DRUGS USED IN HYPERTHYROIDISM

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Learning objectives

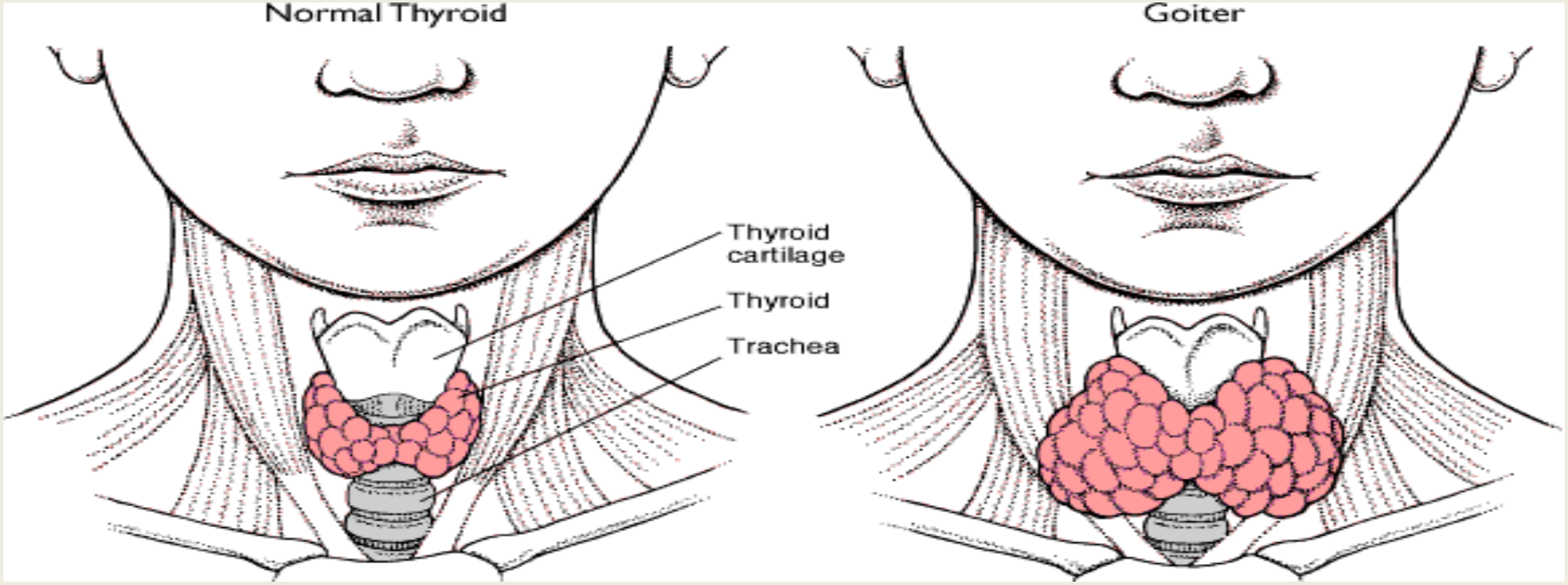
By the end of this lecture, students should be able to:

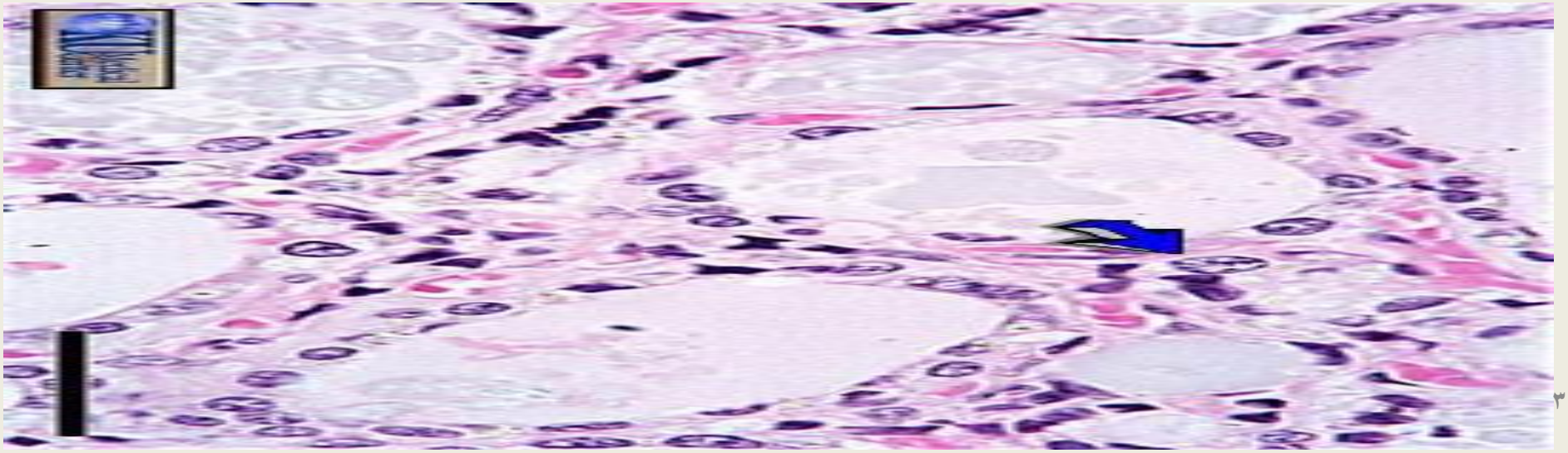
- **Describe different classes of drugs used in hyperthyroidism and their mechanism of action**

