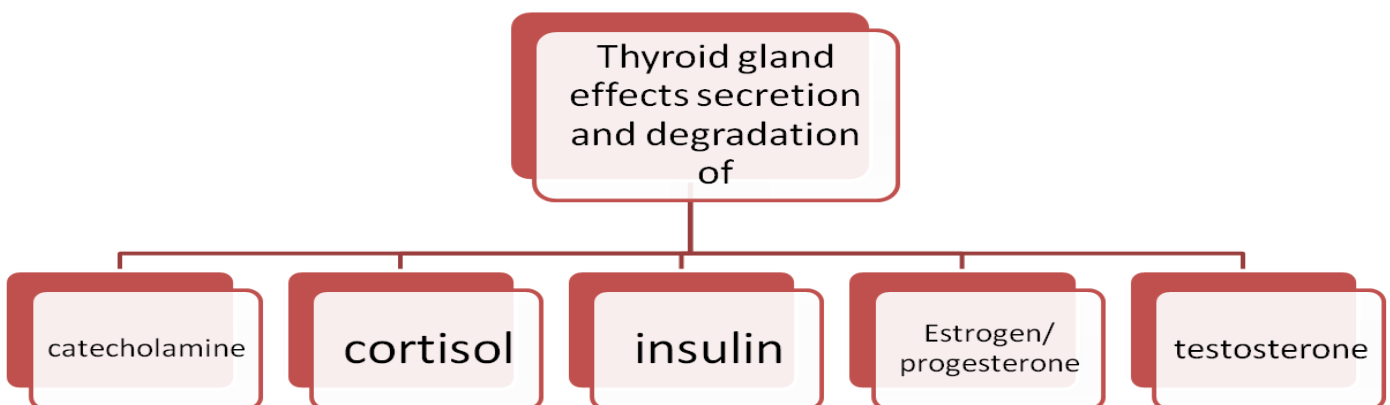
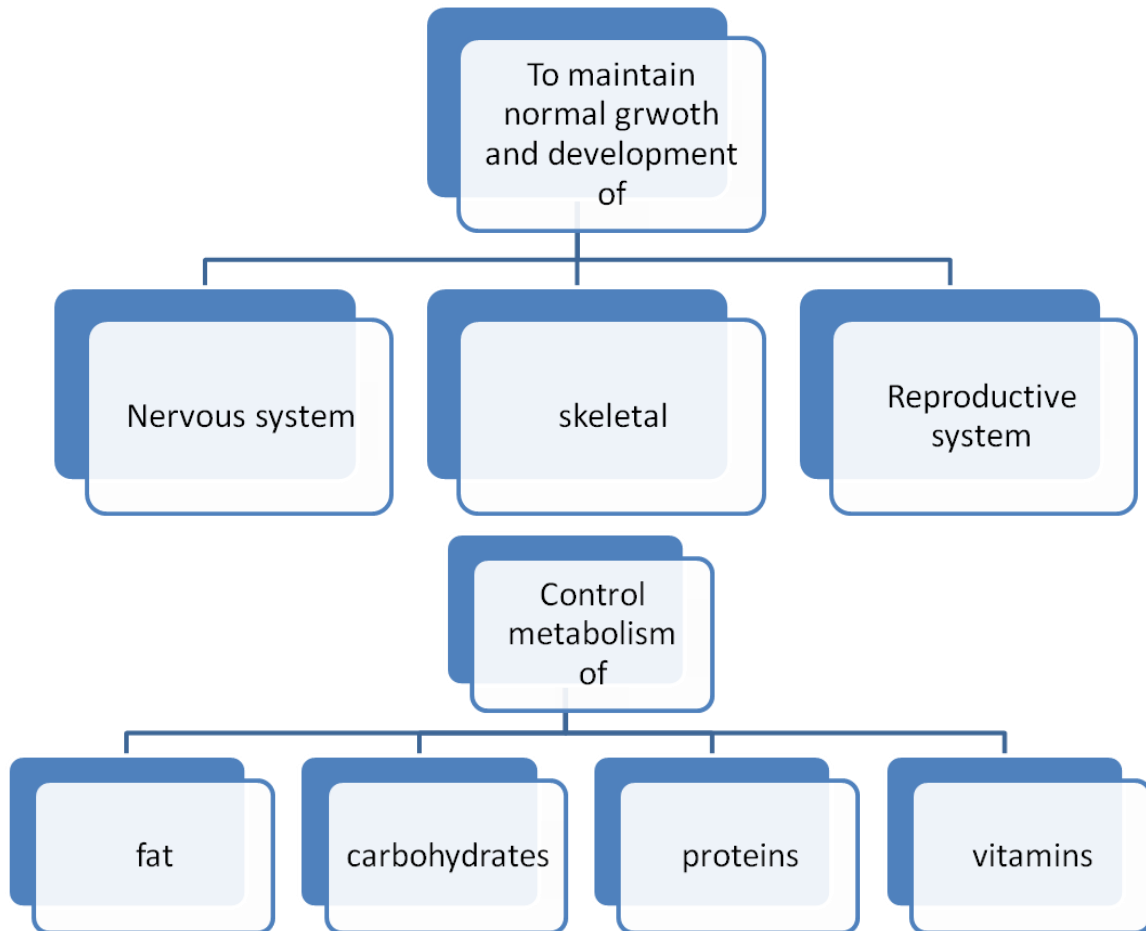
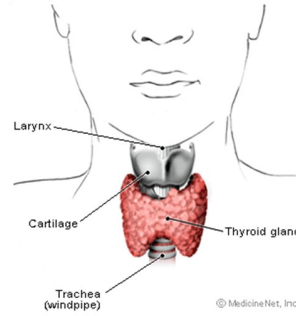
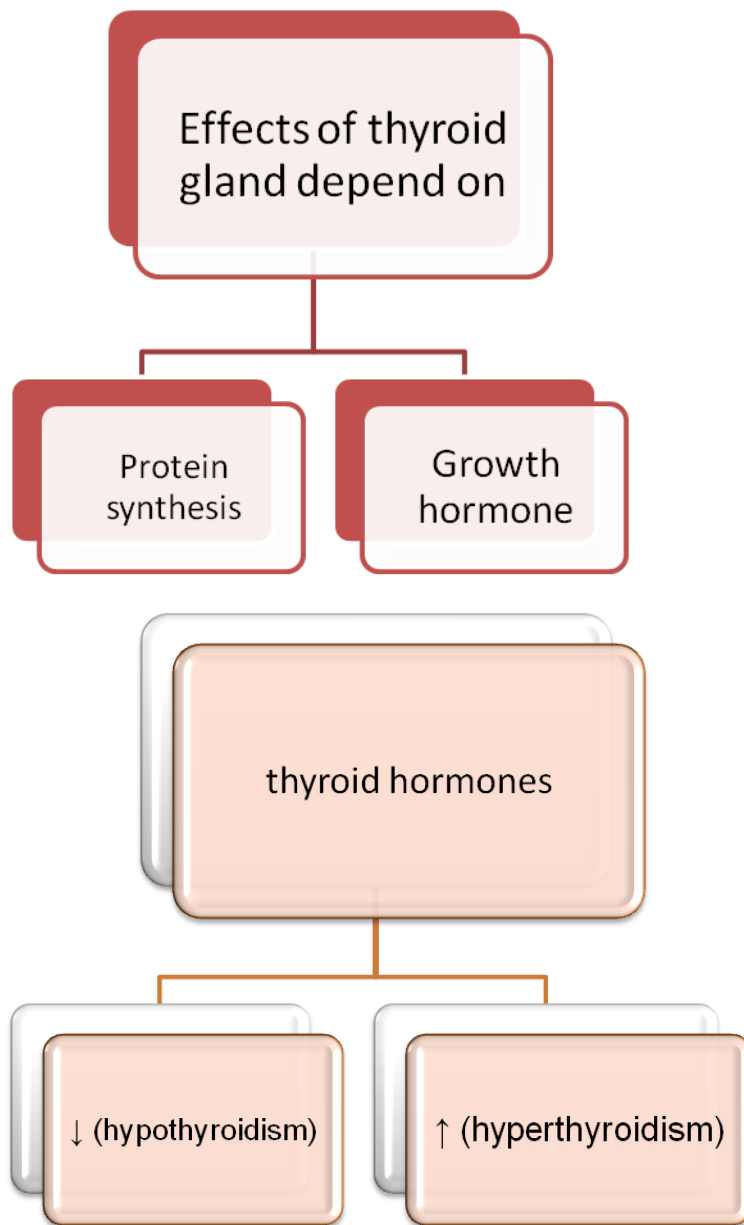


