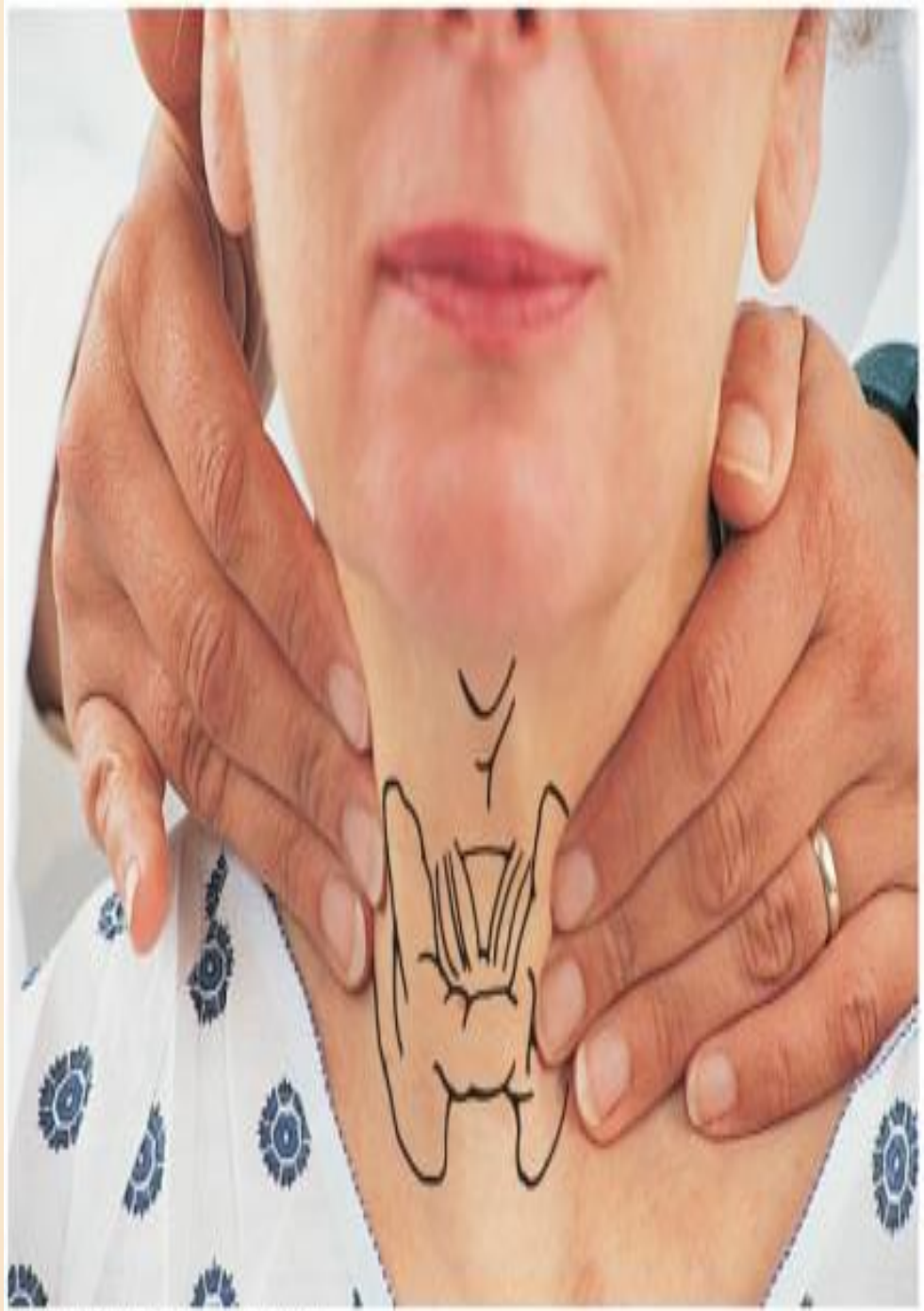
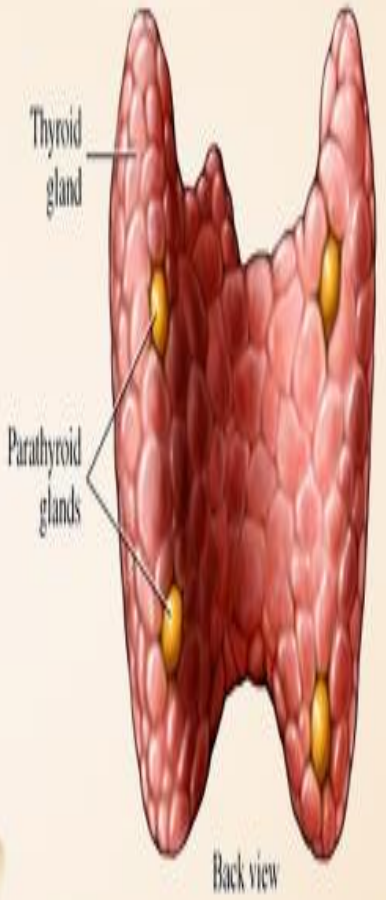
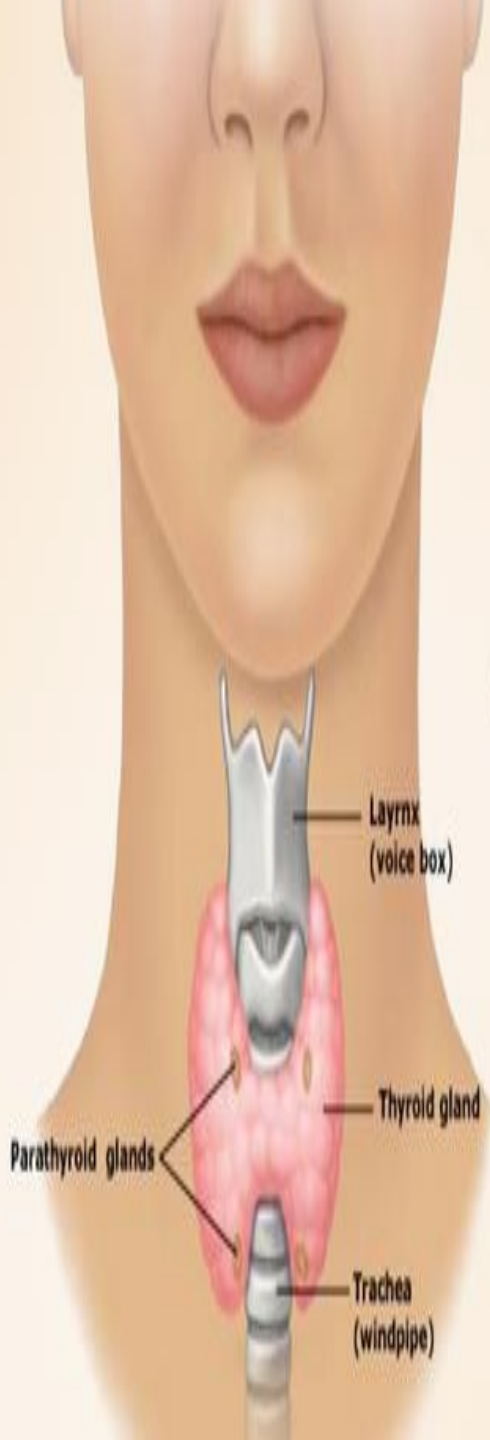