- **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

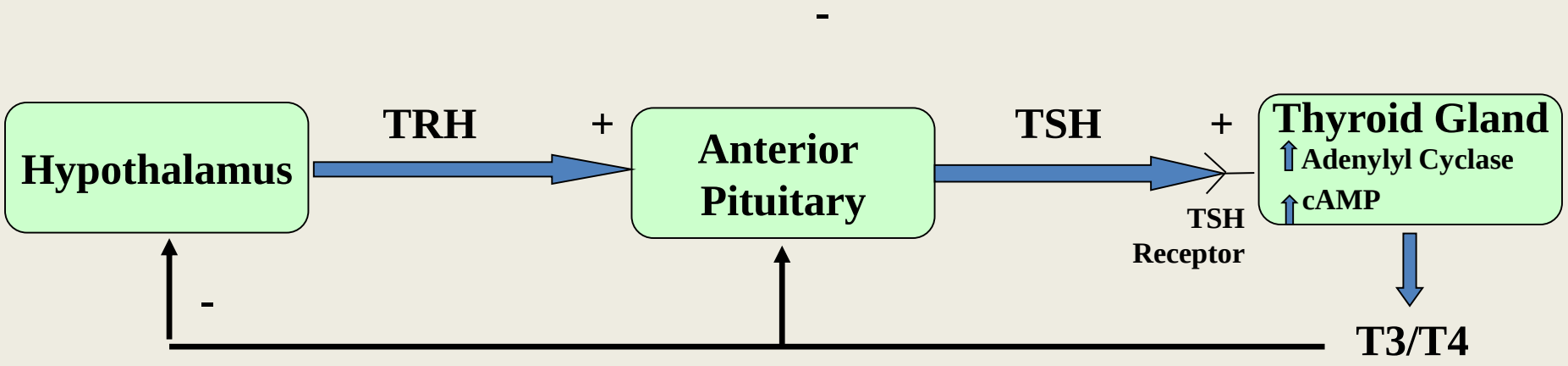
- **Dietary iodine is absorbed in the GI tract, then taken up by the thyroid gland (or removed from the body by the kidneys)**
- **Iodide taken up by the thyroid gland is oxidized by peroxidase in the lumen of the follicle:**