# Thyroid and anti-thyroid Drugs

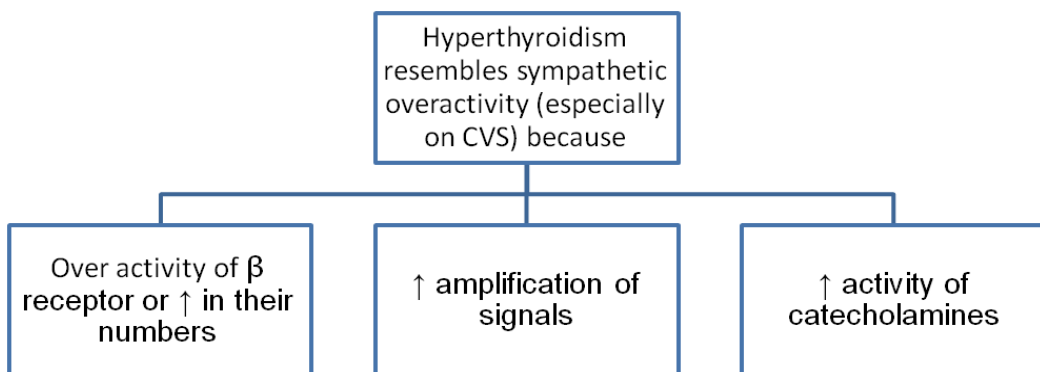
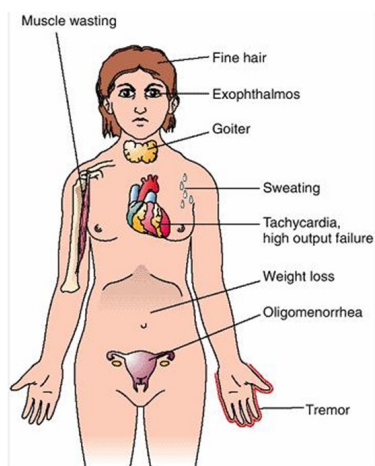
Thyroid gland secretes two hormones:  
1-  $T_3$  (triiodothyronine)  
2-  $T_4$  (tetraiodothyronine)



