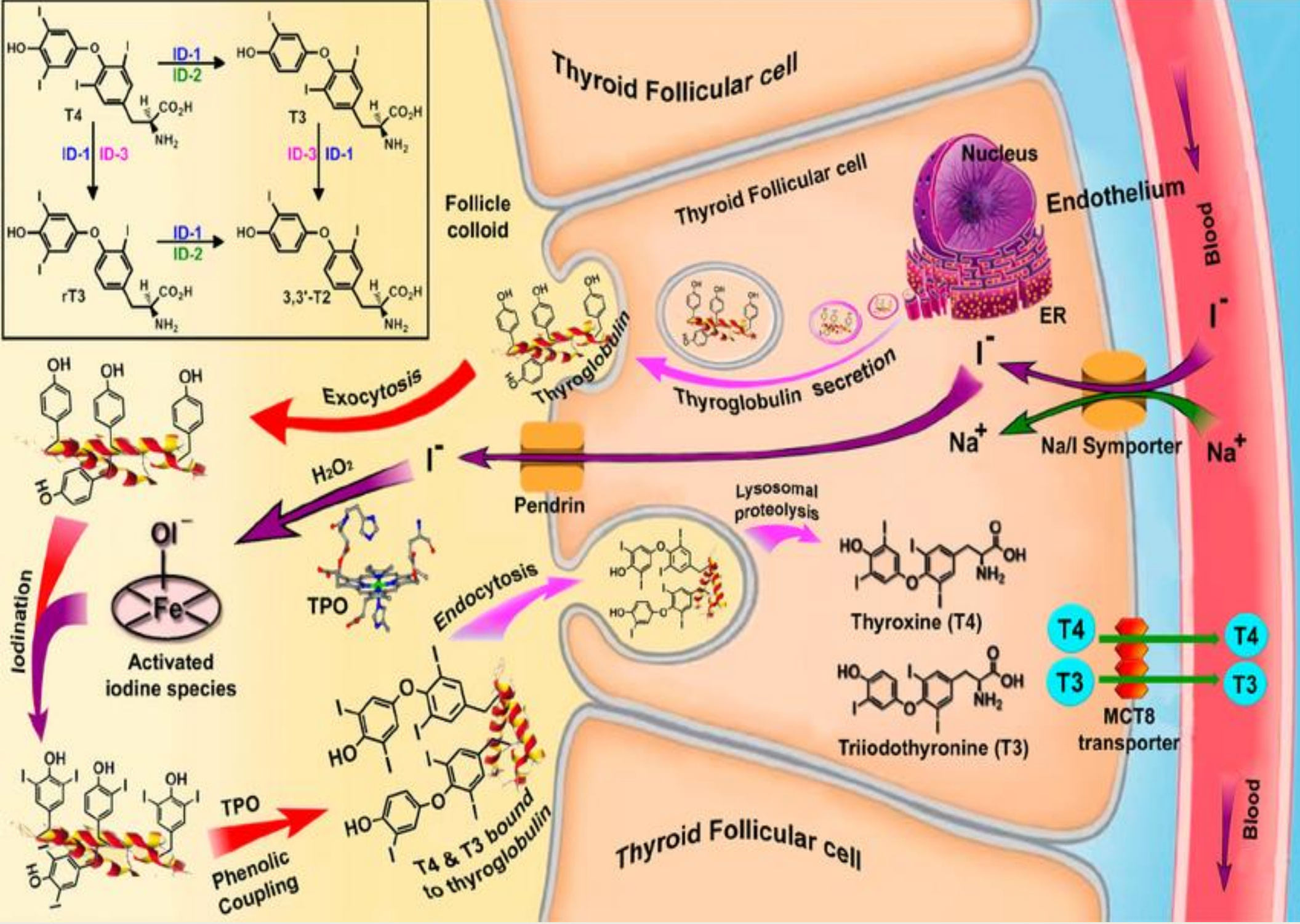
Thyroid Regulation



Thyroid Hormones

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




T4
T3
rT3
3,3'-T2
ID-1
ID-2
ID-3
Thyroid Follicular cell
Follicle colloid
Nucleus
Endothelium
Blood
ER
Thyroglobulin
Thyroglobulin secretion
Exocytosis
I^-
Na^+
Na/I Symporter
H_2O_2
Pendrin
Lysosomal proteolysis
Endocytosis
TPO
OI^-
Fe
Activated iodine species
Iodination
Thyroxine (T4)
Triiodothyronine (T3)
MCT8 transporter
Phenolic Coupling
T4 & T3 bound to thyroglobulin

