

# THE THYROID GLAND

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# Thyroid Gland

## Lecture 1;

### Objectives:

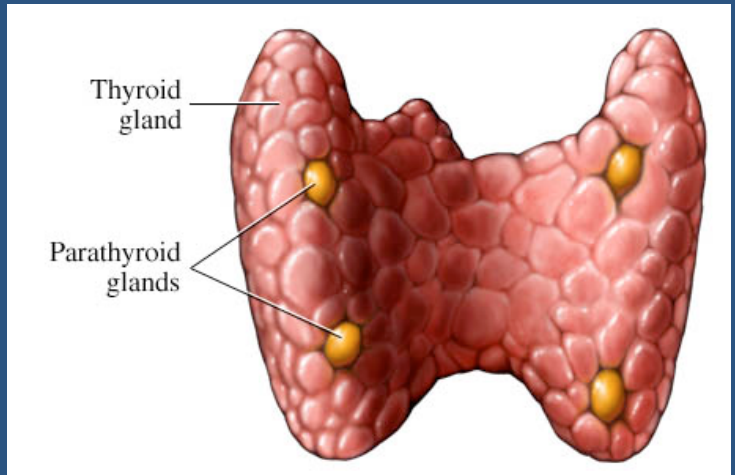
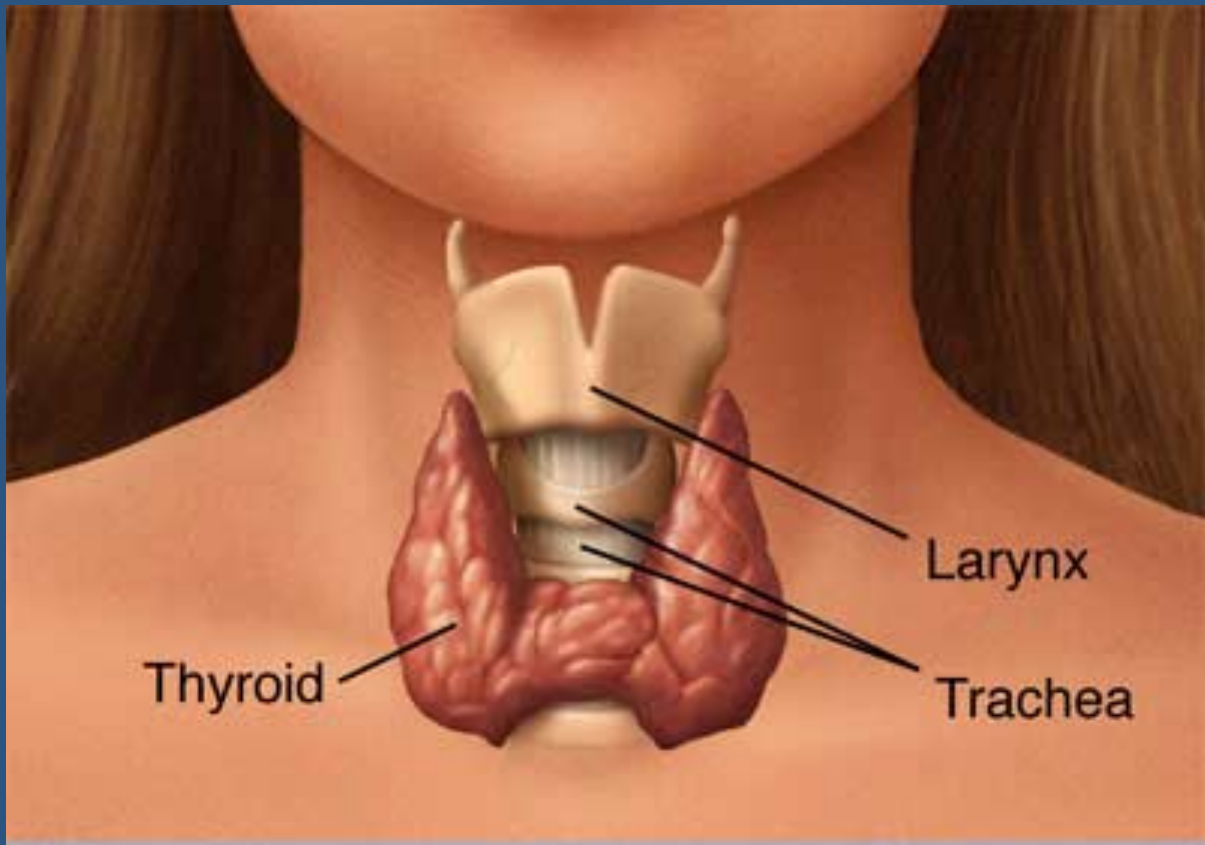
- 1- Describe the synthesis of thyroid hormones.
- 2- Diagram the control over the thyroid gland.
- 3- Compare between the hormones released by the thyroid gland.
- 4- Discuss the actions of the thyroid hormones.

# Thyroid Gland (Hypo and hyperthyroidism)

## Lecture 2;

### Objectives:

- 1- Identify the terms goiter, hypo and hyperthyroidism.
- 2- List the causes and types of goiter, hypo and hyperthyroidism.
- 3- Discusses the clinical picture of hypo and hyperthyroidism.
- 4- Explain the laboratory tests to diagnose hypo and hyperthyroidism.
- 5- Outline management regimen for hypo and hyperthyroidism.