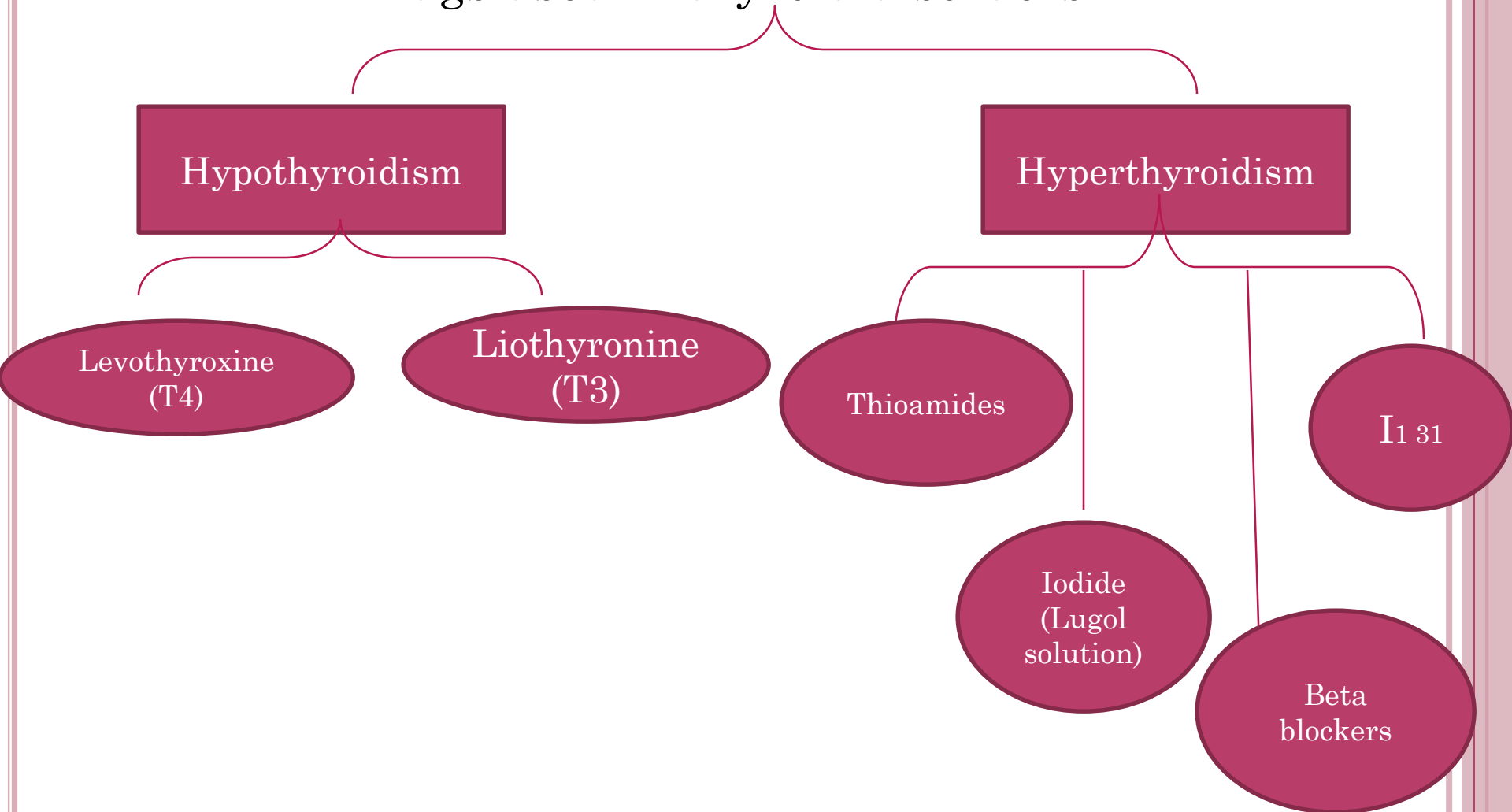
# DRUGS USED IN THYROID DISORDERS

By : Azza Osman Yousif

MSc in clinical pharmacology



○ Drugs used in thyroid disorders



# THYROID DISORDERS

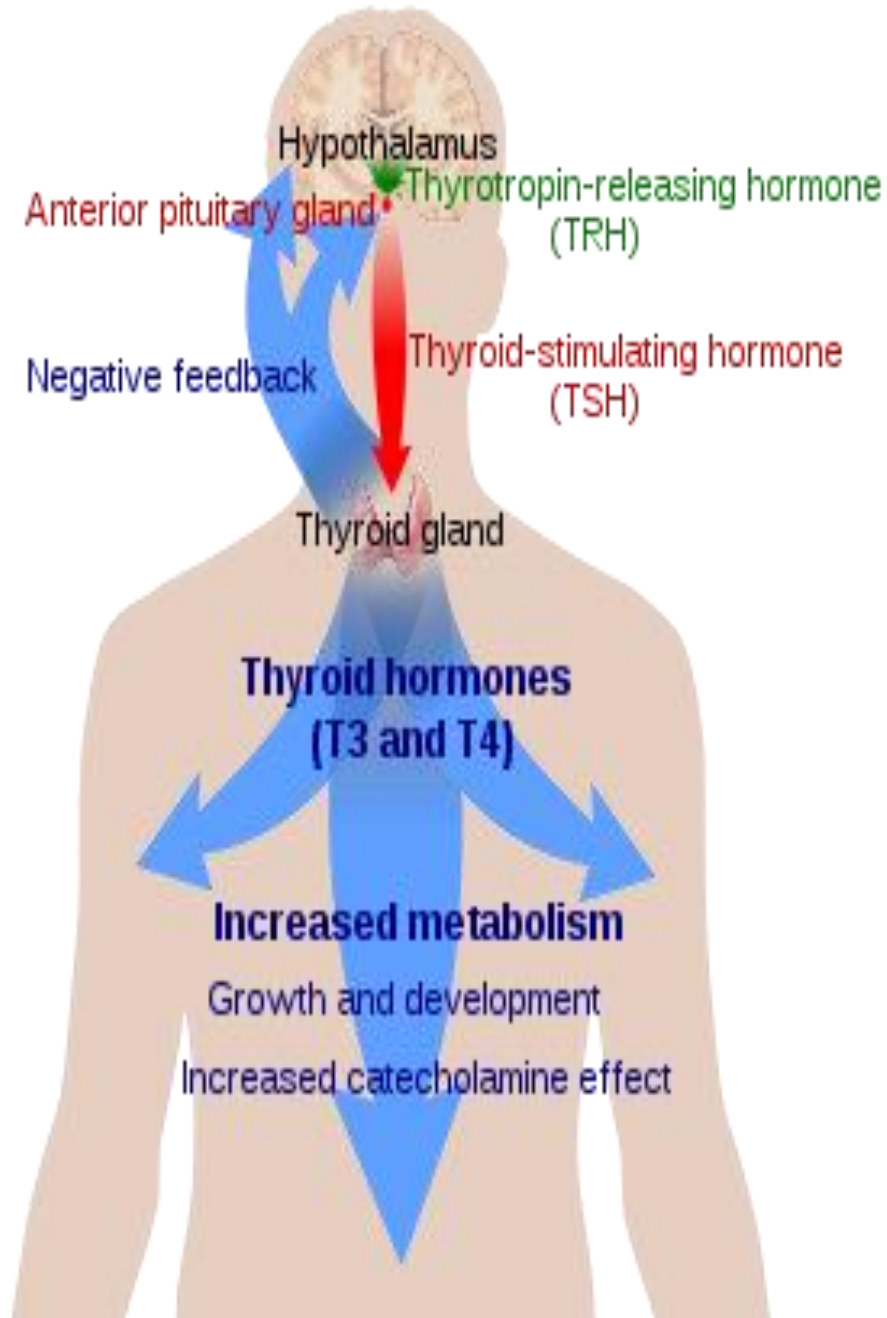
**Thyroid gland secretes three main hormones :**