$$I^- \xrightarrow{\text{Peroxidase}} I_2$$

- **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

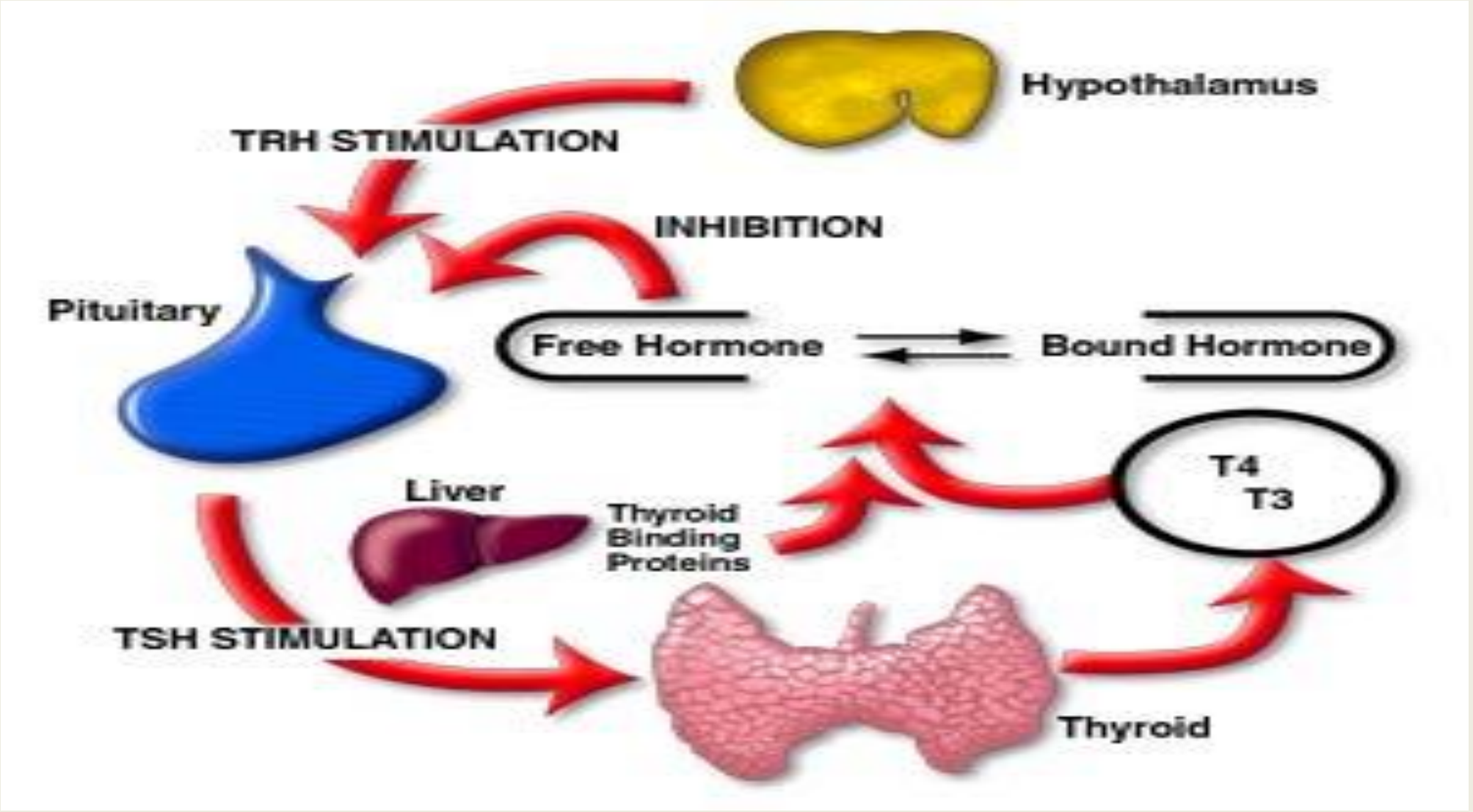


Thyroid Regulation

- **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**