Thyroid Hormones Synthesis

1. iodine trapping :uptake of iodine by the thyroid gland

2. oxidation of iodine: (to its active form)

   thyroid peroxidase (key enzyme of the synthesis)

3. iodide organification : the iodination of tyrosyl groups of thyroglobulin

   produces : MIT and DIT

4. formation of T4 and T3 from MIT and DIT :

   thyroid peroxidase

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 (radioactive iodine uptake) RAIU

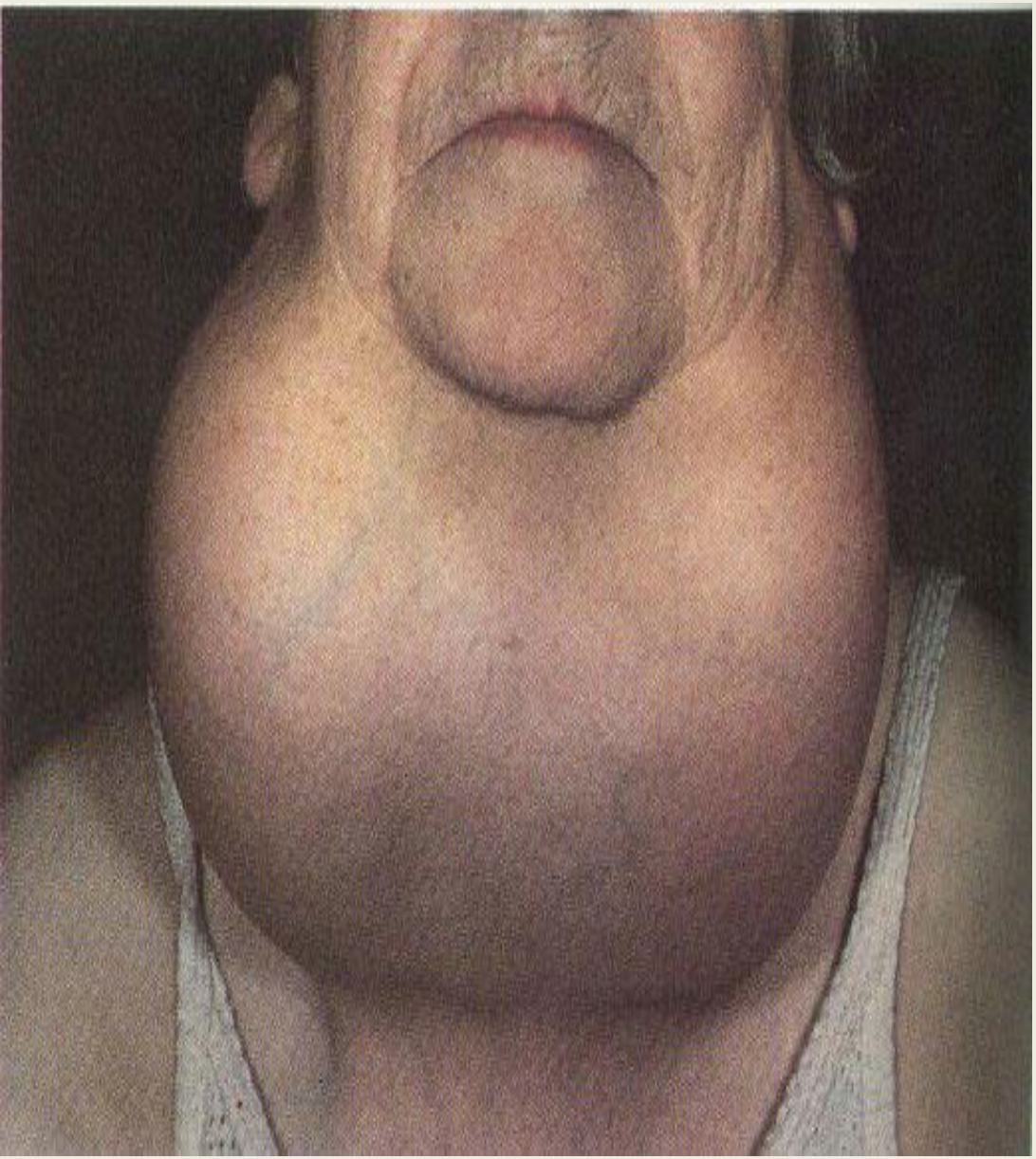
- Graves diseases (60-80%)
- Multinodular goitre (14%)
- Adenomas / carcinomas