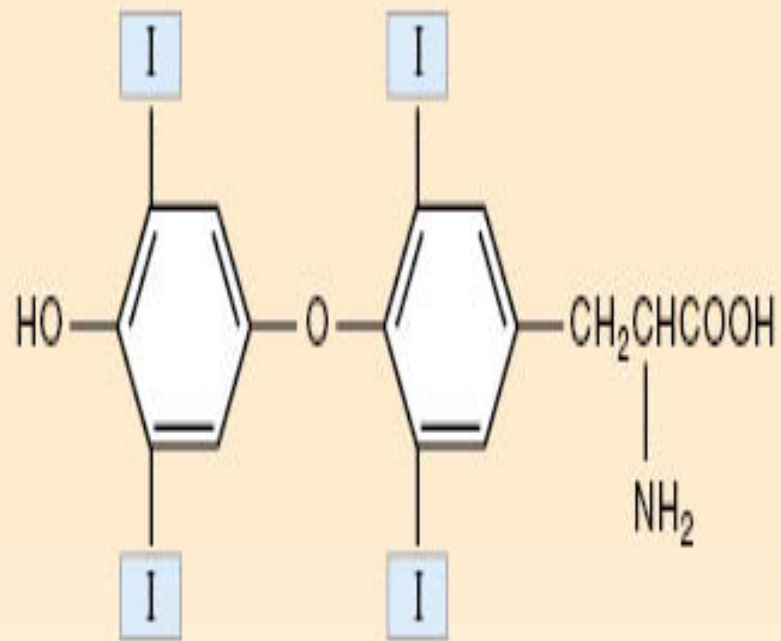


- **It is located below the larynx on either sides and anterior to the trachea.**
- **The first recognized endocrine gland.**
- **20g in adult.**

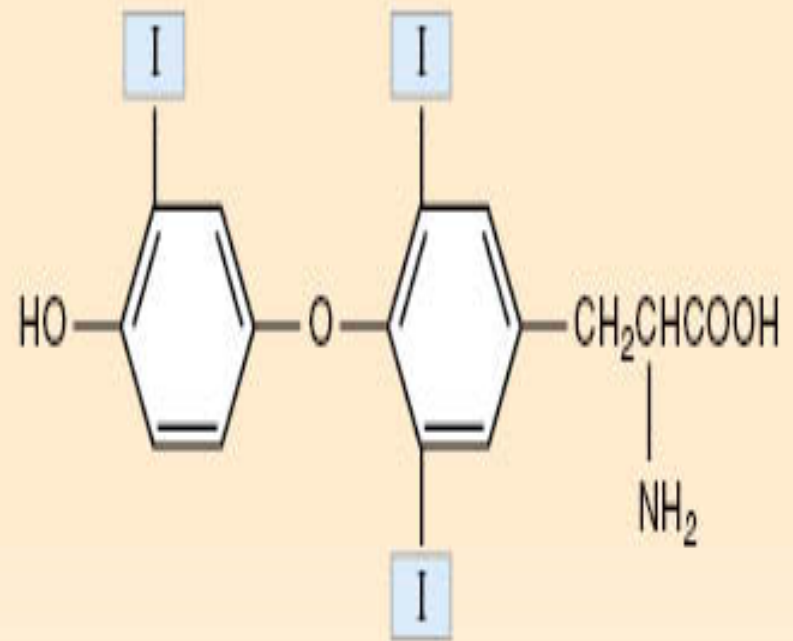
# HORMONES

- T4 (tetraiodothyronine) (thyroxine) 90%.
- T3 (Triiodothyronine) 10%.
- Reverse T3
- Calcitonin.

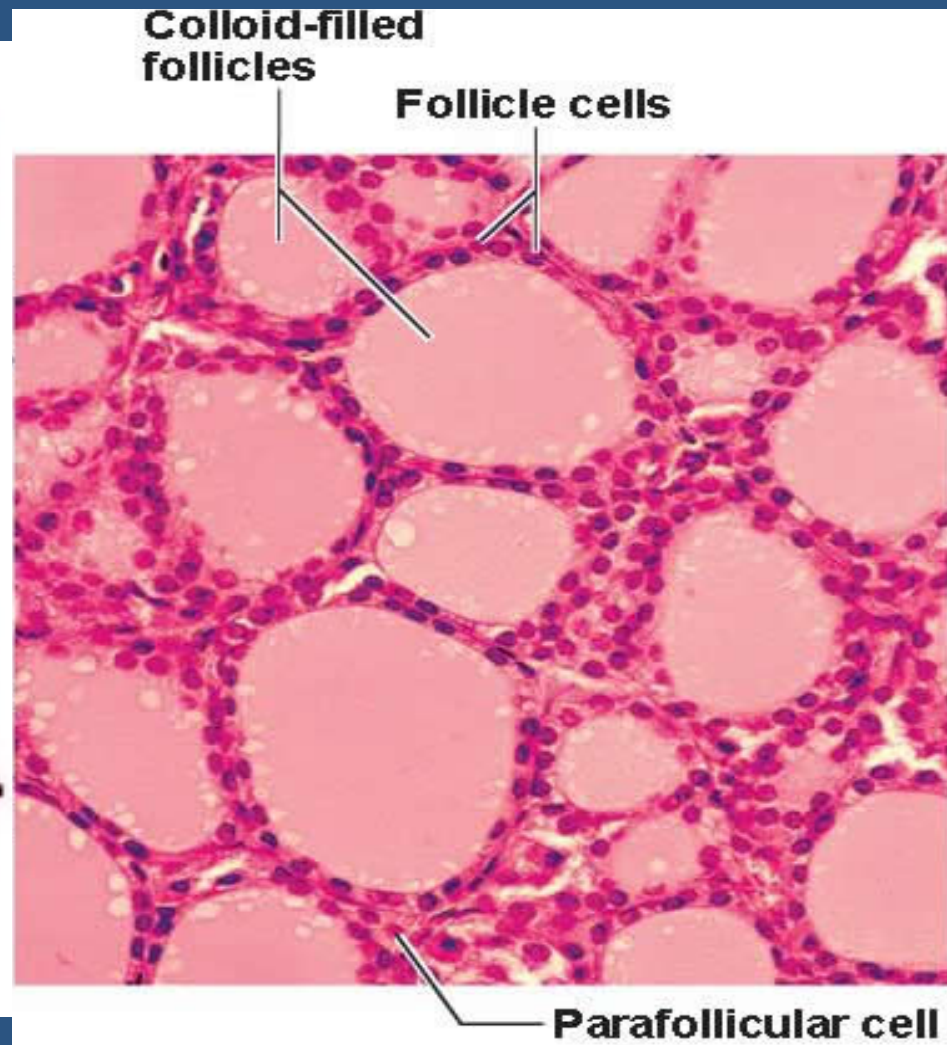
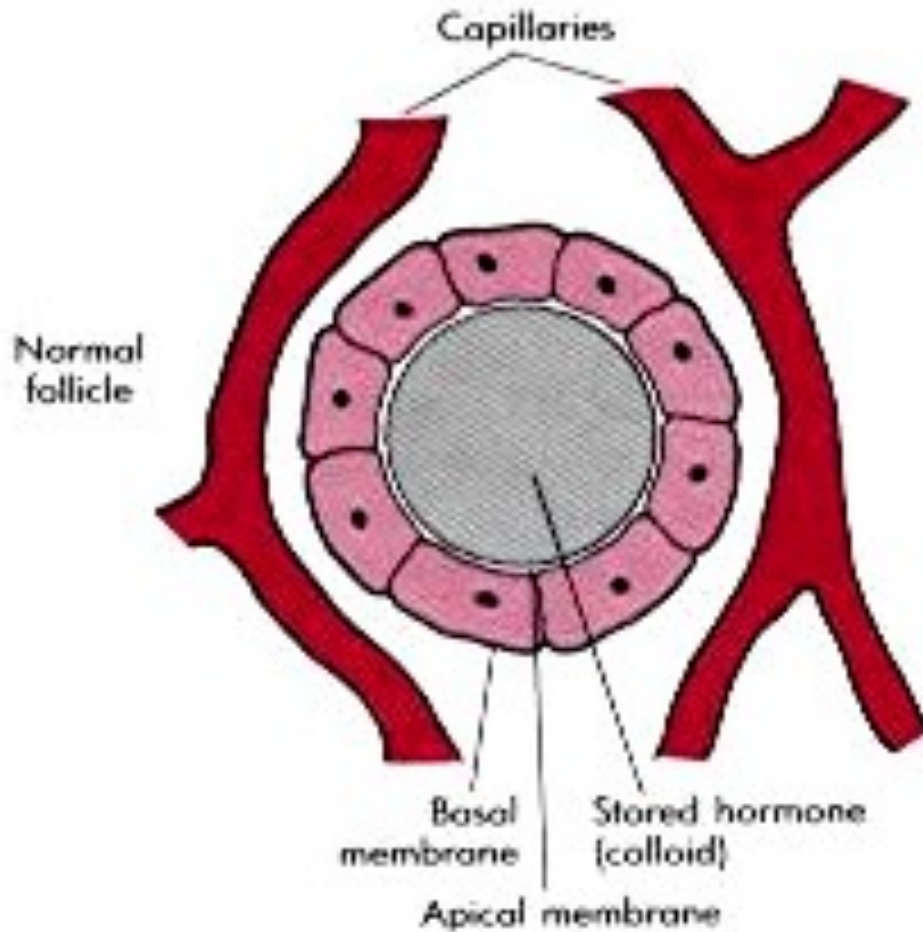
Thyroxine (T<sub>4</sub>)