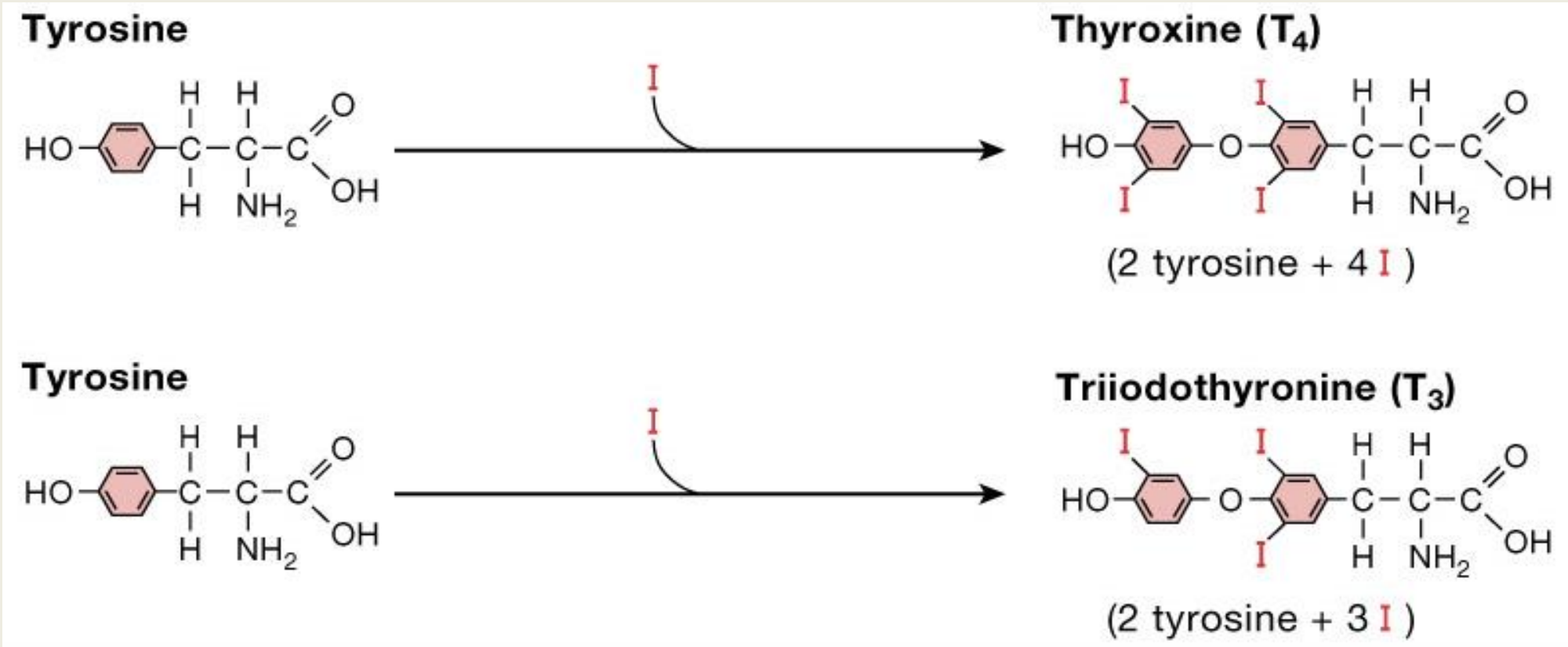
Thyroid Regulation

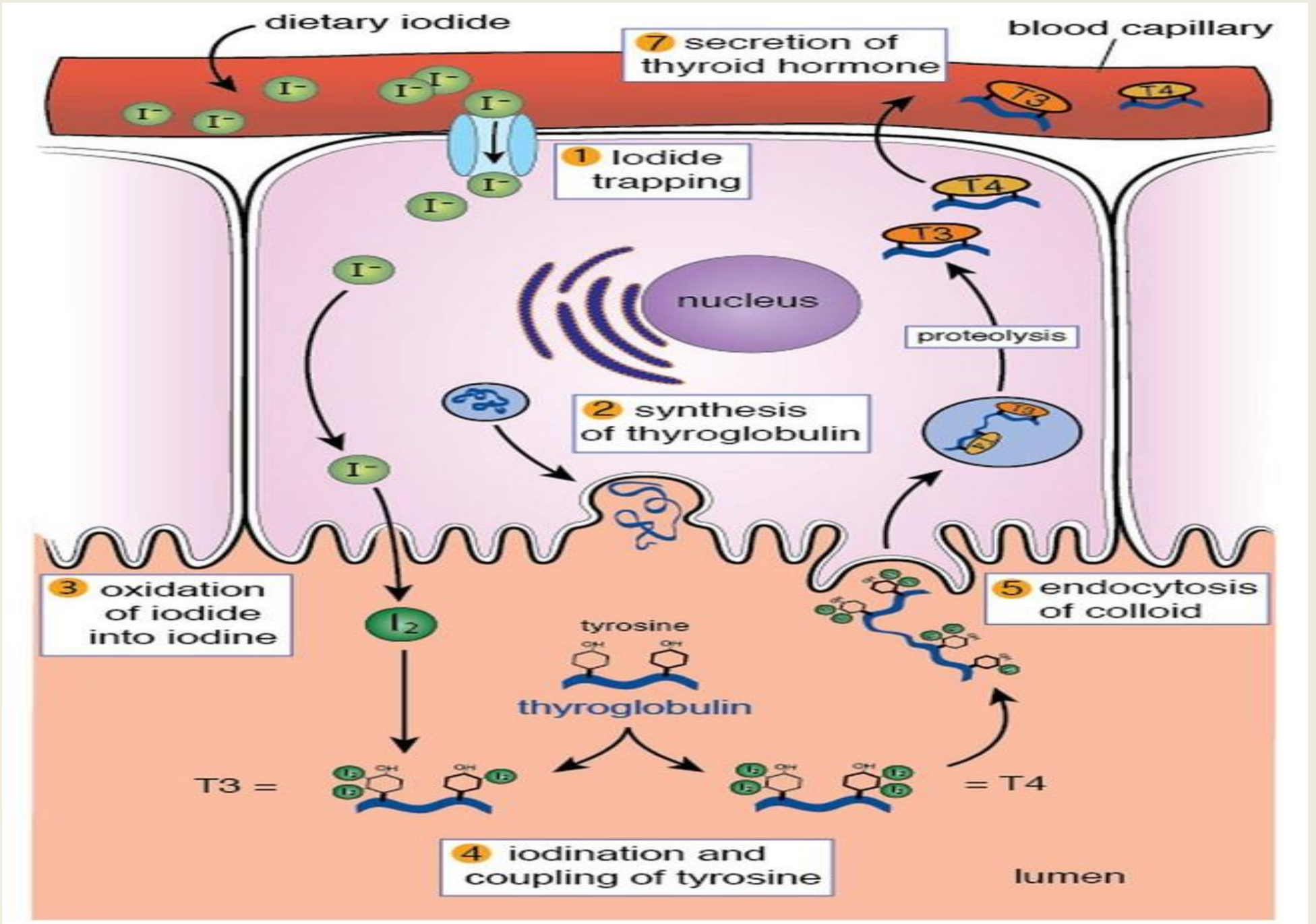


TRH (thyrotropin releasing hormone)
TSH (thyroid stimulating hormone or thyrotropin)