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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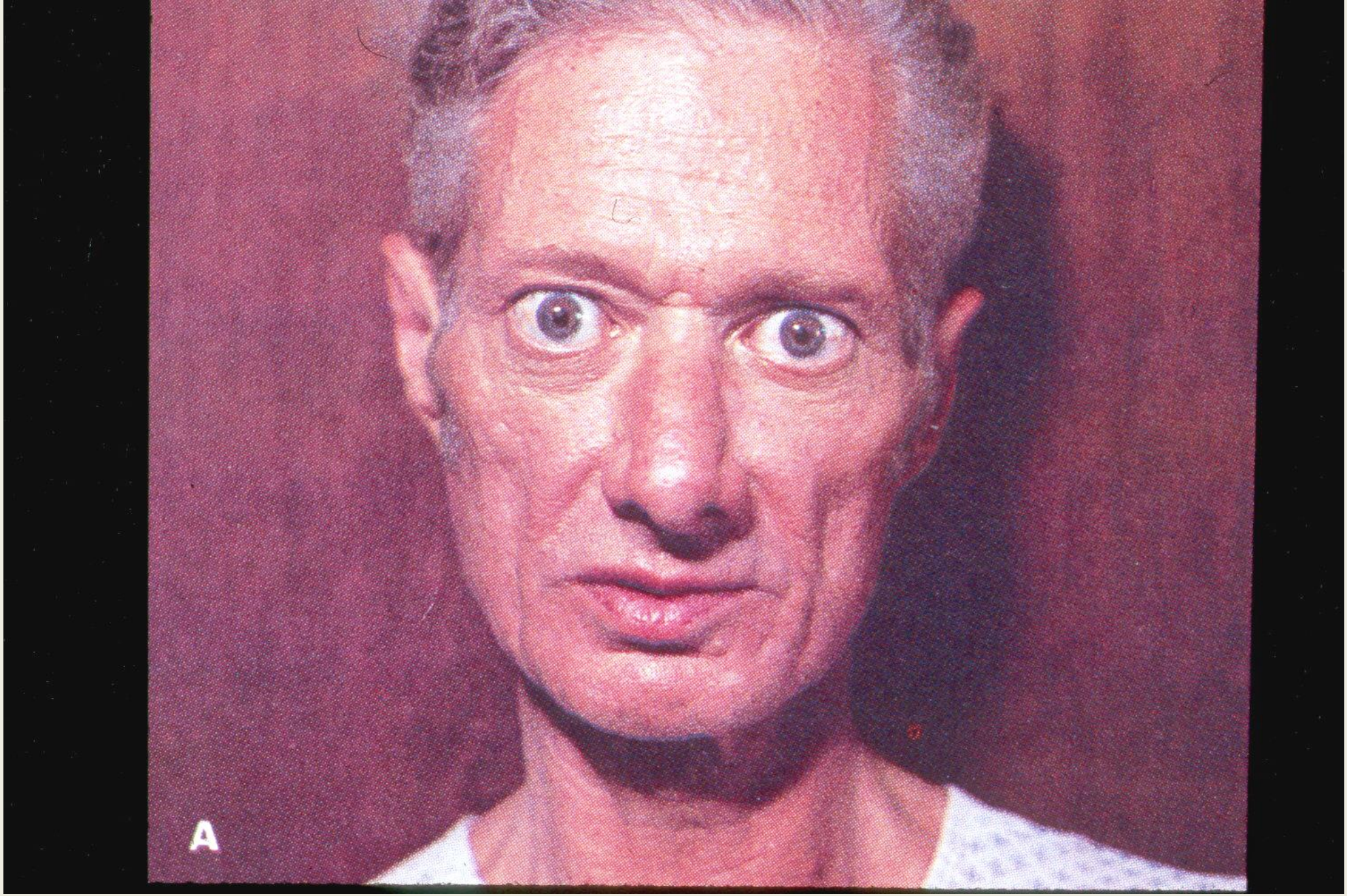
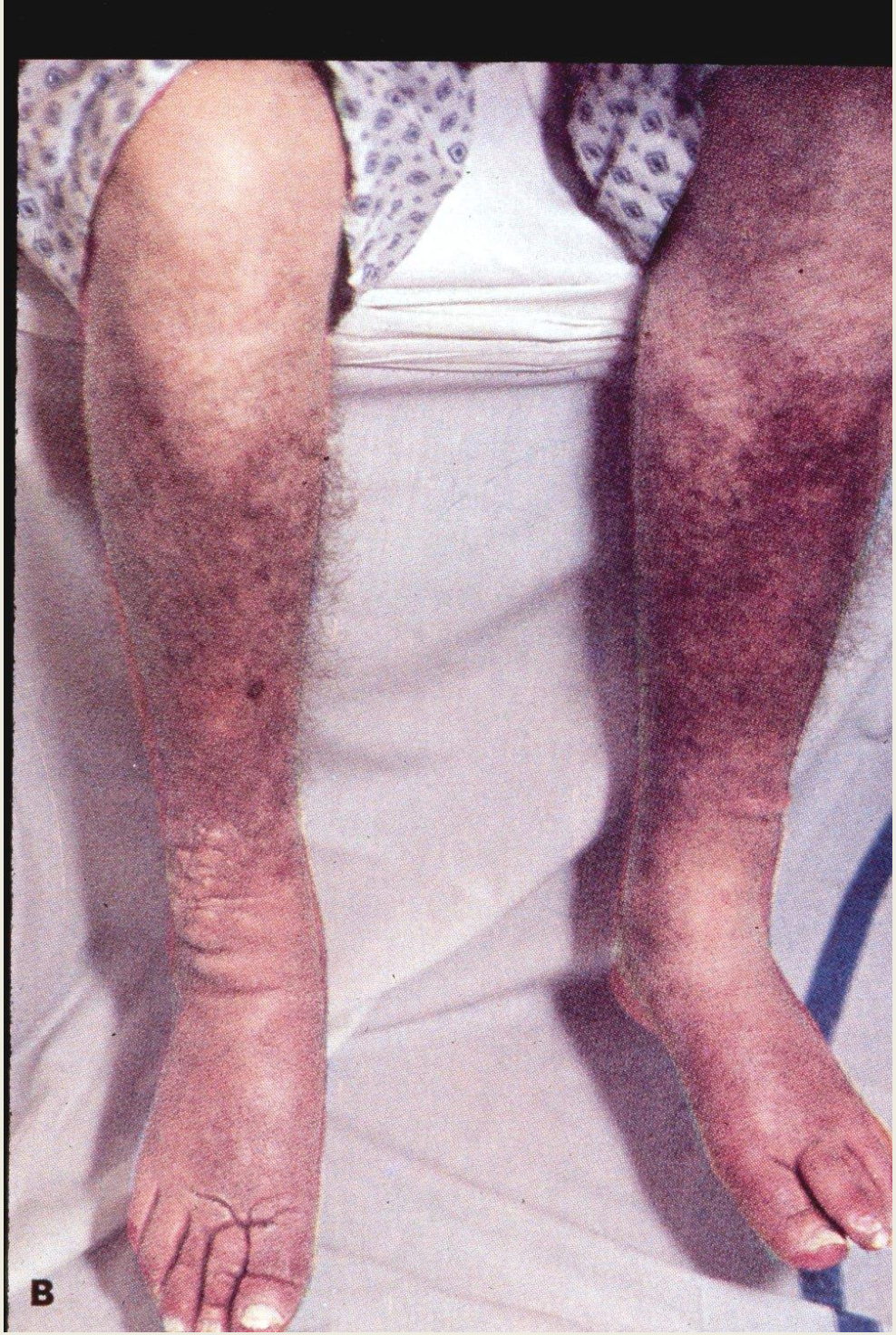
SEVERE
PROGRESSIVE
EXOPHTHALMOS
TESTING FOR
RESILIENCY