Triiodothyronine (T<sub>3</sub>)

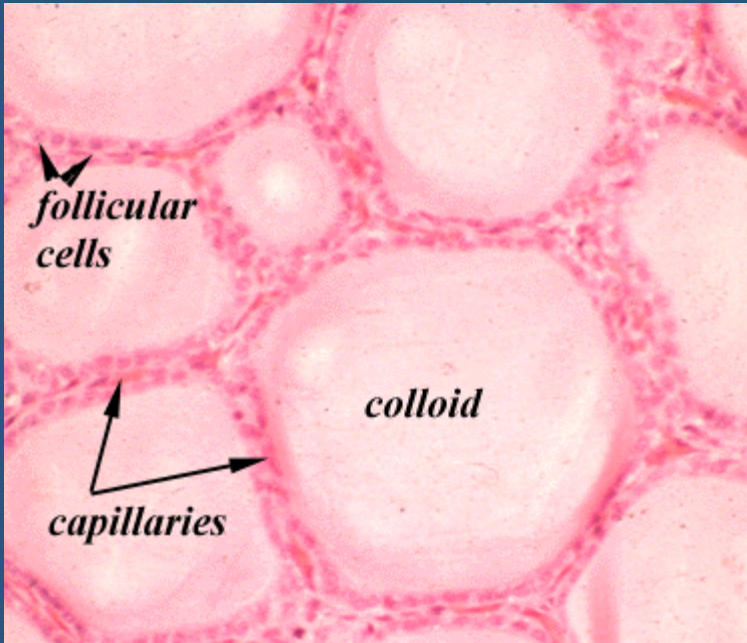


# SYNTHESIS



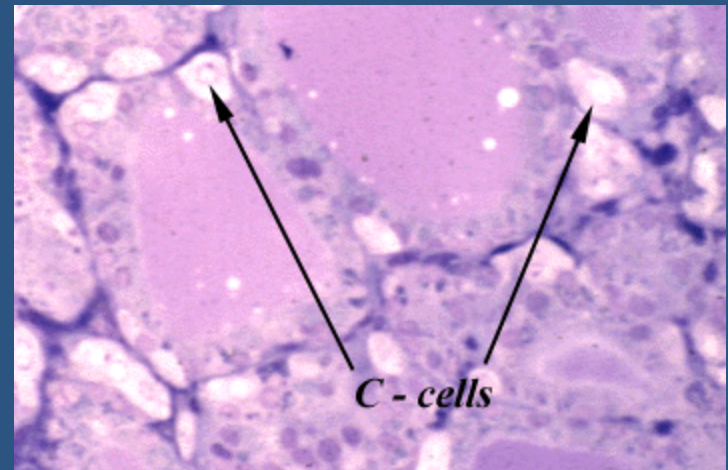
**(b) Photomicrograph of thyroid gland follicles (125x)**