Thyroid Hormones

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

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

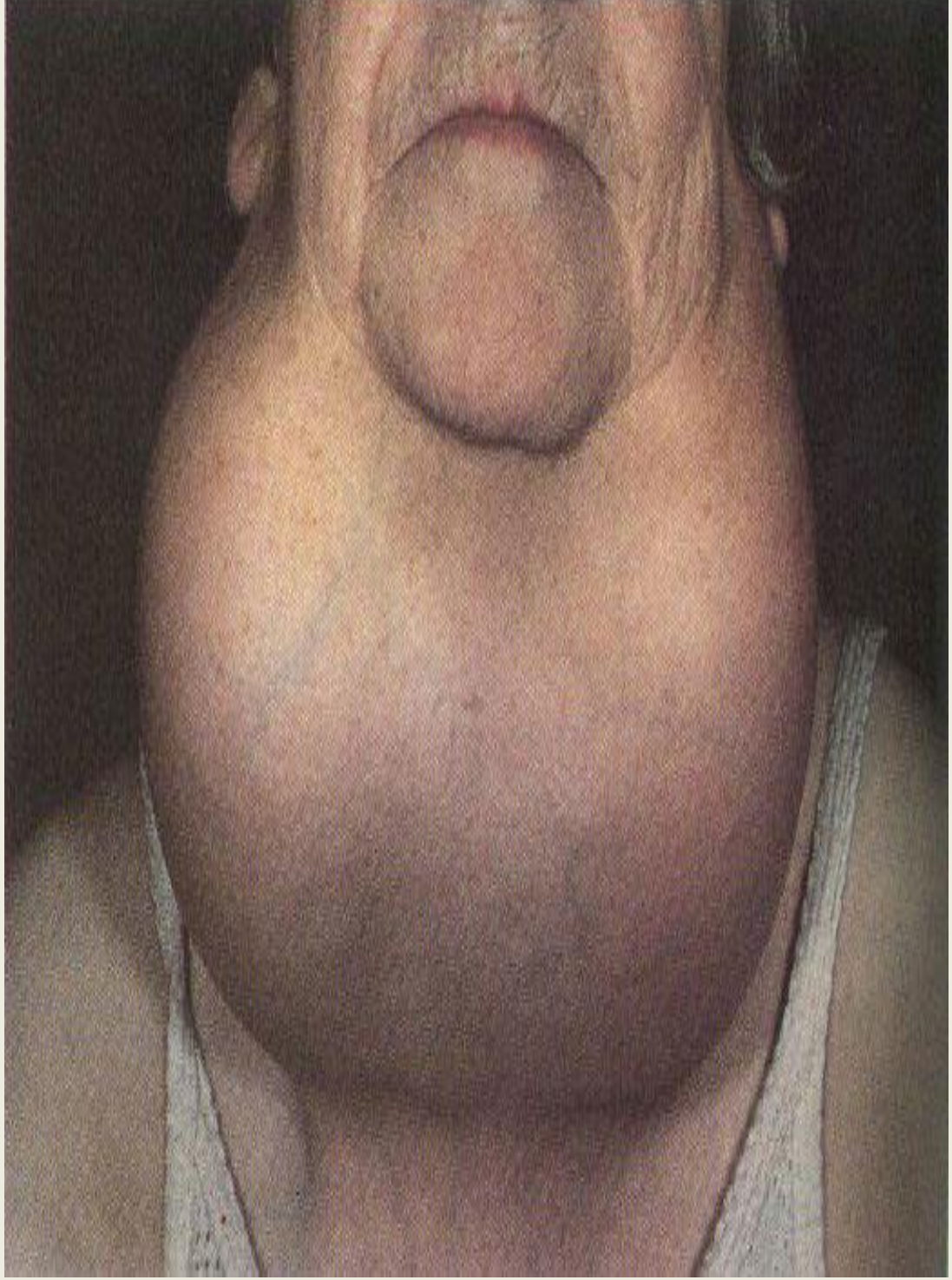
With low RAIU