51 year old male with Graves Disease



Pretibial myxedema and “square toes” in the same patient on the prior slide

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:

- Thyroid Enlargement
- Warm, moist skin
- Exophtalmus
- Pretibial myxedema
- Arrhythmias

Treatment of Hyperthyroidism

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

THIOAMIDES

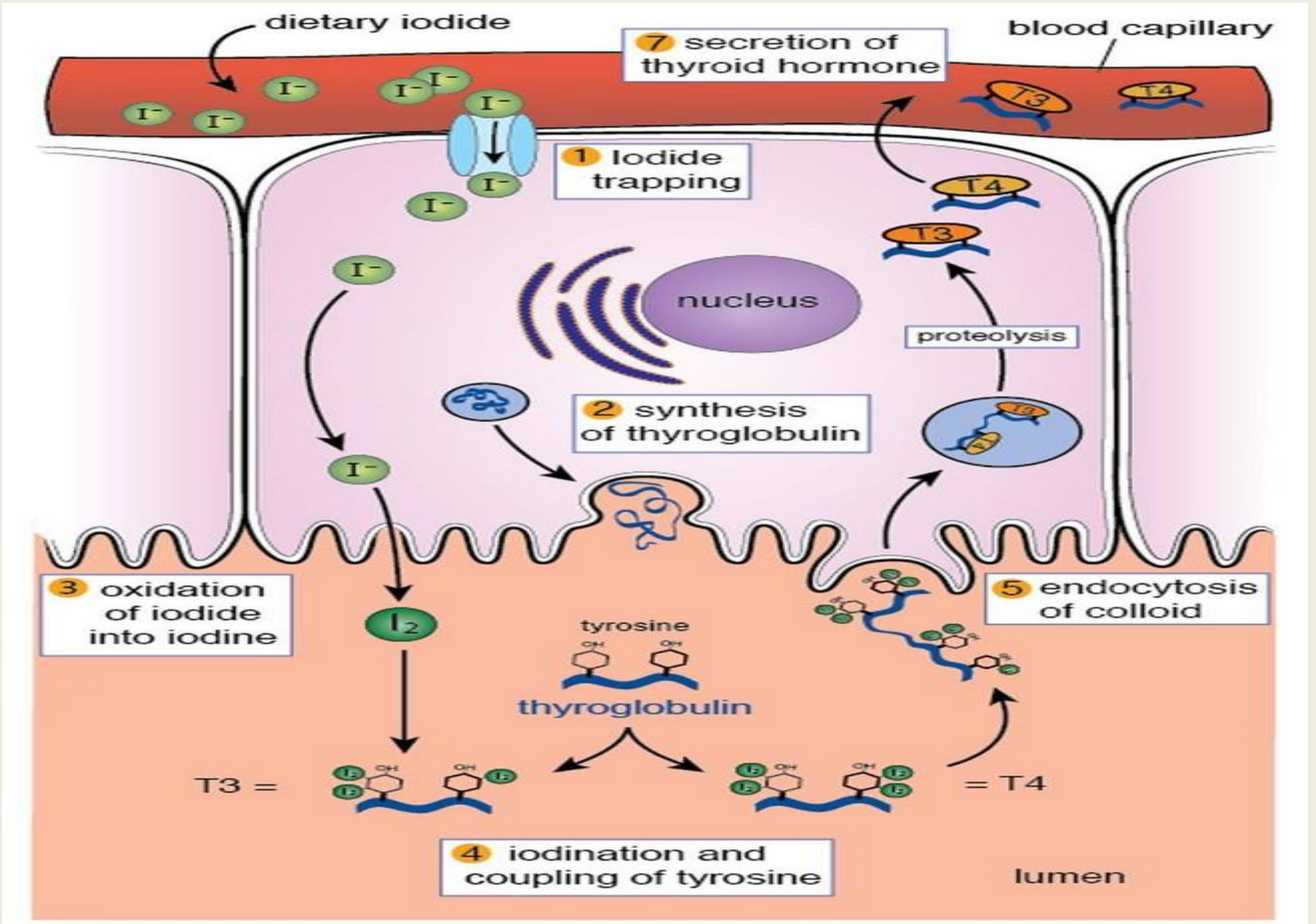
- **Propylthiouracil (PTU)**
- **Methimazole**
- **Carbimazole**