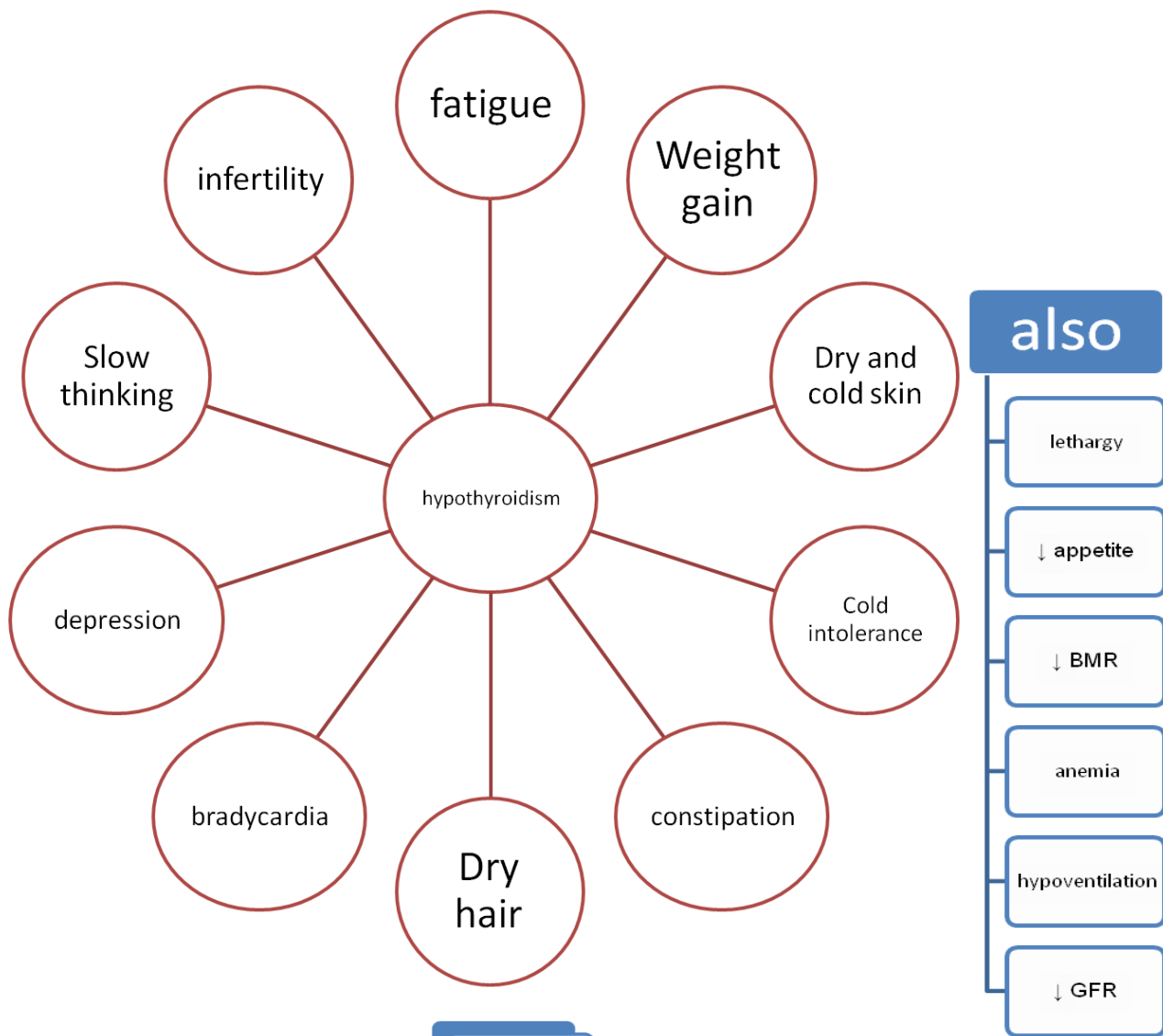


### manifestation of hyperthyroidism





## manifestation of hypothyroidism

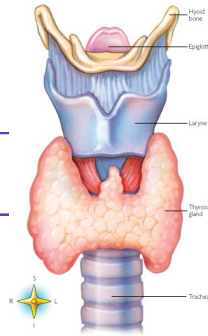


### Causes of hypothyroidism

- drugs
- autoimmune
- Blocked hormone formation
- Impaired synthesis of  $T_4$
- Destruction of the gland
- Iodine deficiency
- Receptor blocking antibodies
- Pituitary or hypothalamic disease

Deficiency of thyroxine in early life/pregnancy →  
1- irreversible mental retardation (cretinism).  
2- dwarfism

# Synthesis of thyroid hormones



Iodide (I<sup>-</sup>) is taken by the gland

Iodide → iodine (I)  
By thyroidal peroxidase enzyme

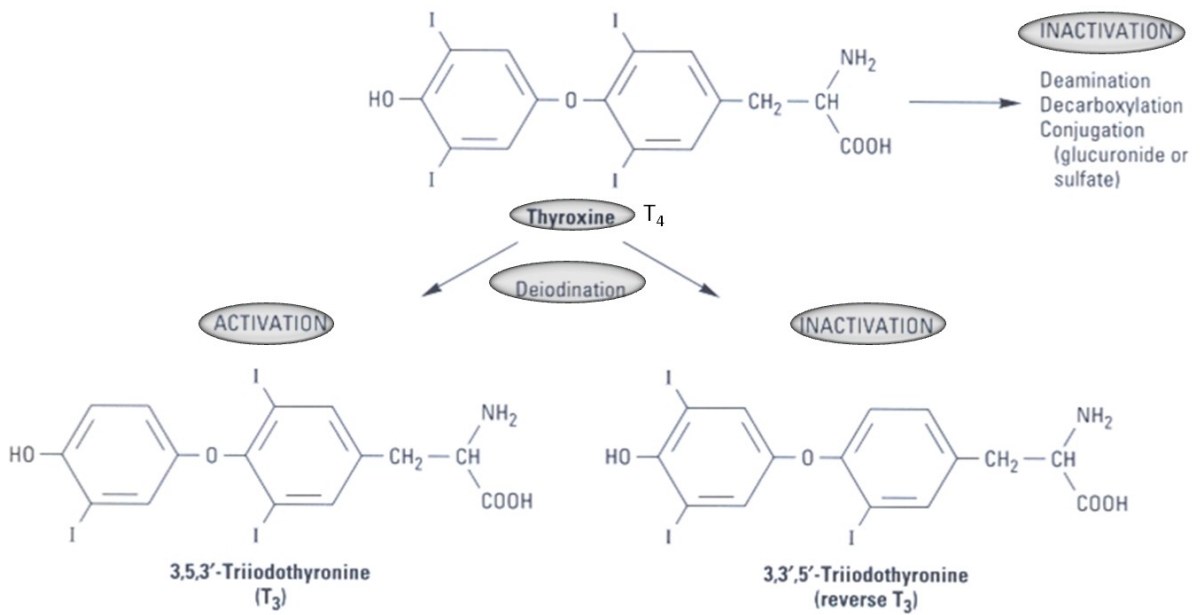
Iodine + tyrosine = monoiodotyrosine (MIT) + diiodotyrosine (DIT)  
This is called organification or iodination