- 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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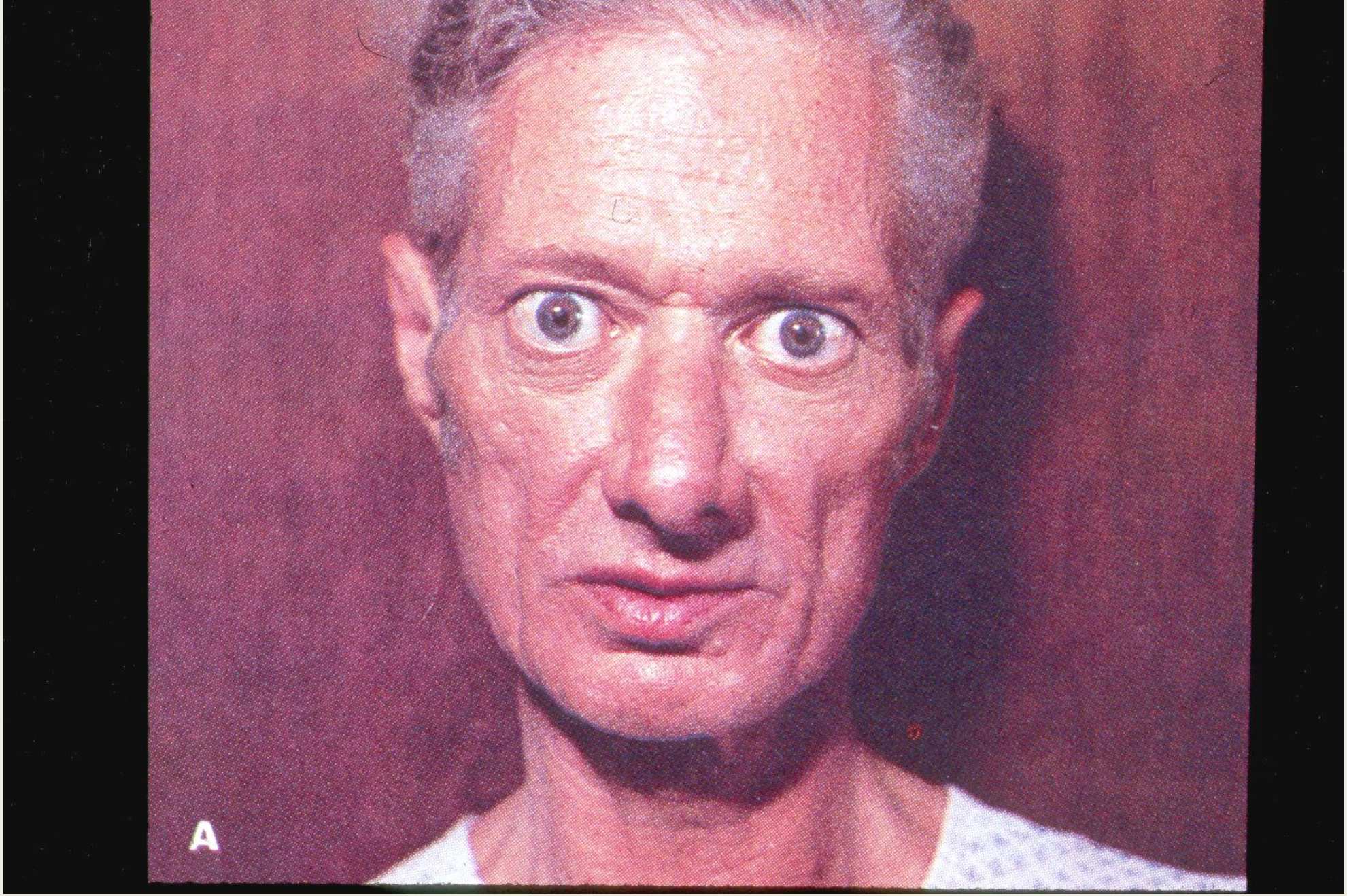
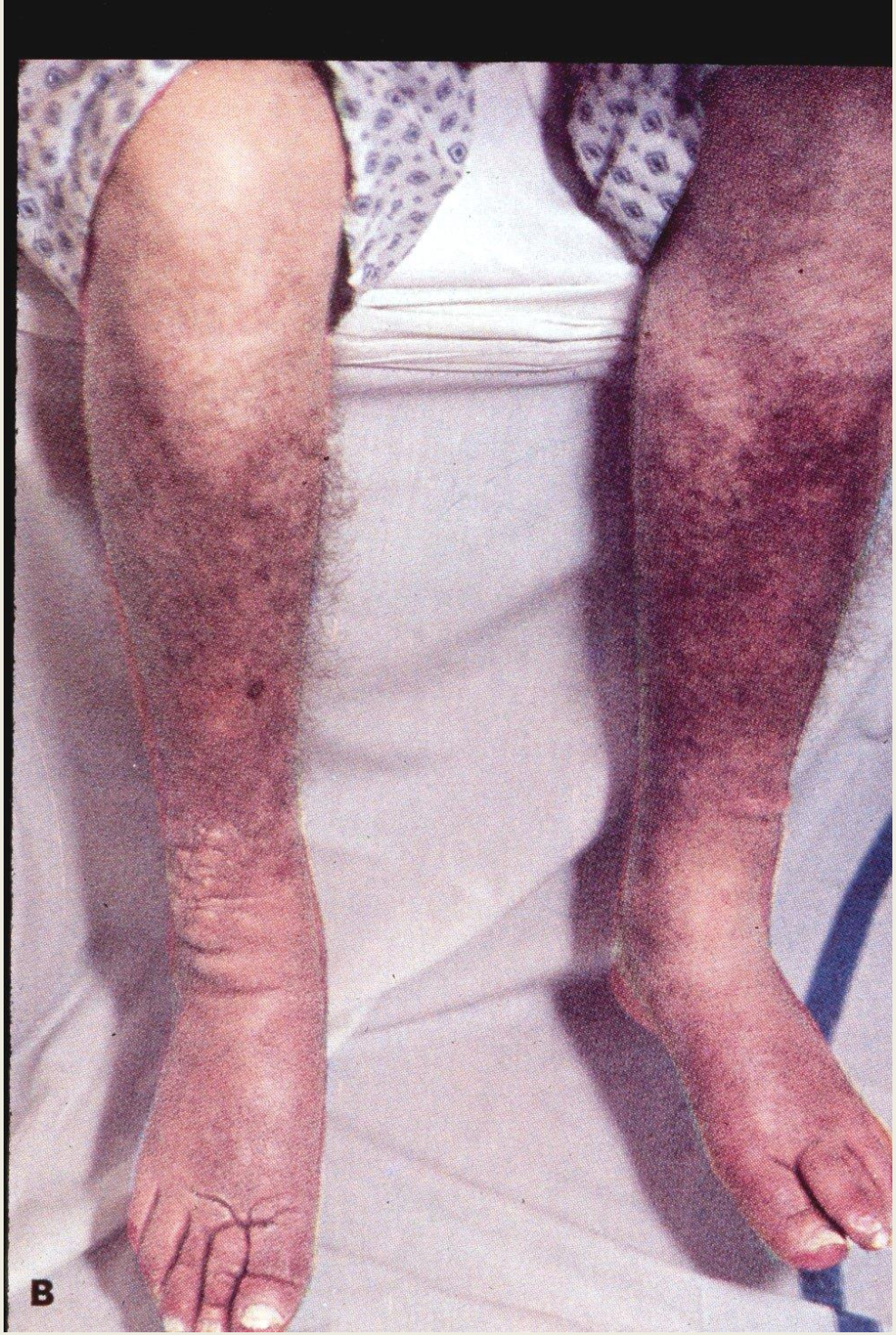
SEVERE
PROGRESSIVE
EXOPHTHALMOS
TESTING FOR
RESILIENCY