(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**


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

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

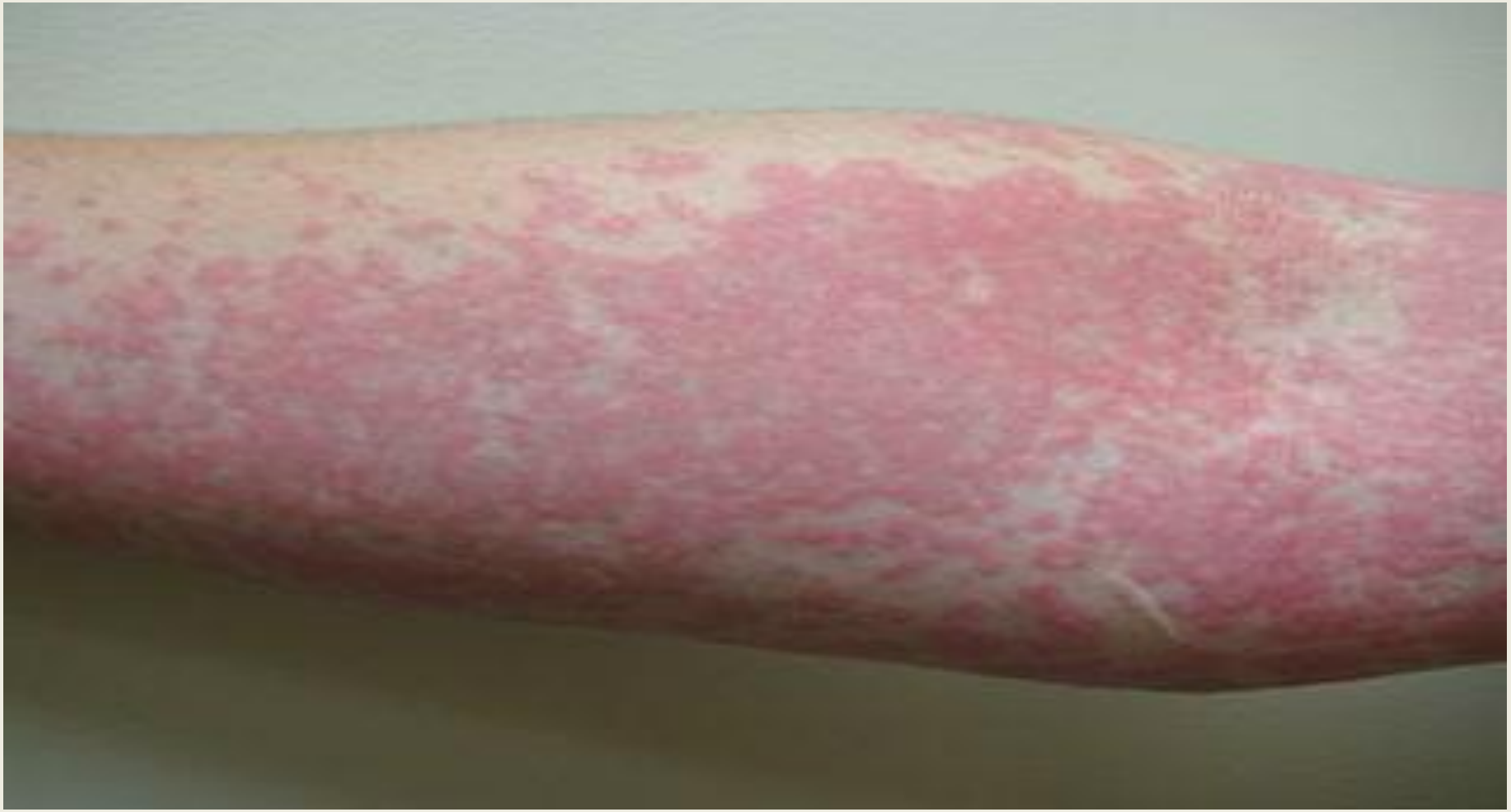
Pharmacokinetic comparison between Propylthiouracil and Methimazole