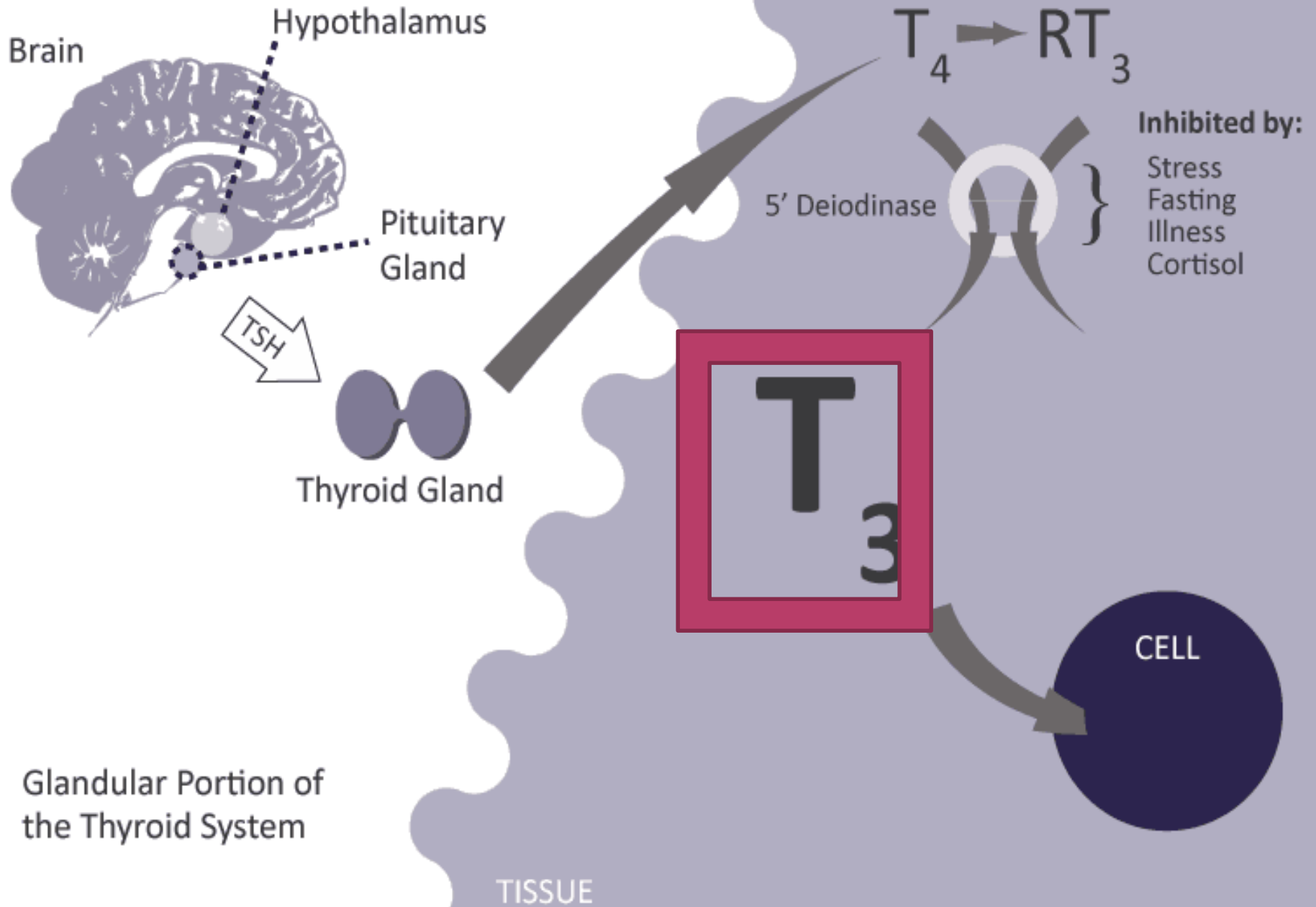
1. Thyroxine (T<sub>4</sub>).
2. Tri-iodothyronine (T<sub>3</sub>).
3. Calcitonin.

- ❑ **T<sub>3</sub> and T<sub>4</sub>** are important for **normal growth** and development and for controlling **energy metabolism**.
- ❑ Calcitonin is involved in the control of plasma calcium concentration.



# Thyroid system





# SYNTHESIS , STORAGE AND SECRETION OF THYROID HORMONES

The functional unit of the thyroid is the **follicle**.

Each follicle consists of a single layer of epithelial cells around a cavity (follicle lumen) which contains **thyroglobulin**.

Thyroglobulin is a large glycoprotein containing about **115 tyrosine residues**.