**2 DIT = T<sub>4</sub>**  
**MIT + DIT = T<sub>3</sub>**  
**Ratio of T<sub>4</sub> to T<sub>3</sub> = 5:1**  
**In circulation T<sub>3</sub> is derived from T<sub>4</sub> (by deiodination)**

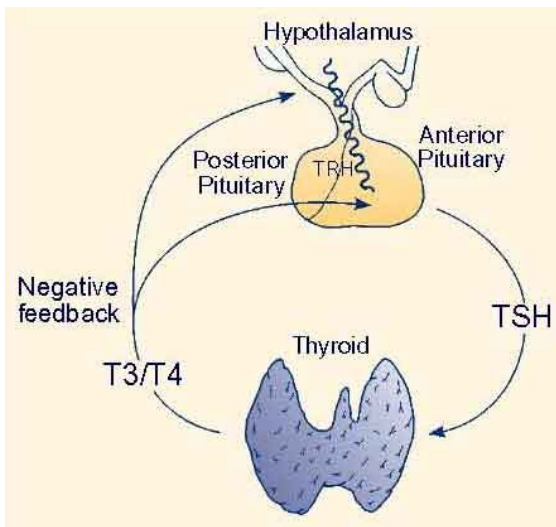
T<sub>4</sub> and T<sub>3</sub> are reversibly bound to thyroxine binding globulin (TBG) In circulation

Starvation, pregnancy, and steroid hormones affect their binding but their free concentration are maintained

# Peripheral metabolism



# Thyroid regulation

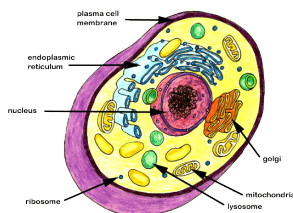


Also: levels of iodine in blood regulates thyroidal secretion

*Natural hormones are L-isomers  
Synthetic hormones are D-isomers  
Synthetic have 4% activity of natural*

## Mechanism of action

$T_4$  and  $T_3$  enter to the cell



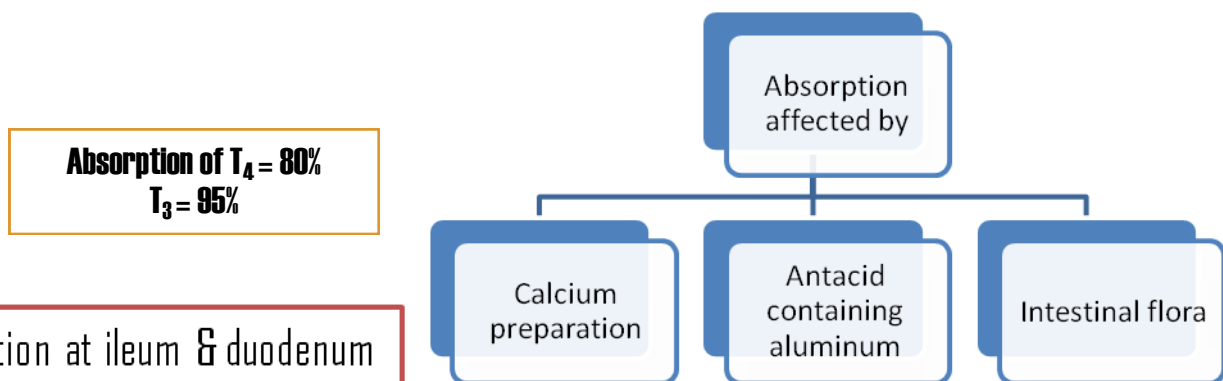
$T_4 \rightarrow T_3$  and enters nucleus

$T_3$  binds to its receptors  $\rightarrow$  formation of mRNA  $\rightarrow$  protein synthesis

# Comparison between $T_4$ and $T_3$

- $T_4$  production is more than  $T_3$
- $T_4$  is converted to  $T_3$  in periphery
- $T_3$  is more potent than  $T_4$  (Physiologically)
- $T_3$  acts faster than  $T_4$
- $T_3$  enters cell easily than  $T_4$
- $T_3$  binds to receptors in nucleus.