**T3, T4**

**Calcitonin**

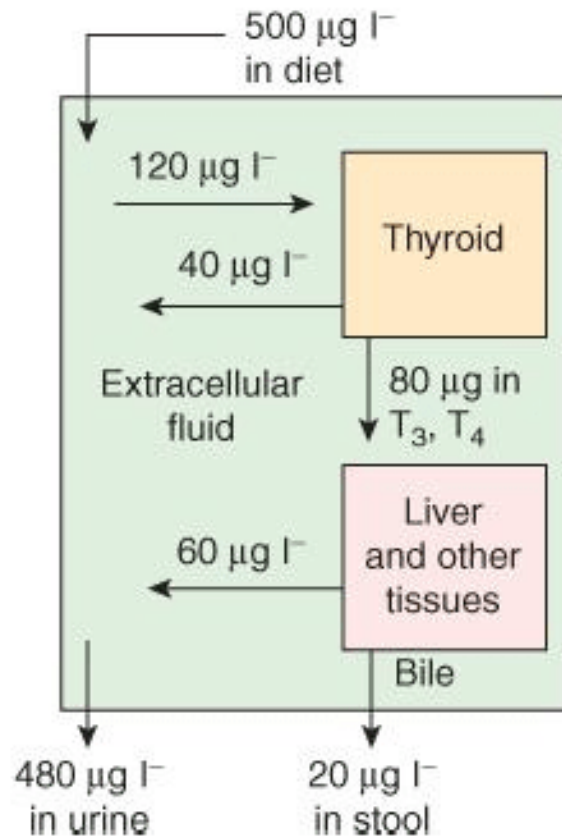


# THREE UNIQUE FEATURES

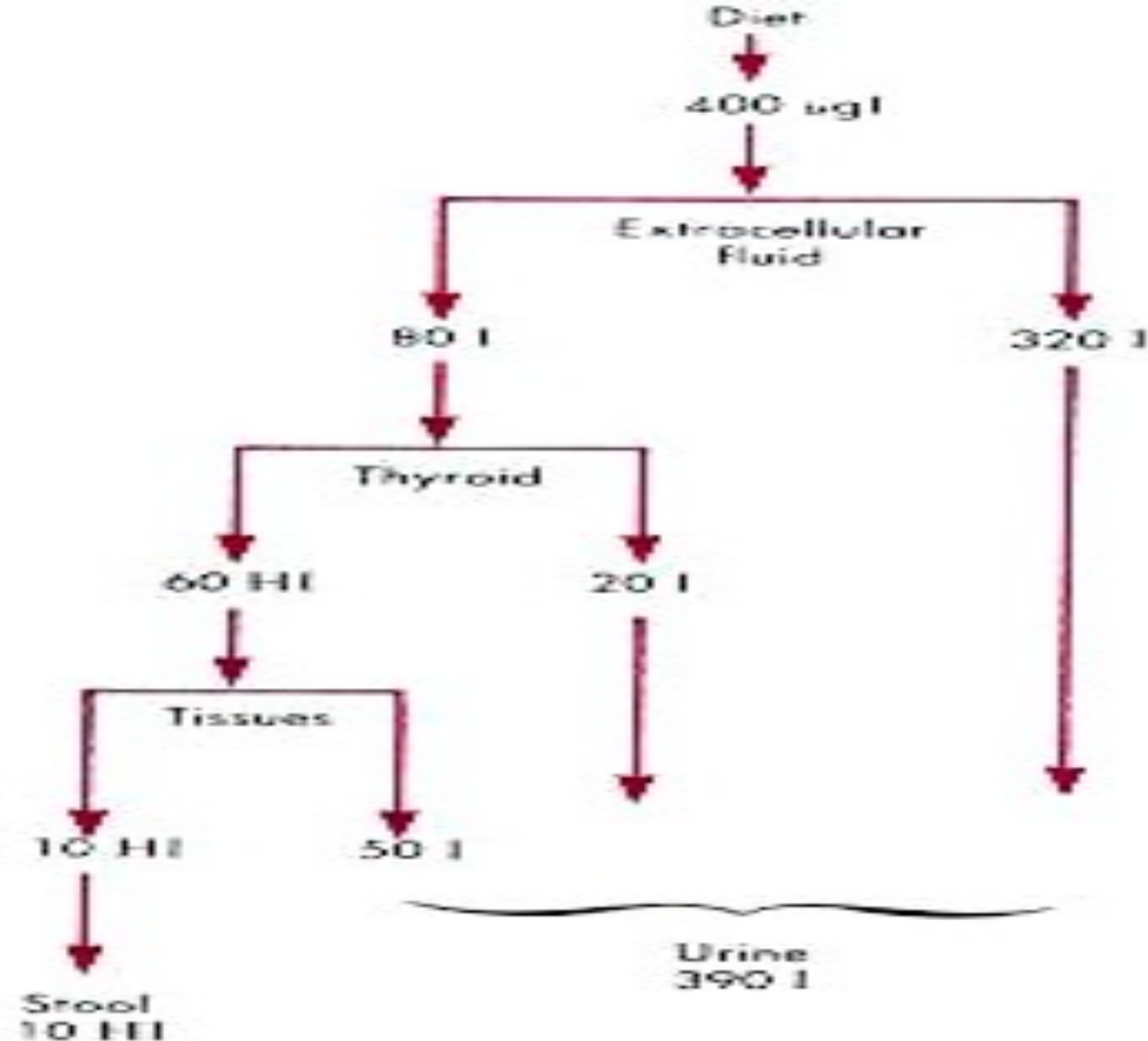
**1- Contains a large amount of iodine.**

- supplied in diet.

- 1mg/week.



**FIGURE 19-5 Iodine metabolism.** The figure shows the movement of iodide amongst various body compartments on a daily basis.



■ Fig. 49-2 Average daily iodide turnover in humans (United States). Note that 20% of the intake is taken up by the thyroid gland and 15% turns over in hormone synthesis and disposal. The unneeded excess is excreted in the urine. *I*, Iodide; *HI*, hormonal iodide.