51 year old male who presented with urinary retention and proved to have 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:

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

Treatment of Hyperthyroidism

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

THIOAMIDES

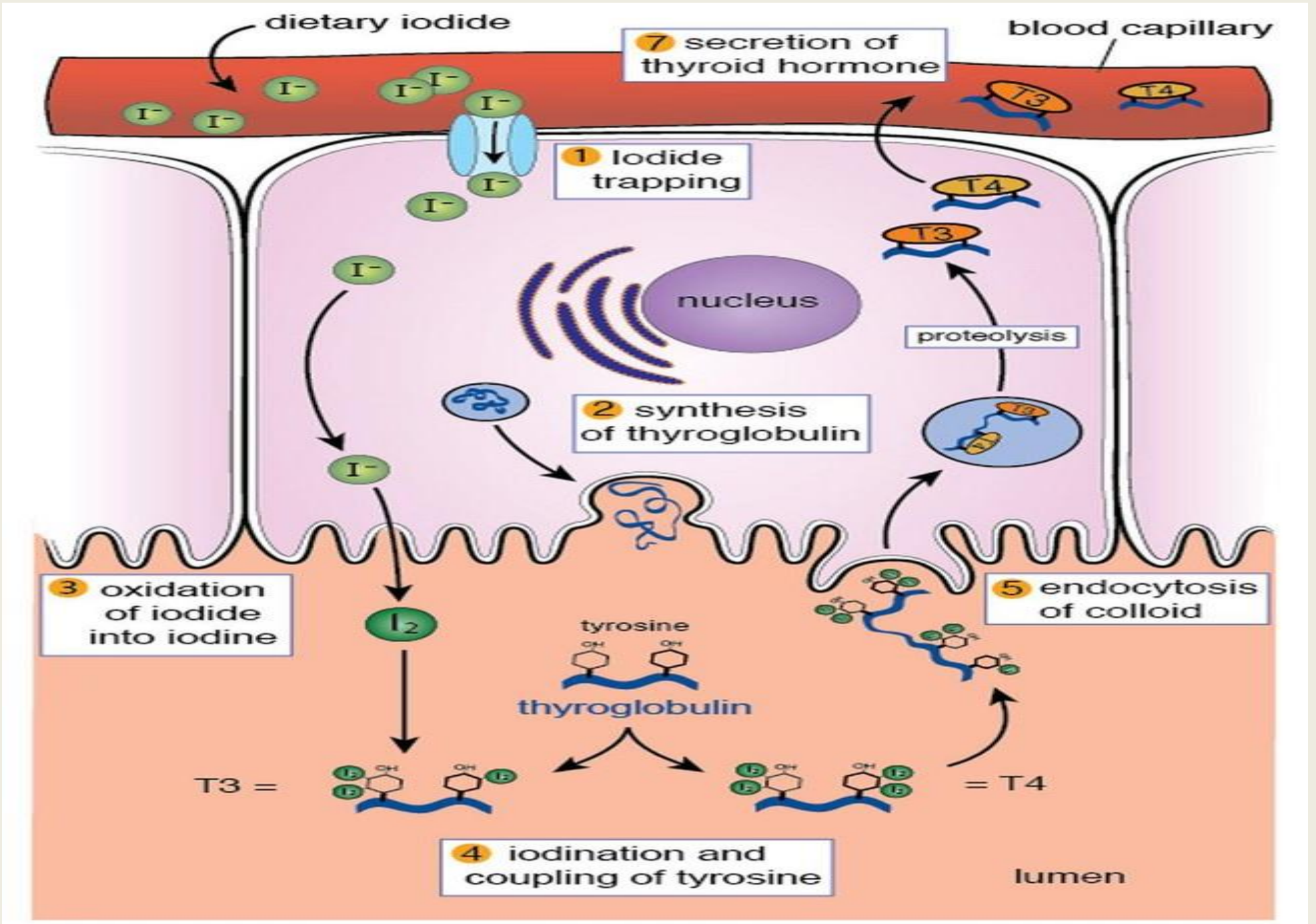
- **Propylthiouracil (PTU)**
- **Methimazole**
- **Carbimazole**