## Pharmacokinetics of administered hormones



Absorption is impaired in case of myxedema with ileus

So we will take the parenteral route

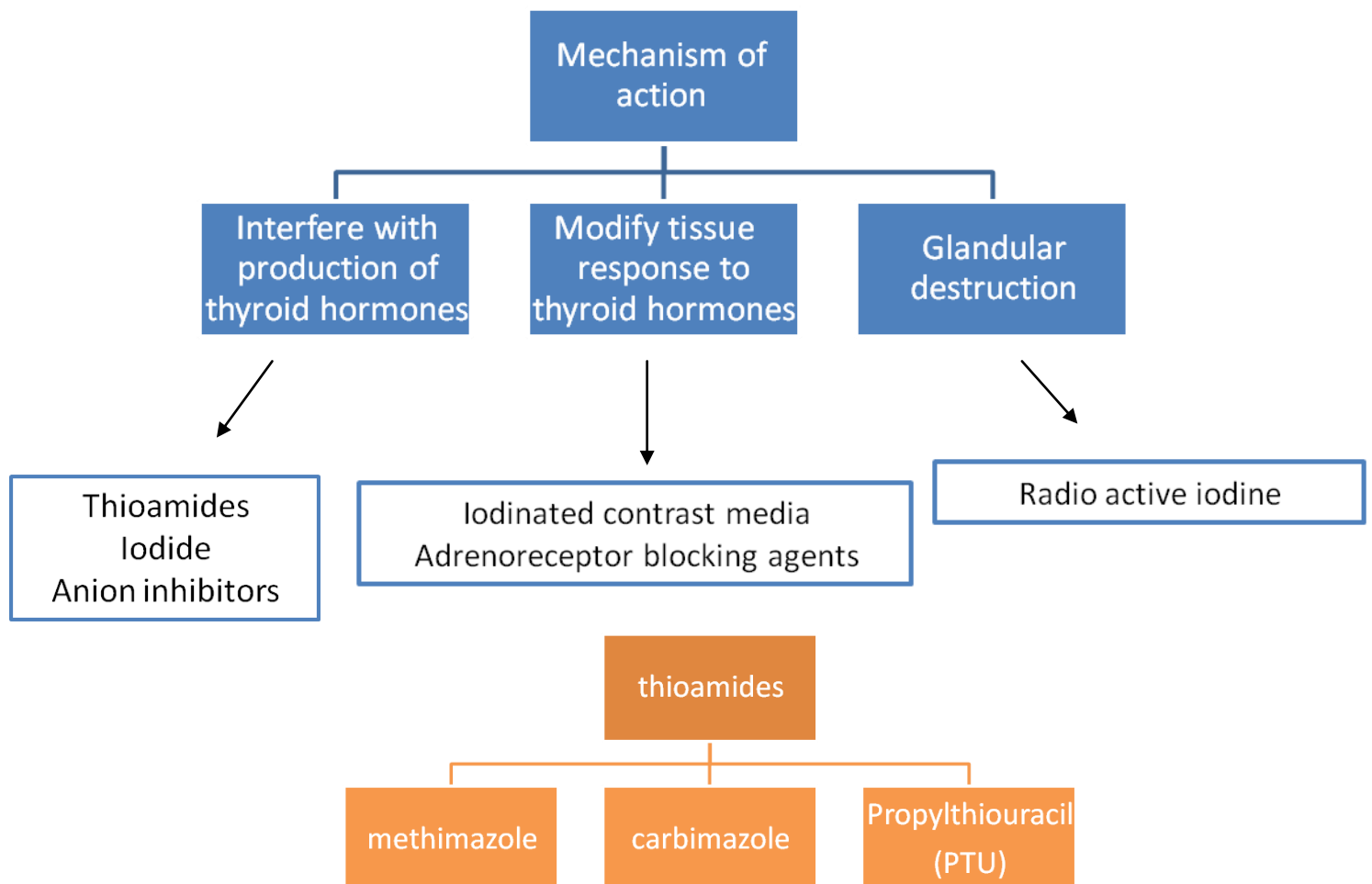
In hyperthyroidism:  
 $\uparrow$  clearance of  $T_3$  and  $T_4$   
 $\downarrow t_{1/2}$   
the opposite is true in hypothyroidism

Enzyme inducers  $\rightarrow$  metabolism of  $T_3$  and  $T_4$

# Thyroid preparations

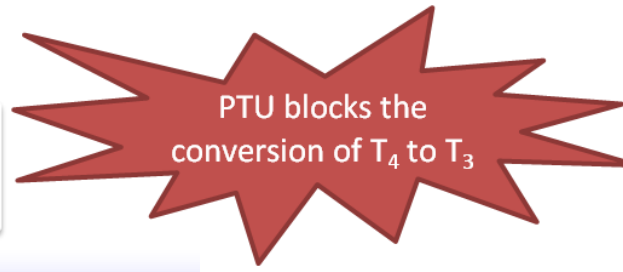
Levothyroxine:(T <sub>4</sub> )	Liothyronine (T <sub>3</sub> )
Preparation of choice for replacement therapy	Not recommended (because of difficulty in monitoring)
T <sub>1/2</sub> = 7 days	24 hours
stable	Rapid acting (more potent)
Administered once daily	Multiple dosing a day
Oral and parenteral preparation	same
No allergic reaction	Avoided in cardiac patient

## Antithyroid agents



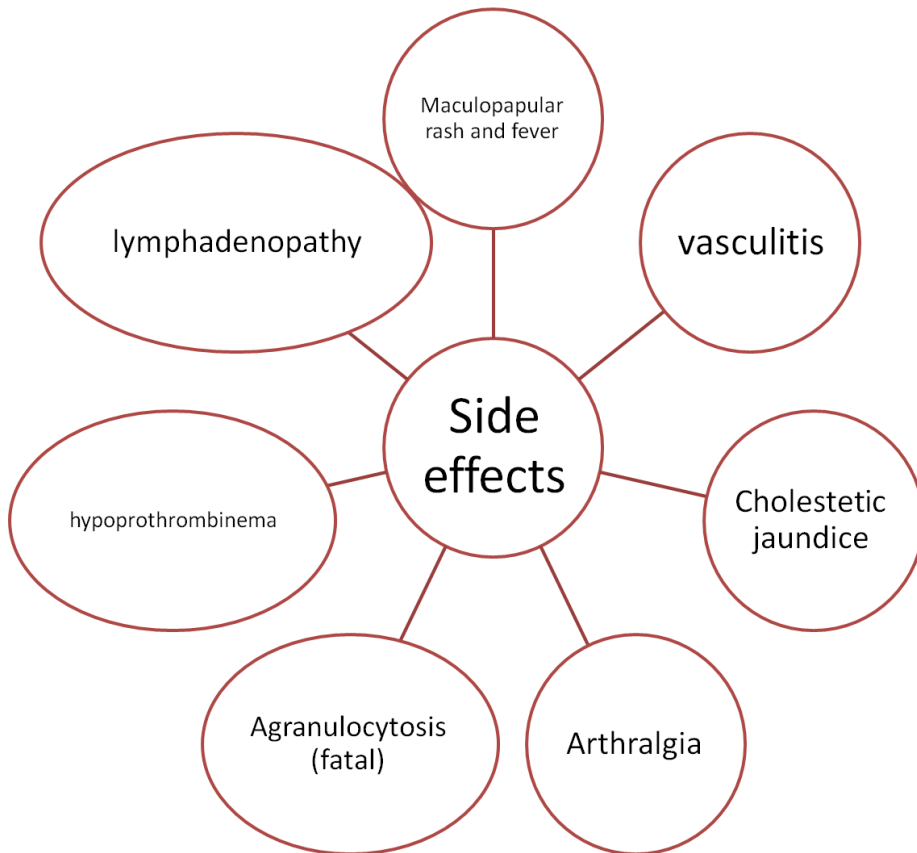
# Mechanism of action

They inhibit organification process also they inhibit coupling of iodotyrosine to form  $T_3$  and  $T_4$