**The main steps are :**

1. **Uptake** of plasma **iodide** by the follicle cells.
2. **Oxidation** of iodide and **iodination** of tyrosine residues of thyroglobulin.
3. **Secretion** of thyroid hormones.





# 1. UPTAKE OF PLASMA IODIDE

Iodide uptake is energy dependent process.  
Two transporters are involved

- a) 1. NIS ( sodium -iodide symporter).
- b) 2. Pendrin (PDS) an I-/Cl- porter.



## 2. OXIDATION OF IODIDE AND IODINATION OF TYROSINE RESIDUES.

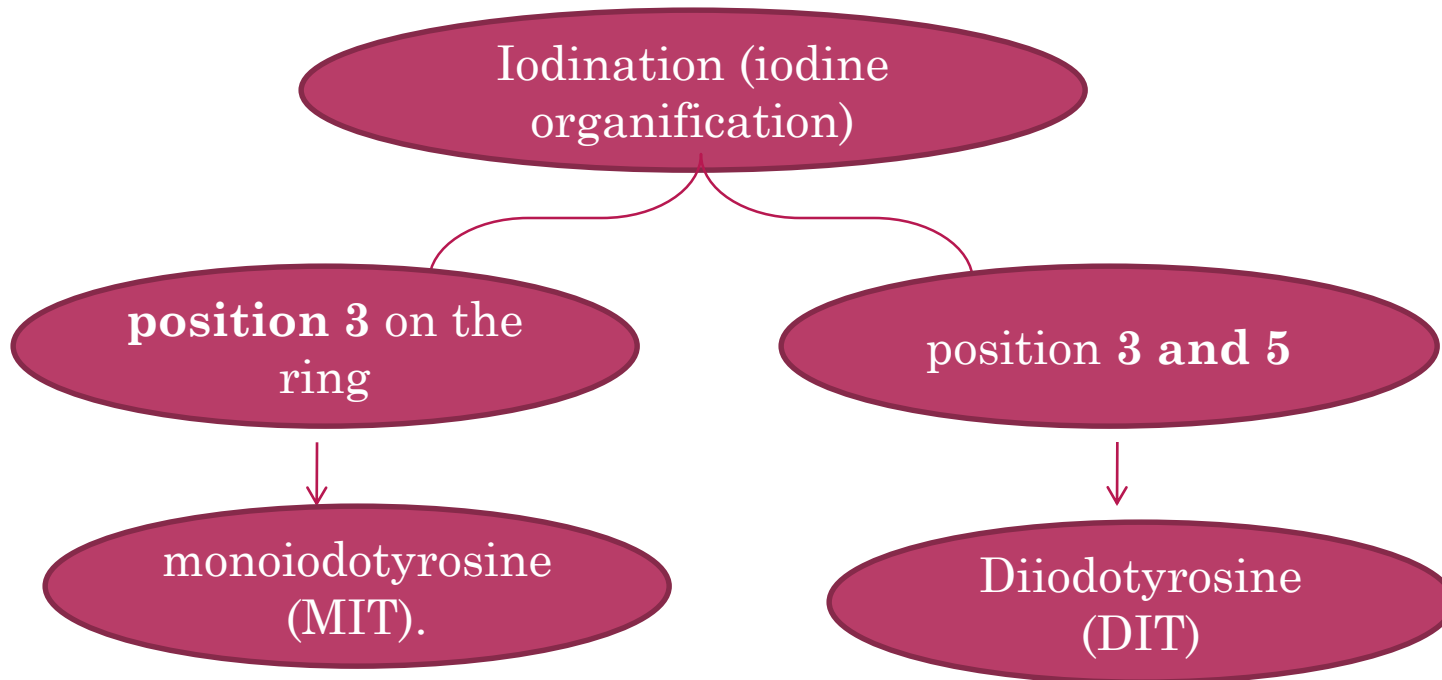
**Thyroperoxidase** is an enzyme that catalyzes the **oxidation** of the iodide and the **iodination** of tyrosine residues in the thyroglobulin.