	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**

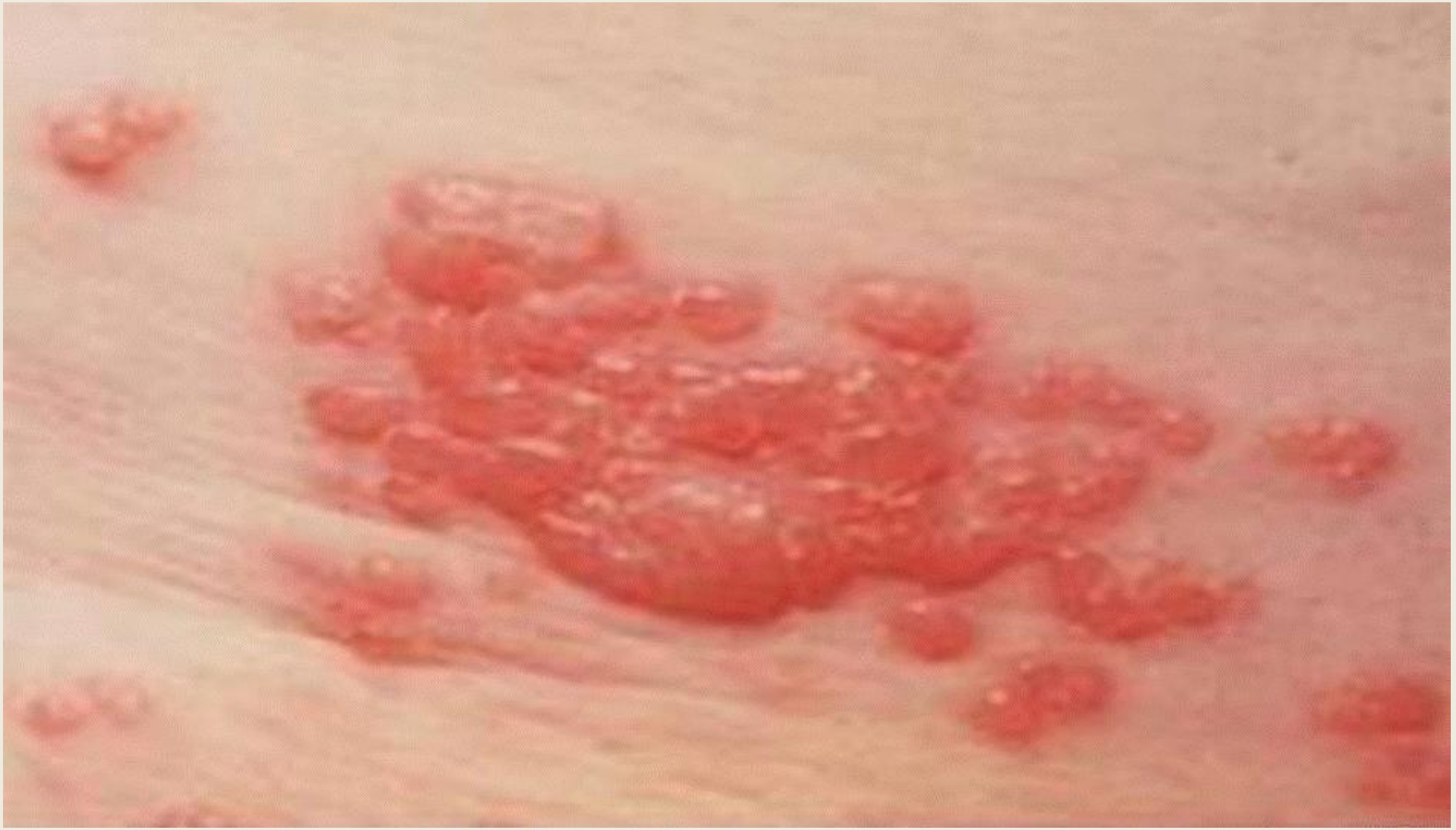
Adverse Effects

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

Urticarial rash



macular rash



Adverse Effects

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

WARNINGS

- **Agranulocytosis:**

Patients on PTU or methimazole should be instructed to immediately report to their physicians any symptoms suggestive of agranulocytosis, such as fever or sore throat.