***The onset of drug is slow requiring 3-4 week before stores of  $T_4$  are depleted***

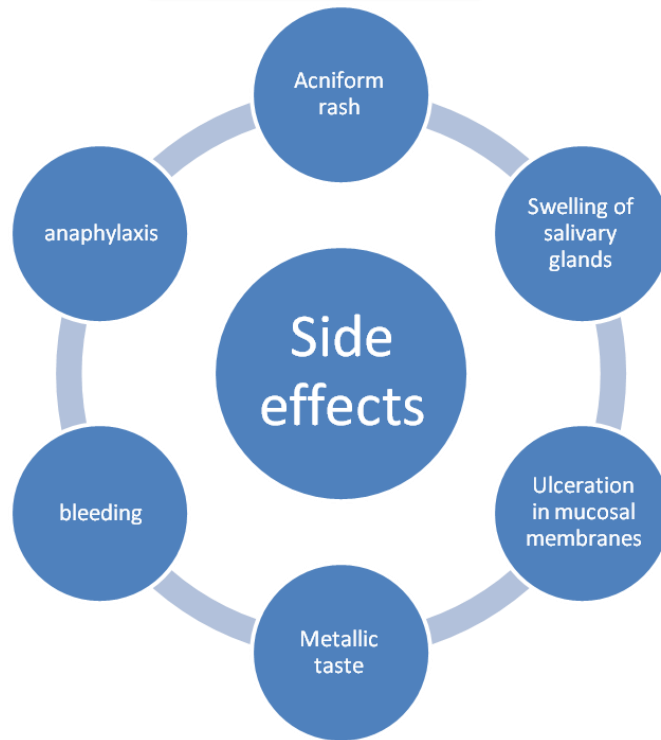
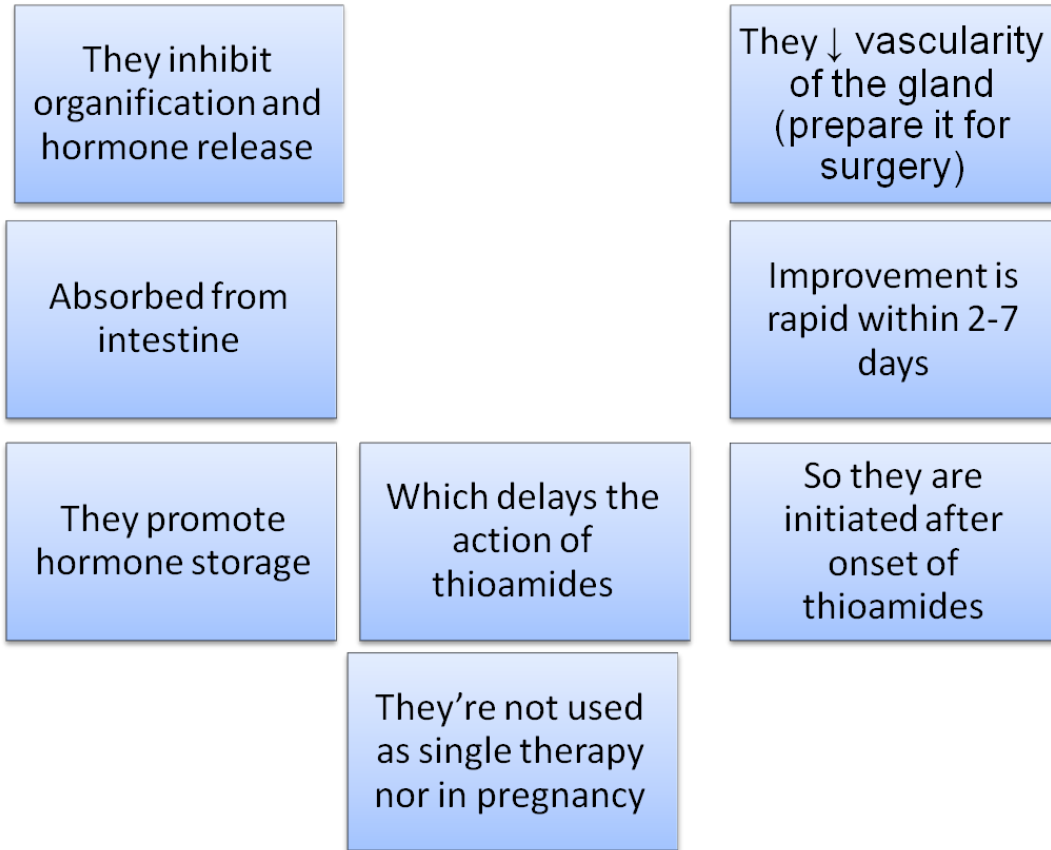
	Propylthiouracil	Methimazole		Propylthiouracil	Methimazole
Absorption	Rapid but incomplete	At variable rates but complete	$T_{1/2}$	1.5 hrs	6 hrs
Volume of distribution	Approximates total body water	same	Administration	Every 6-8 hrs	As a single dose in 24 hrs
Protein binding	more	less	Duration of activity	7 hrs	longer than 24 hrs
accumulation	In thyroid	same	Pregnancy	Preferred, though cross placenta and is conc. in fetal thyroid but is highly protein bound, cross placenta less readily	Cross placenta and concentrated by fetal thyroid
Excretion	Kidneys as inactive Glucuronide in 24 hrs	Excretion slow, 60-70% of drug is recovered in urine in 48 hrs	Nursing mothers	Less secreted in breast milk	secreted