( the reaction needs  $H_2O_2$  as oxidising agent).

Tyrosine residues are iodinated at **position 3** on the ring to form monoiodotyrosine (MIT).

Or iodinated at position **3 and 5** as well.....(DIT).






- Either
- Incorporation of MIT+DIT to give **T3**  
or
- DIT+DIT to give **T4**



The iodinated thyroglobulin forms a **large store** of the thyroid hormone.



### 3. SECRETION

□ The thyroglobulin is taken up into the follicle by **endocytosis** then fused with lysosomes and proteolytic enzymes  Release of T3 and T4.

□ **Note** : the active form is the T3. ( **T4 is converted in the peripheral tissues to T3** ).

□ The hormones are transported in the blood bound mainly to TBG ( thyroid binding globulin).



# REGULATION OF THE THYROID FUNCTION

## 1. **TRH, TSH, T4, T3** :

Thyroglobulin releasing hormone **TRH** released from the **hypothalamus** , Releases thyroid stimulating hormone (thyrotropin )**TSH** from the **pituitary** gland.

Thyrotropin stimulates the uptake of iodide as well as synthesis and release of thyroid hormone.






Then **TSH** Act on the thyroid gland and control all the aspects of thyroid hormones :

- ❑ Uptake of iodide by the follicle.
- ❑ Synthesis and secretion of thyroglobulin.
- ❑ Generation of  $H_2O_2$  and iodination of tyrosine.
- ❑ Endocytosis.
- ❑ Secretion of  $t_3$  and  $t_4$ .
- ❑ Blood flow to the gland.
- ❑ **It also has a growth-promoting effect that causes thyroid cell hyperplasia and an enlarged gland (goiter).**



- ❑ The production of TSH is also regulated by a **negative feedback** effect of the thyroid hormones (T3 more active than T4) on the anterior pituitary gland.
- ❑ Somatostatin also reduces TSH release.

## 2. Iodide concentration:

Reduced iodine intake  Reduced plasma iodide conc.  
 Decreased T3, T4 production.  Increase  
in TSH.





## Note:

The **size and vascularity** of the thyroid is reduced by an increase of iodide (**reduced TSH**).



# ACTIONS OF THYROID HORMONES

- Thyroid hormones bind to **intracellular receptors** that control the expression of genes responsible for many metabolic processes.



- ❑ **Metabolism** : increase basal metabolic rate, increase in metabolism of carbohydrates, fats, proteins.
- ❑ **The heart**: increase heart rate and output and increased tendency to dysrhythmia.
- ❑ **Growth and development**: critical for **growth** and also essential for **CNS growth** and **maturation**.