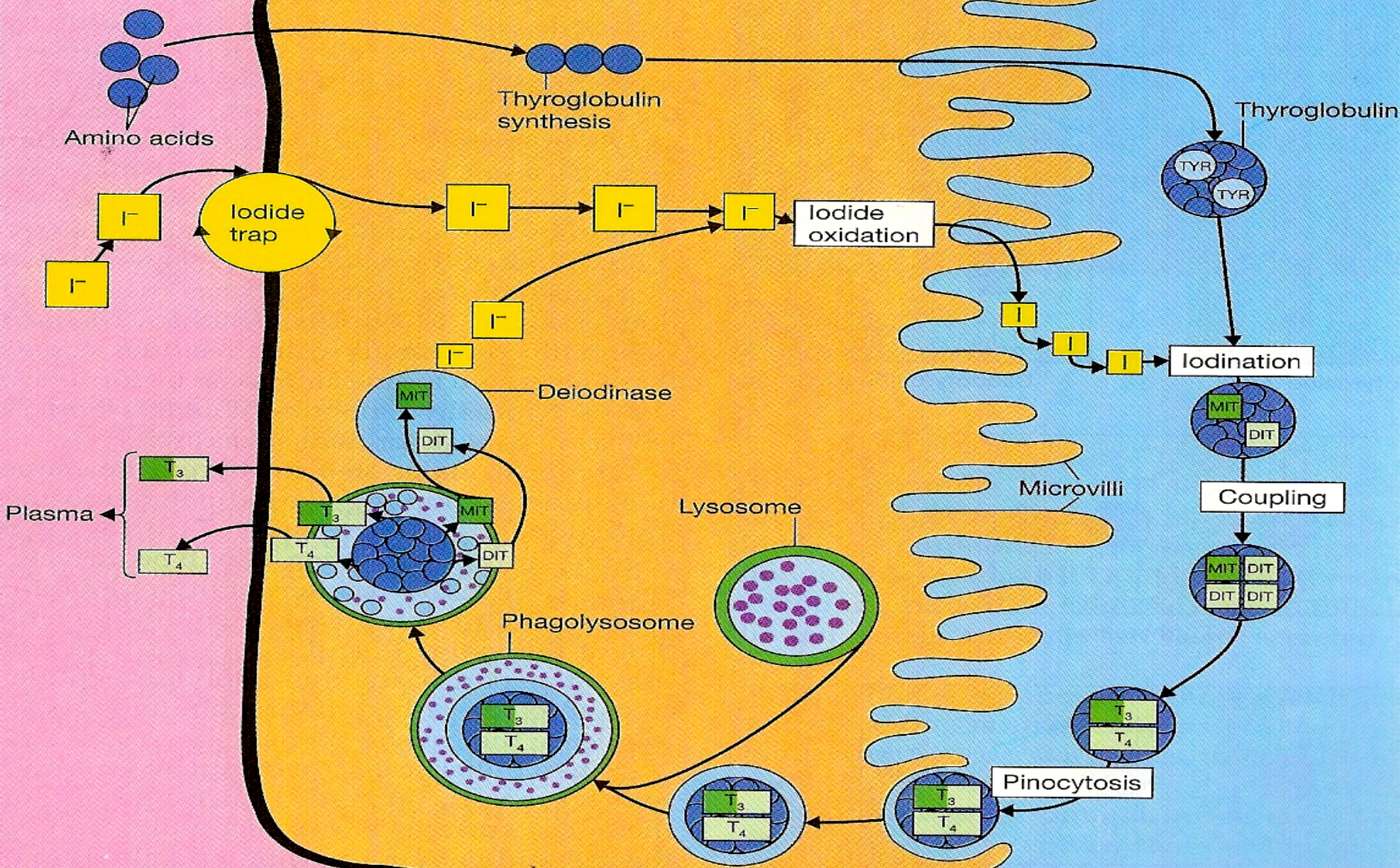
**2- Synthesis is partially intracellular and partially extracellular.**

**3- T4 is the major product.**

INTERSTITIAL FLUID

# STEPS of BIOSYNTHESIS

COLLOID



Basal surface

Apical surface

# Thyroid Hormones [T3 - T4]

## Biosynthesis:

*by the follicular cells*

1- **Iodide pump.**

2- **Thyroglobulin synthesis.**

3- **Oxidation** of iodide to iodine.

4- **Iodination** of tyrosine, to form **mono-iodotyrosine (MIT)**  
**& di-iodotyrosine (DIT).**

5- **Coupling;** MIT + DIT = **Tri-iodothyronine, ( T3).**

DIT + DIT = **Tetra-iodothyronine, (T4)/ Thyroxine.**

6- **Release.**

# STEPS IN BIOSYNTHESIS

## 1- THYROGLOBULIN FORMATION AND TRANSPORT:

- Glycoprotein.
- Tyrosine.
- Rough endoplasmic reticulum and Golgi apparatus.



## 2- IODIDE PUMP OR IODIDE TRAP:

- Active transport.
- It is stimulated by TSH.
- Wolff-chaikoff effect  
(A reduction in thyroid hormone levels caused by administration of a large amount of iodine).
- Ratio of concentration from 30-250 times.

## 3- OXIDATION OF IODIDE TO IODINE:

- Thyroid peroxidase.
- It is located in or attached to the apical membrane.

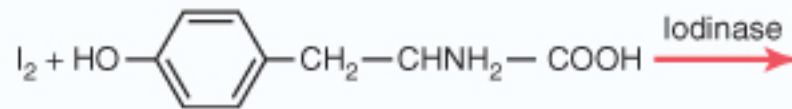
# 4- ORGANIFICATION OF THYROGLOBULIN

- Binding of iodine with thyroglobulin.
- Catalyzed by thyroid peroxidase, to form MIT/DIT
- Remain attached to thyroglobulin until the gland stimulated to secret.

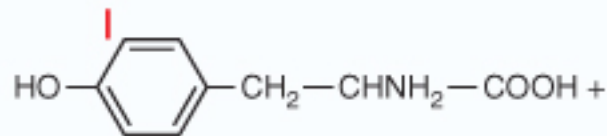
## 5- COUPLING REACTION:



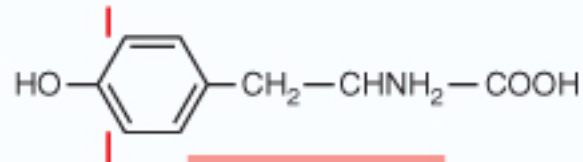
- Catalyzed by thyroid peroxidase.
- It is stored as colloid.
- Is sufficient for 2-3 months.