(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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= T4
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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

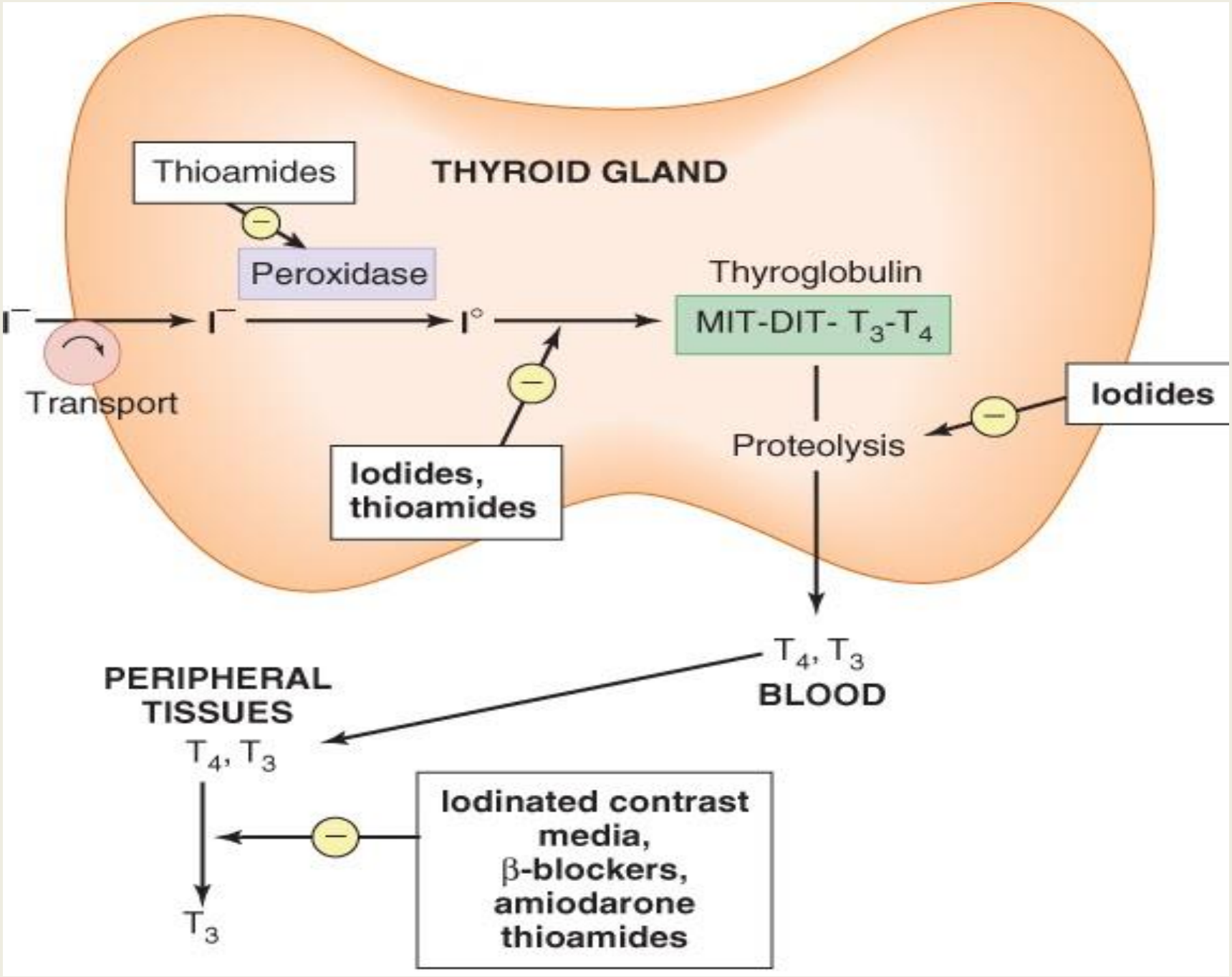
Adverse Effects (cont.)

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

- **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

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**