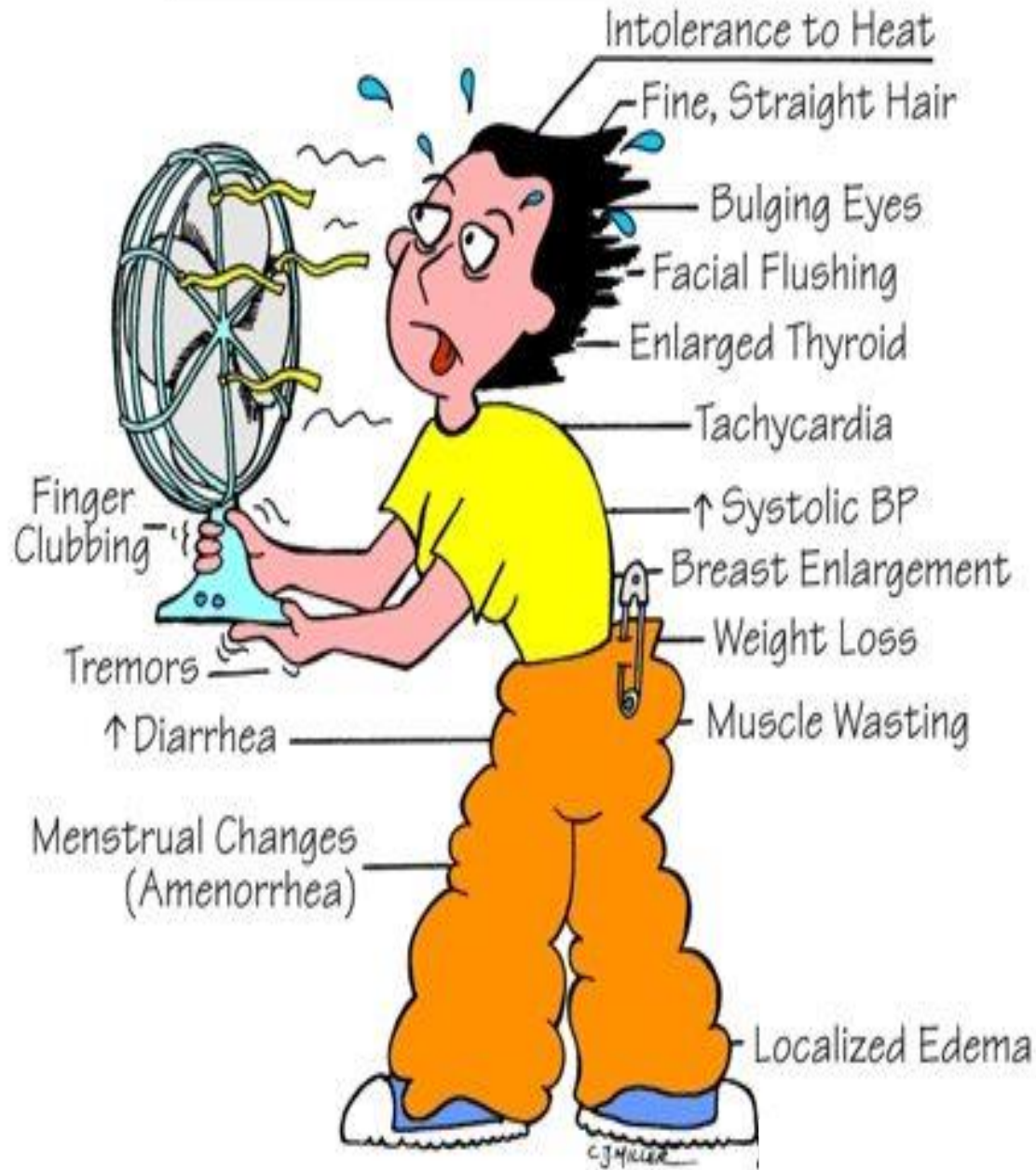


# THYROID ABNORMALITIES

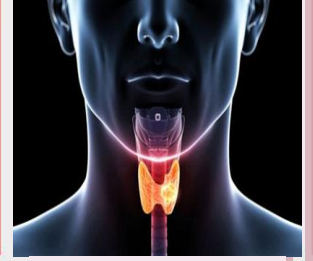
- A. Hyperthyrodism .
- B. Simple , non toxic goitre.
- C. Hypothyrodism.



# HYPERTHYROIDISM



# Thyroid Disorders

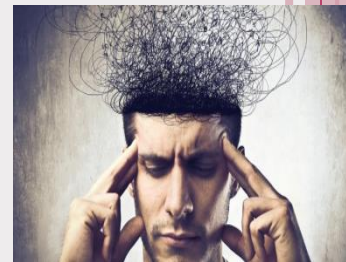


## Hyperthyroidism

Is the condition that occurs due to **excessive production** of **thyroid** hormone by the **thyroid gland**

## Thyrotoxicosis

Is the condition that occurs due to **excessive thyroid hormone** of **any cause** and therefore includes hyperthyroidism



Excessive activity of the thyroid hormones, Resulting in **high metabolic rate** , increase in skin temperature and sweating , marked sensitivity to heat, nervousness, tremor, tachycardia, increased appetite and weight loss.



## The common type of thyrotoxicosis is :

### Diffuse toxic goitre :

- ❑ Also called ( graves' disease or **exophthalmic** goitre {eyeball protrusion}) : An autoimmune disorder, **B lymphocytes** produce an **antibody** that activates the **TSH receptor**.
- ❑ Because these lymphocytes are not susceptible to negative feedback, patients with Graves' disease can have very high blood concentrations of thyroid hormone at the same time that their blood concentrations of TSH are very low.