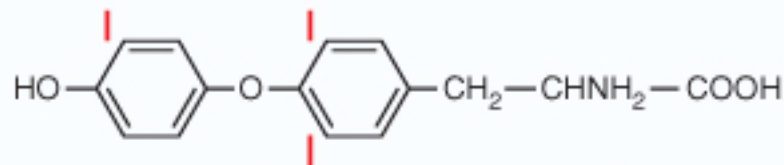
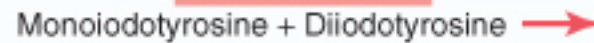
**Tyrosine**



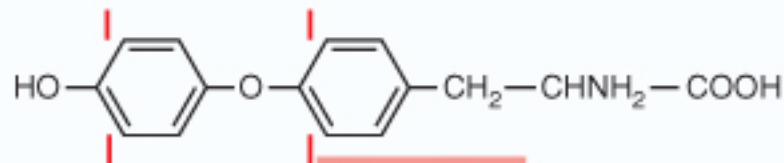
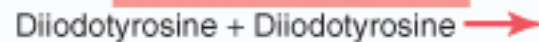
**Monoiodotyrosine**



**Diiodotyrosine**



**3,5,3'-Triiodothyronine**



**Thyroxine**

6- Endocytosis of thyroglobulin.

7- Fusion of lysosomes immediately with the vesicles.

8- Hydrolysis of the peptide bond to release *DIT+MIT+T4+T3* from the thyroglobulin.

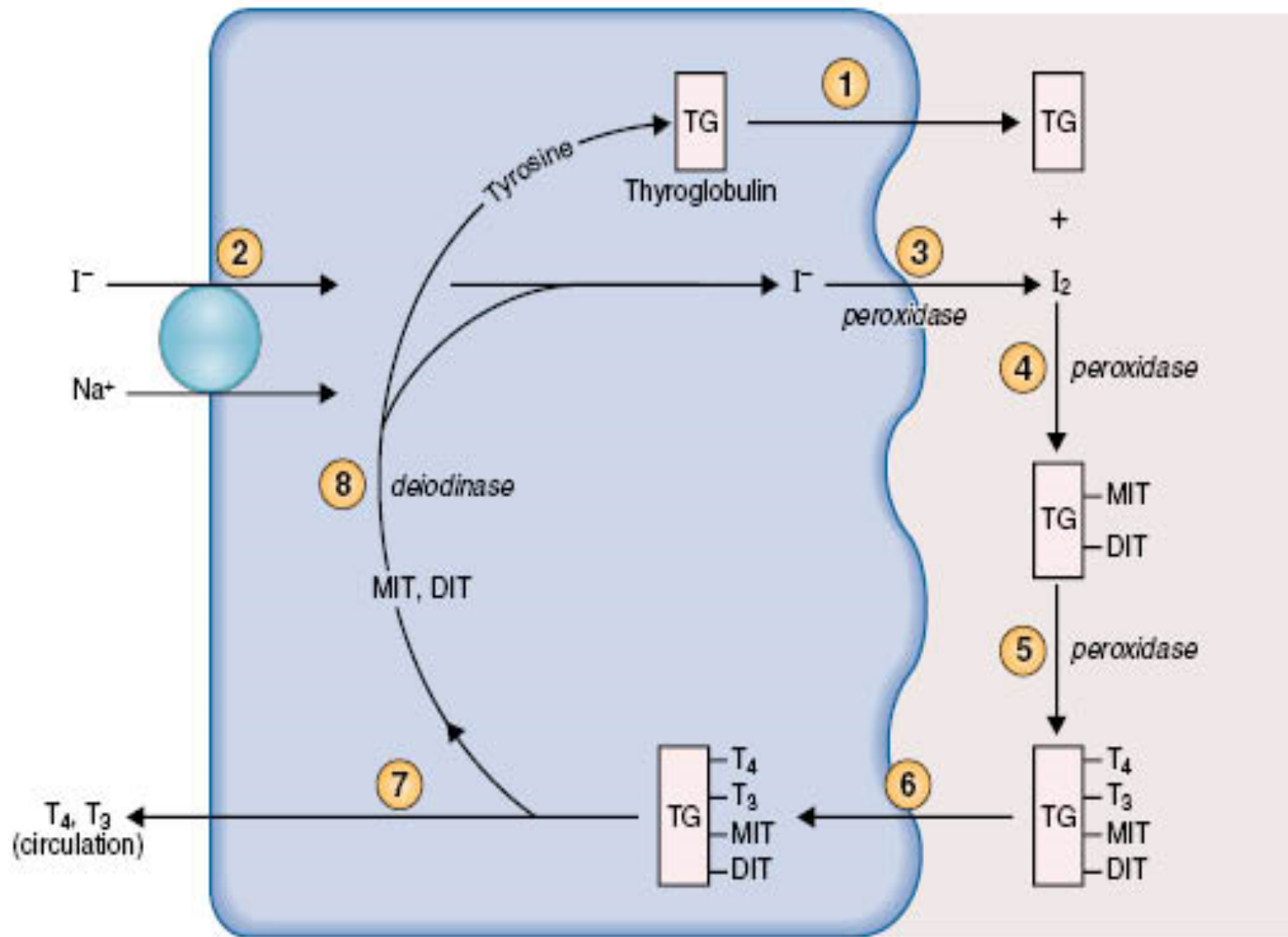
9- Delivery of T4 and T3 to the systemic circulation.

10- Deiodination of DIT and MIT by thyroid deiodinase (recycling).

Blood

Follicular epithelial cell

Follicular lumen





Event	Site	Enzyme	Inhibitor
1 Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 Na <sup>+</sup> - I <sup>-</sup> cotransport	Basal membrane		Perchlorate, thiocyanate
3 Oxidation of I <sup>-</sup> → I <sub>2</sub>	Apical (luminal) membrane	Peroxidase	PTU
4 Organification of I <sub>2</sub> into MIT and DIT	Apical membrane	Peroxidase	PTU
5 Coupling reaction of MIT and DIT into T <sub>3</sub> and T <sub>4</sub>	Apical membrane	Peroxidase	PTU
6 Endocytosis of TG	Apical membrane		
7 Hydrolysis of T <sub>4</sub> and T <sub>3</sub> ; T <sub>4</sub> and T <sub>3</sub> enter circulation	Lysosomes	Proteases	
8 Deiodination of residual MIT and DIT Recycling of I <sup>-</sup> and tyrosine	Intracellular	Deiodinase	

# THYROID HORMONES IN THE CIRCULATION

## **1- Bound:**

- 70- 80% bound to thyroxine-binding globulin (TBG) synthesized in the liver.
- The remainder is bound to albumin.