It occurs in 3-12% of patients



# iodides

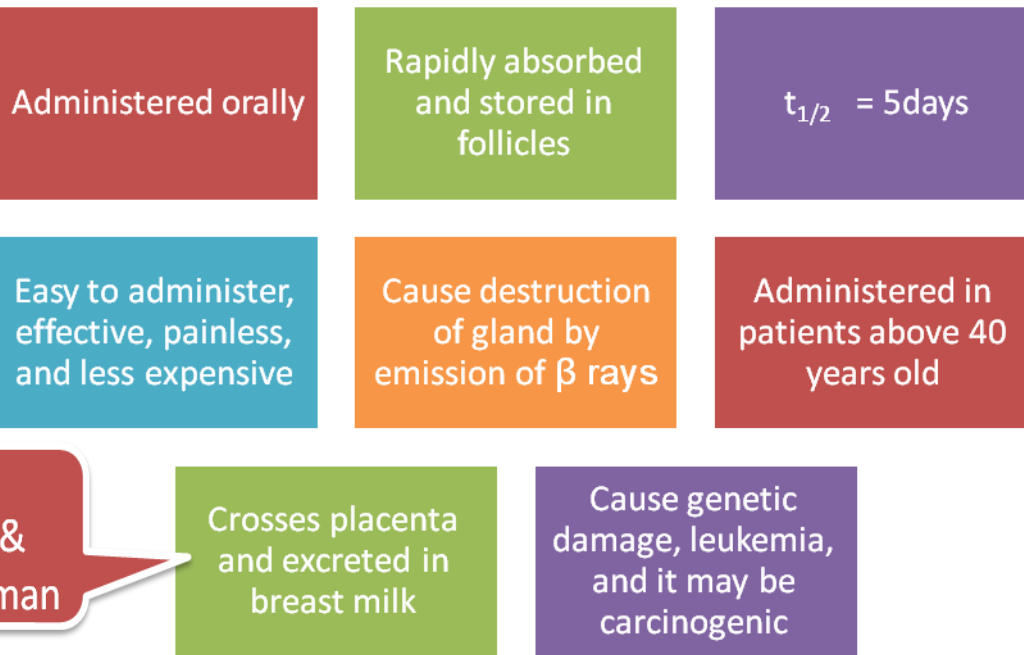


Anion inhibitors
Perchlorate $\text{ClO}_4$
Pertechnetate $\text{TcO}_4$
Thiocyanate $\text{SCN}$

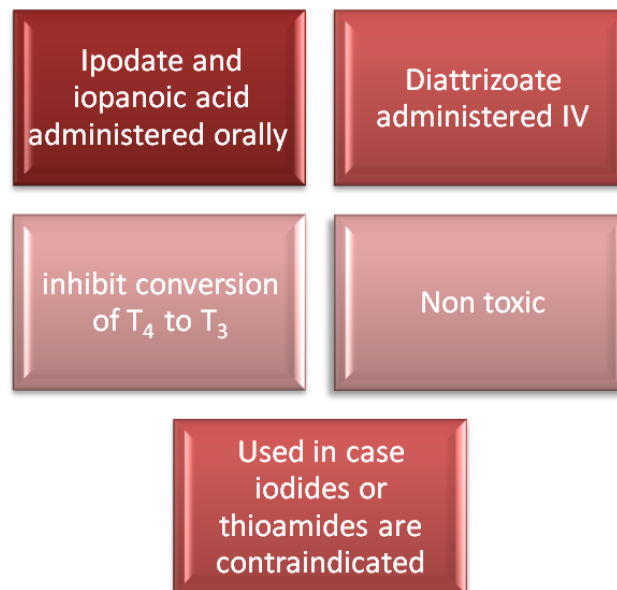
## Anion Inhibitors

*They competitive inhibitor of iodide transport mechanism  
Large doses of these drugs are required.  
They're rarely used now because they lead to aplastic anemia*

# Radioactive iodine ( $I^{131}$ )



# Iodinated contrast media



# Adrenoreceptors blocking agents

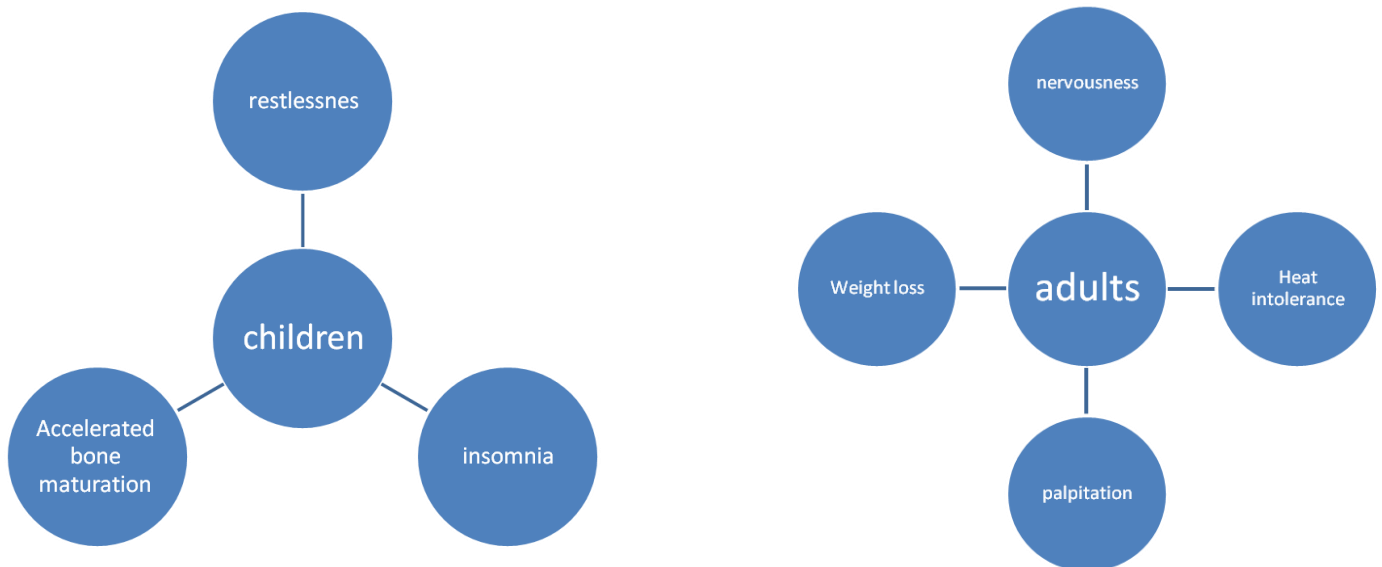
They're used to treat the symptoms only  
We use  $\beta$  blockers without intrinsic sympathomimetic activity (e.g. propranolol)  
If we can't use  $\beta$  blockers we will use diltiazem  
Diltiazem is used in patient having thyrotoxicosis associated with heart failure