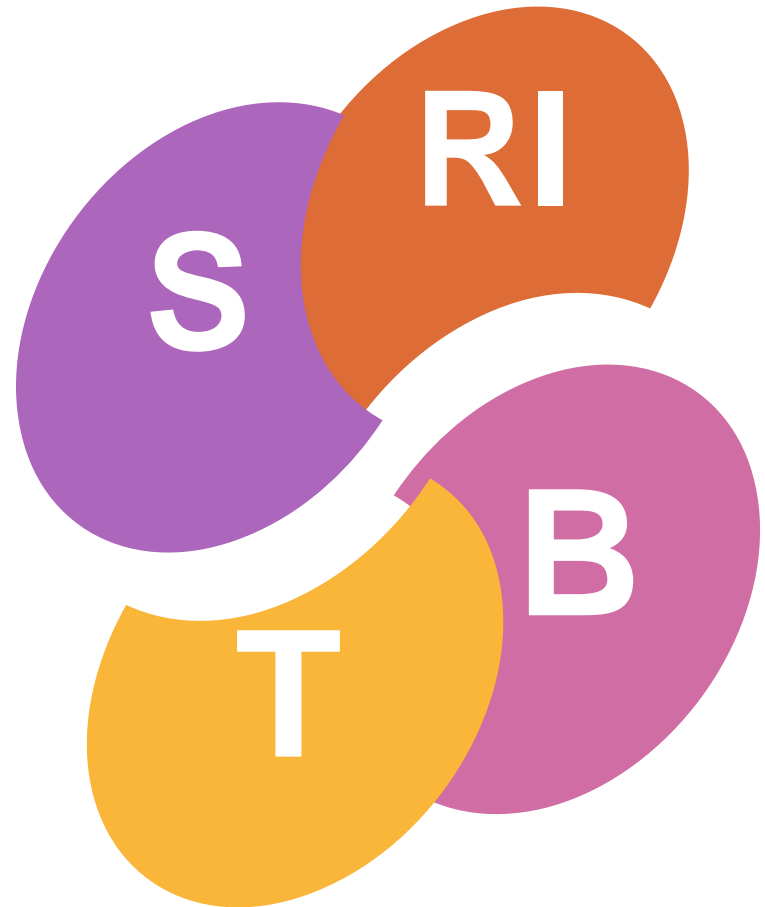
# Treatment Options

Surgery

Radioactive iodine

Thioureas

Beta-Blockers



# DRUGS USED TO TREAT HYPERTHYROIDISM

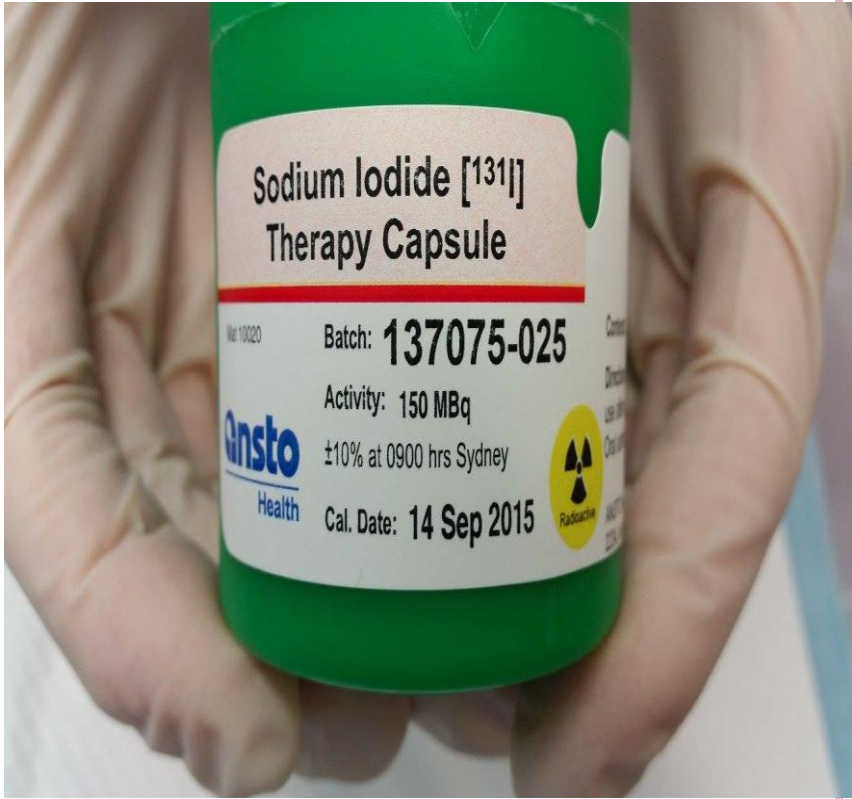
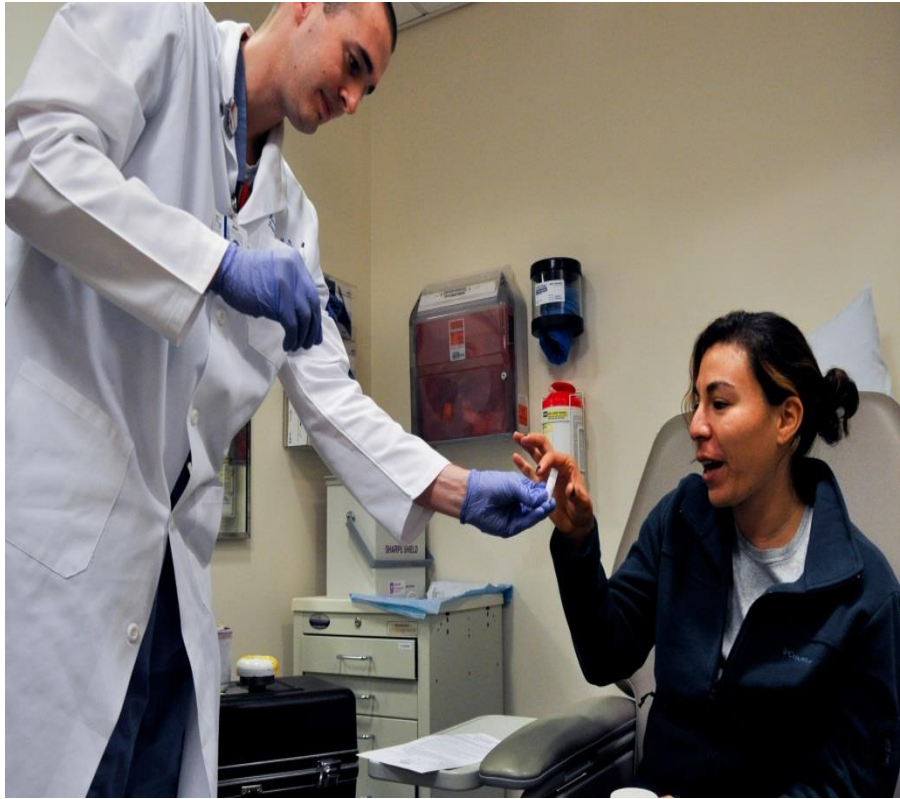
## 1. Radioiodine:

Iodine isotope used is  $I_{131}$ . Usually as sodium salt Given orally.

### -Mechanism of action:

The iodide isotope given orally is taken up by the thyroid gland and incorporated into thyroglobulin, then **emits toxic radiation** that damage the tissue.





❑ **Side effects :**

Hypothyroidism will occur ( treated with levothyroxine).

❑ **Cautions and contraindications:**

Should not be used in pregnant or nursing women.