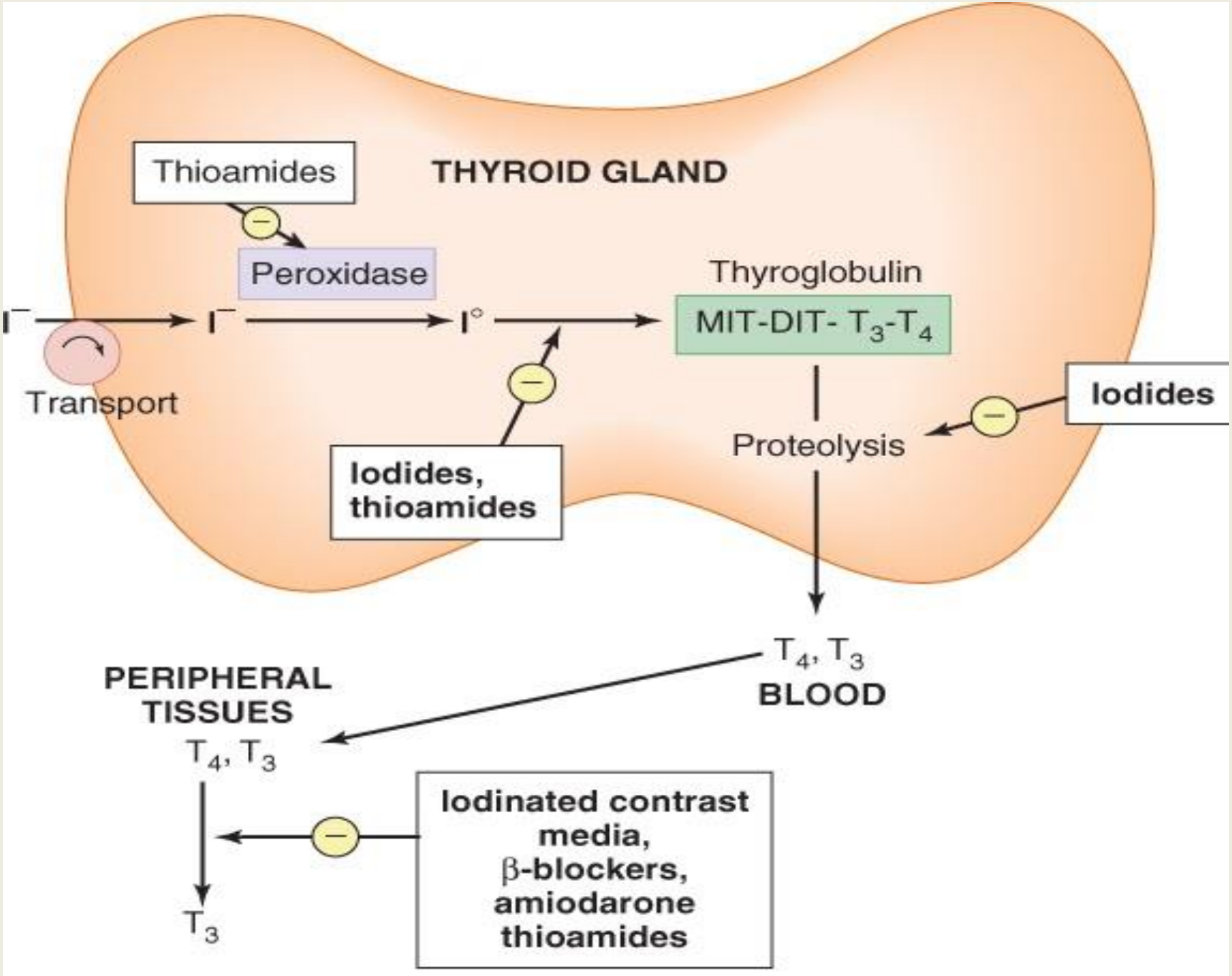
- **Congenital Malformations:**

Methimazole crosses the placental causing fetal harm, when administered in the first trimester of pregnancy

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

- **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} 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

D. Cooper,N Engl J Med 2005;352:905-17

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 | **Remission**

↓ ↓

Definitive radioiodine therapy in adults

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

Monitor thyroid function every 12 mo indefinitely

D. Cooper,N Engl J Med 2005;352:905-17

THYROIDECTOMY

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