# Clinical pharmacology

## hypothyroidism

- **Diagnosed by:** ↓ free thyroxine and ↑ TSH.
- **Treatment: levothyroxine.** Administered in an empty stomach
- **Takes 6-8 weeks to reach steady level.**
- **Given once daily.**
- **In long standing conditions, older patients, and patients with cardiac ailments, treatment is started with reduced dose.**
- **Given in small dose in the first 2 weeks then increase the dose after every 2 weeks.**

### Adverse effects of over dose



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*Chronic over treatment with  $T_4$  lead to: atrial fibrillation and osteoporosis*

---

### Myxedema coma

- *It's the end state of untreated hypothyroidism.*
- *Develops to: stupor, coma, and death.*
- *Treat by leading dose of levothyroxine then administer it daily.*
- *We can't use  $T_3$  because it's cardiotoxic*
- *IV hydrocortisone may be used if there's adrenal and pituitary insufficiency*

# Hypothyroidism and pregnancy

**In pregnant hypothyroid patient you need to increase thyroxine by 20-30% because:**

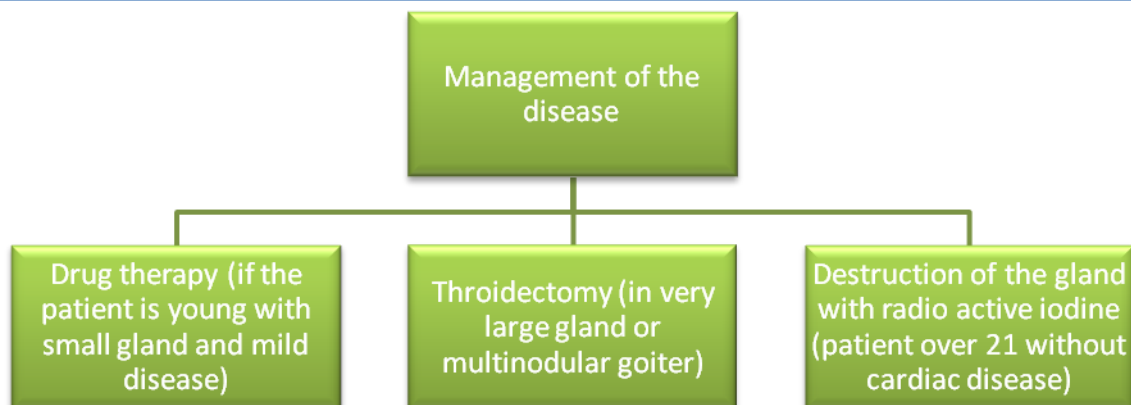
**1- elevated maternal TBG**

**2- early development of fetal brain depends on maternal thyroxine**

## Hyperthyroidism

### Grave's disease

- Most common form of hyperthyroidism.
- Autoimmune disorder.
- B lymphocytes secrete antibodies against thyroid gland.
- $\uparrow T_4$  and  $T_3$  and  $\downarrow TSH$ .
- $\uparrow$  radio iodine uptake.



#### Drug Therapy

- Methimazole/ propylthiouracil.
- May take 1-2 years with 60-70% relapse.
- Start with large dose then daily maintenance dose.
- PTU is better than methimazole. (In pregnancy)
- Lead to  $\uparrow TSH$  (prevented by levothyroxine)

#### thyroidectomy

Before 2 weeks of the surgery give the patient KI twice daily to diminish vascularity

## Radioactive Iodine

- In patients with cardiac disease, severe disease, or elders use methimazole then stop treatment for 5-7 days. Then use  $I^{131}$
- Lead to: hypothyroidism in 80% of patients
- Use  $\beta$  blockers as adjunct therapy To control symptoms

## Thyroid Storm

- Sudden exacerbation of all the symptoms of thyrotoxicosis.
- Life threatening syndrome (death may occur due to heart failure and shock).
- Treatment:
  1. Propranolol.
  2. KI.
  3. Iodate.
  4. PTU.
  5. Hydrocortisone to prevent shock.
  6. If above methods fail: plasmapheresis or pretonial dialysis.

## Thyrotoxicosis and Pregnancy

- $I^{131}$  or subtotal thyroidectomy prior to pregnancy.
- Don't use radioactive iodine during pregnancy.
- Instead use PTU but keep the dose minimum

## questions

Match:

A-  $I^{131}$

B- Diatrizoate

C- propranolol

D- PTU

E-  $T_3$

- 1- produced in periphery when  $T_4$  is administered
- 2- Radiocontrast medium useful in thyrotoxicosis
- 3- produces a permanent reduction in thyroid activity.

- In graves disease the cause of hyperthyroidism is an antibody that binds to:
  - TRH receptor
  - TSH receptor
  - Thyroid hormone receptors
  - Thyroglobulin promoting its degradation and release of thyroid hormones
  - TBG displacing thyroid hormones

- Methimazole reduces serum concentration of  $T_3$  by:
  - Accelerating the peripheral metabolism of  $T_3$
  - Inhibiting the proteolysis TBG
  - Inhibiting the secretion of TSH
  - Inhibiting Iodide uptake by the cells in the thyroid
  - Preventing the addition of iodine to tyrosine residues on thyroglobulin
- When initiating drug therapy for an elderly patient with long-standing hypothyroidism it is important to begin with small doses to avoid:
  - Exophthalmos
  - Acute renal failure
  - Hemolysis
  - Over stimulation of the heart
  - Seizures
- True or False
- Thioamides associated toxicity:
  - Agranulocytosis
  - Skin rash
  - Vasculitis
  - Liver dysfunction
  - hypoprothrombinemia
- Antithyroid drugs contraindicated in pregnancy:
  - Thioamides
  - Iodide salts
  - Radioactive iodine
- Thyroid storm:
  - It is important to use a rapid onset drug
  - We use diatrizoate
  - We use levothyroxine
  - We use PTU
  - We use radioactive iodine