❑ **Clinical uses:**

1. Treatment of hyperthyroidism.
2. Diagnostic for thyroid functions.
3. Treatment of thyroid cancer.



**2. Thioureylene (thioamides) :** ( carbimazole, methimazole and propylthiouracil).

❑ **M.O.A :**

Inhibit **thyroperoxidase** enzyme.

❑ **NOTE :** Propylthiouracil has additional mechanism as it **inhibits the peripheral conversion of T4 to T3.**



## Pharmacokinetics :

Given orally.

**Carbimazole** is rapidly converted to its active metabolite methimazole. ( prodrug)

Drug effects may take weeks to appear , because t<sub>4</sub> have **long half life** and because there maybe large store of the hormones in the thyroid gland. (often requiring 3–4 wk for full effect).

They cross the placenta ( **effect is less with propylthiouracil ,preferred in pregnancy** ).



❑ **Side effects:**

rare but the most serious: **Neutropenia and agranulocytosis** .

❑ **Common side-effects:**

Rashes , headaches, nausea , jaundice, joint pain.



### 3. Iodine/Iodide:

- Lugol's solution (iodine and potassium iodide) and saturated solution of potassium iodide.
- Inhibit iodination of thyroglobulin possibly by reducing the H<sub>2</sub>O<sub>2</sub> generation.
- They also inhibit the release of T<sub>3</sub> and T<sub>4</sub>.
- Their onset of action occurs rapidly, within 2–7 d. However, the effects are transient; the thyroid gland “escapes” from the iodide block after several weeks of treatment.





❑ **Clinical uses:**

- ✓ Preparation of the patient to thyroidectomy.
- ✓ Thyroid storm.

❑ **Side- effects:**

Allergic reaction, fever, lacrimation, conjunctivities ,  
pain in salivary gland .



#### 4. Other drugs:

- ❑ **Betablockers** ( to reduce tachycardia , tremor and aggitation) .
- ❑ **Guanethidine**: eye drops used to cause eyelid retraction.
- ❑ **Corticosteroid** and **surgical decompressor** to reduce exophthalmia.



## NOTE :

- The iodine-containing antiarrhythmic drug amiodarone, can cause:
  - **Hypothyroidism:** through its ability to block the peripheral conversion of T<sub>4</sub> to T<sub>3</sub>.
  - **Hyperthyroidism through :**
    - An iodine-induced mechanism in persons with an underlying thyroid disease such as multinodular goiter.
    - An inflammatory mechanism that causes leakage of thyroid hormone into the circulation.



- Amiodarone-associated **hypothyroidism** is treated with **thyroid hormone**.
- Iodine-associated **hyperthyroidism** caused by amiodarone is treated with **thioamides**, whereas the **inflammatory version** is best treated with **corticosteroids**.
- Iodinated radiocontrast media (eg, oral diatrizoate and intravenous iohexol) rapidly suppress the conversion of T4 to T3 in the liver, kidney, and other peripheral tissues.



A dramatic landscape featuring three prominent buttes under a stormy sky. A bright lightning bolt strikes the leftmost butte. The scene is illuminated by a warm, orange glow, suggesting a sunset or sunrise. The sky is dark and filled with heavy, dark clouds.

# THYROID STORM

**Thyroid Storm**

# THYROID STORM

- Is a life threatening medical emergency , decompensated thyrotoxicosis , high fever, tachycardia , tachypnea dehydration, delirium, coma , nausea , vomiting and diarrhea.
- May be precipitated by :
  - Infection
  - Surgery
  - Radioactive iodine therapy
  - Withdrawal of anti-thyroid drug.



- Treatment of thyroid storm should include the following :
  1. Suppression of thyroid hormone formation and **secretion**. ( PTU and iodide) .
  2. Anti-adrenergic : beta blockers ( esmolol).
  3. Administration of corticosteroids: antipyretic effect and stabilize the blood pressure.
  4. Treatment of complication or the precipitating factor: for fever paracetamol is preferred over aspirin and other NSAIDs???



## **B. SIMPLE, NON TOXIC GOITRE**

A dietary deficiency of iodine , if prolonged , causes rise in TRH and TSH which leads to increase in the **size** of the thyroid gland to produce normal amount of hormone.





# HYPOTHYROIDISM



## C. HYPOTHYROIDISM

- ❑ Decreased activity of the thyroid gland.
- ❑ **Symptoms and sign:** low metabolic rate , low speech , deep hoarse voice , lethargy , bradycardia, sensitivity to cold and mental impairment. And also thickening of the skin.
- ❑ **Hashimoto's thyroiditis** :autoimmune disease in which antibodies directed against thyroglobulins.
- ❑ **Radioiodine** is another cause of hypothyroidism.



# DRUGS USED TO TREAT HYPOTHYROIDISM

## ❑ **Thyroid replacement therapy:**

-**Levothyroxine** : given orally (on an empty stomach) is the first line treatment.

-**Liothyronine** ( tri-iodothyronine), given IV, has faster onset but shorter duration, reserved for acute emergencies ( myxoedma).

## ❑ **Side effects:**

Overdose may cause hyperthyroidism .

Cardiac dysrhythmia, angina.



- Toxicity is that of thyrotoxicosis .
- Older patients, those with cardiovascular disease, and those with longstanding hypothyroidism are highly sensitive to the stimulatory effects of T4 on the heart.
- Such patients should receive lower initial doses of T4.



## MYXEDEMA COMA

- Decompensated hypothyroidism ; hypothermia and advanced stage of hypothyroid symptoms. Need immediate and aggressive therapy.
- IV bolus levothyroxine .
- Initial treatment with IV liothyronine or combination of both T4 and T3 can be used. ?
- Corticosteroids : to rule out coexisting adrenal suppression.
- Supportive treatment .



*The ~~End~~  
Beginning*