## **2- Unbound (Free):**

0.03% of  $T_4$

0.3% of  $T_3$ .

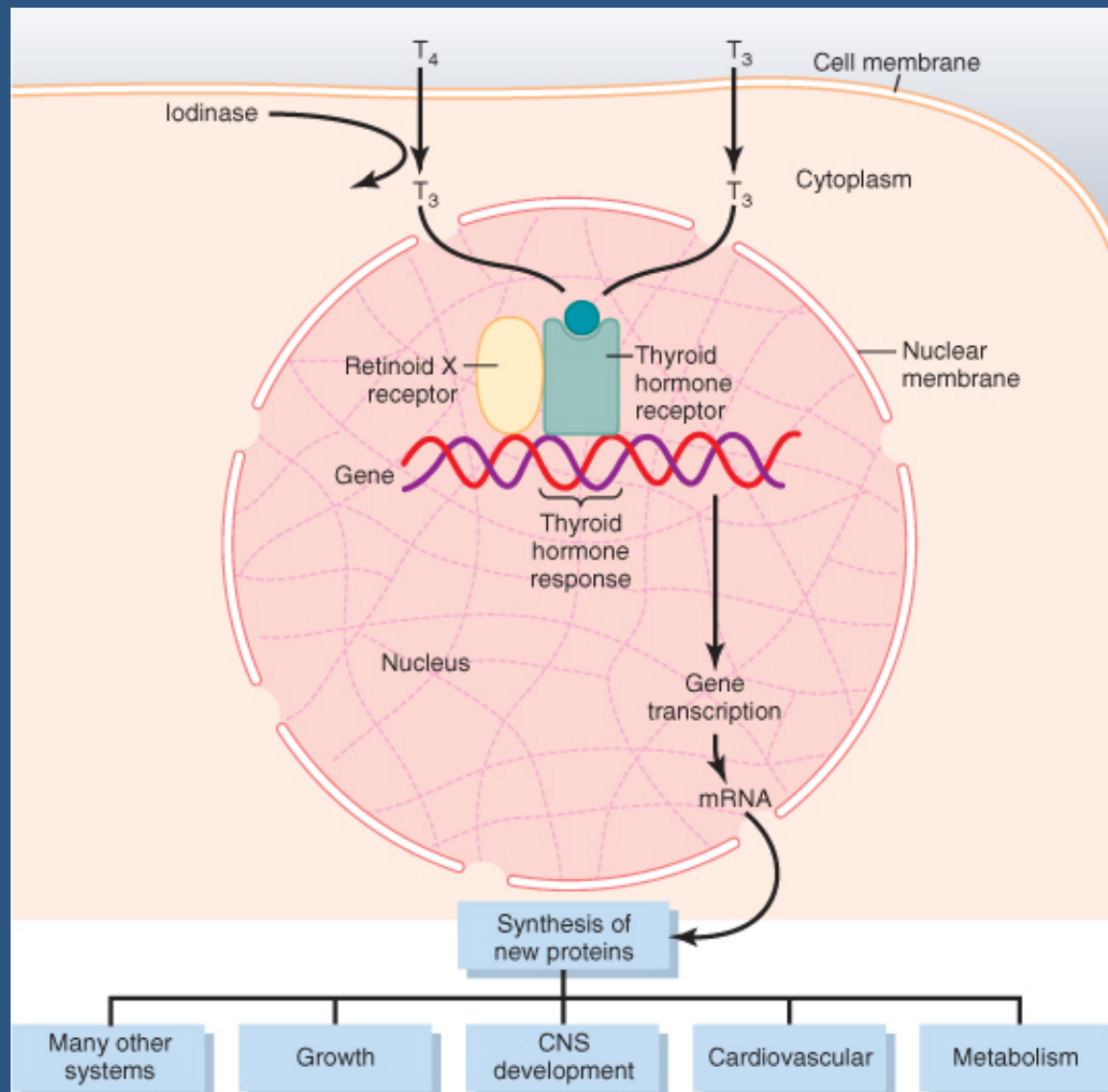
## In hepatic failure:

↓ TBG → ↑ free T3/T4 → *inhibition*  
of thyroid secretion.

## In pregnancy:

↑ estrogen → ↑ TBG → ↓ freeT3/T4  
→ *stimulation* of thyroid secretion.

# RELEASE OF T4 AND T3 TO THE TISSUES



# RELEASE OF T4 AND T3 TO THE TISSUES

1. The release is slow because of the high affinity of the plasma binding proteins.
  - $\frac{1}{2}$  of T4 in the blood is released every 6 days.
  - $\frac{1}{2}$  of T3 in the blood is released every one day.

- 2- T4 & T3 readily diffuse through the cell membrane.
- 3- Stored in the targeted tissues (days to weeks).
- 5- Most of T4 is deionized to T3 by iodinase enzyme.
- 6- In the nucleus, T3 mainly binds to "thyroid hormone receptor" and influence transcription of genes.

# ACTION OF THYROID HORMONES

- Before binding to the nuclear receptors 90% of T4 is converted to T3.

[T3 + nuclear receptor → activation of thyroid regulating element on DNA → ↑ DNA transcription  
formation of mRNA → translation of mRNA  
specific protein synthesis → (target tissue specific)]

## 1- Basal Metabolic Rate (BMR):

- Is the energy requirement under basal condition (mental and physical rest 12-18 hours after a meal).
- Complete lack of thyroid hormones  $\longrightarrow$  40-50% $\downarrow$  in BMR.
- Extreme increase of thyroid hormones  $\longrightarrow$  60-100% $\uparrow$  in BMR.



## 2- Metabolism

### **A) Effect on carbohydrate metabolism:**

- 1- increase glucose uptake by the cells.
- 2- increase glycogenolysis.
- 3- increase gluconeogenesis.
- 4- increase absorption from the GIT.

## **B) Effects on fat metabolism:**

- 1- increase lipolysis.
- 2- decrease plasma cholesterol by increase loss in feces.
- 3- increase oxidation of free fatty acids.

## **C) Effect on protein metabolism:**

overall effect is *catabolic* leading to decrease in muscle mass.

■ **The metabolic effects are due to the induction of metabolic enzymes:**

1- cytochrome oxidase.

2- NADPH cytochrome C reductase.

3- alpha- glycerophosphate dehydrogenase.

4- malic enzymes.

5- several proteolytic enzymes

# 3- Effects on the Cardiovascular system:

- increase heart rate. →
  - increase stroke volume. ↗
  - decrease peripheral resistance.
- Cardiac output  
up to 60%**

\*end result is increase delivery of oxygenated blood to the tissues.

The cardiovascular effects are due to:

1- Thyroid hormones potentiate the effect of *catecholamine* in the circulation → activation of  $\beta$ -adrenergic receptors.

2- Direct induction of:

- a) myocardial  $\beta$ -adrenergic receptors.
- b) sarcoplasmic reticulum.
- c)  $\text{Ca}^{+2}$  ATPase.
- d) myosine.

## 6- Effects on the CNS:

### A) Peri-natal period:

Thyroid hormones are essential for maturation of the CNS.

decrease of hormones secretion



**irreversible** mental retardation

- Screening is necessary to introduce hormone replacement .

## 6- Effects on the CNS:

*cont.*

### **B) In adult:**

Increase in thyroid hormone secretion:

- 1- hyperexcitability.
- 2- irritability.

Decrease in thyroid hormones secretion:

- 1- slow movement.
- 2- impaired memory.
- 3- ↓ mental capacity.

## 7- Effects on bone:

- a) promote bone formation.
- b) promote ossification.
- c) promote fusion of bone plate.
- d) promote bone maturation.



# 8- Effects on Respiration:

- 1- increase ventilation rate.
- 2- increase dissociation of oxygen from Hb by increasing RBC 2,3-DPG (2,3 diphosphoglycerate).

# 9- Effects on the GIT:

1- increase appetite and food intake.

2- increase of digestive juices secretion.

3- increase of G.I tract motility.

excess secretion → diarrhea.

lack of secretion → constipation.

# 10- Effects on Autonomic nervous system:

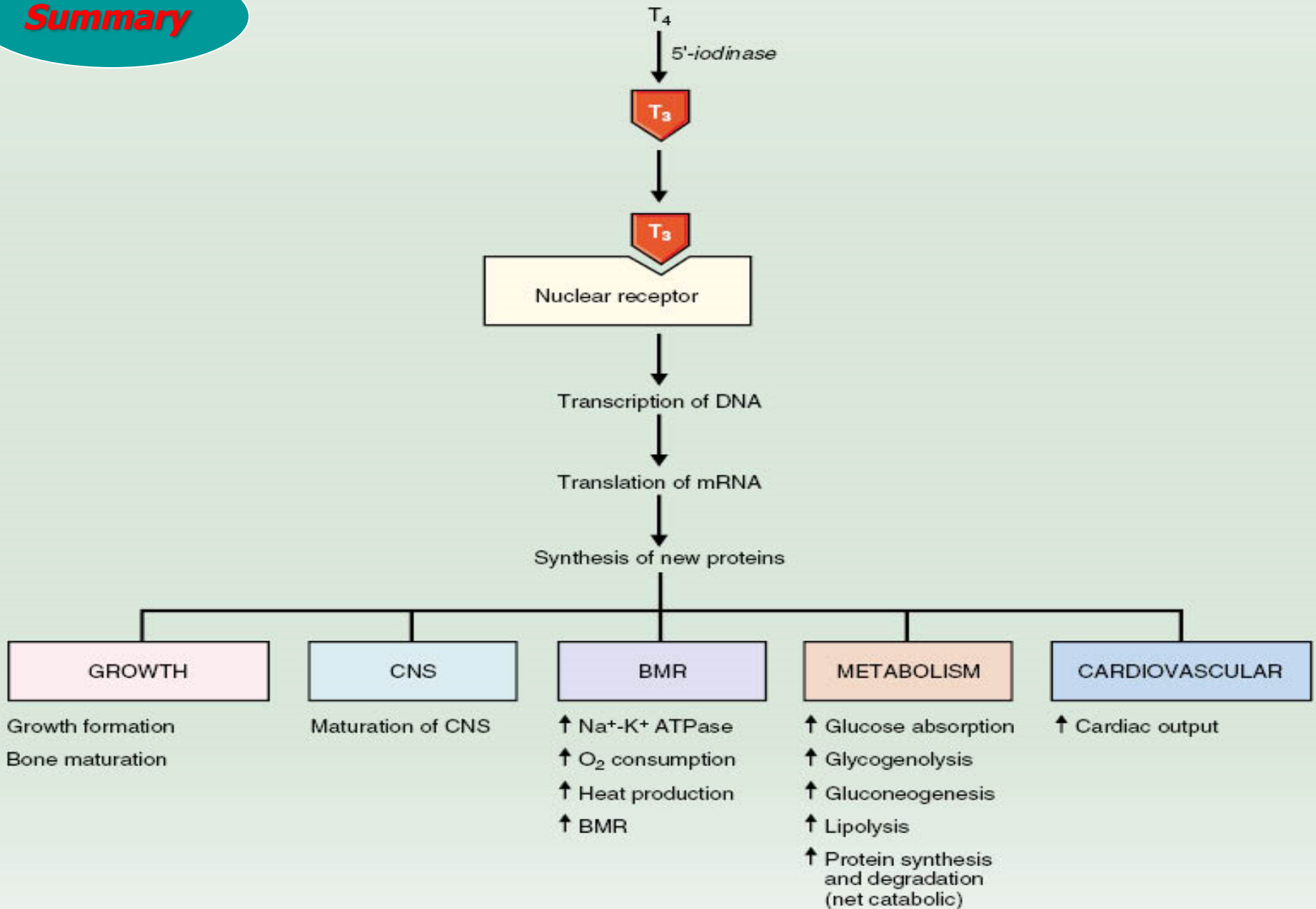
Produced the same action as *catecholamines* via  $\beta$ -adrenergic receptors including:

- a) increase BMR.
- b) increase heat production.
- c) increase heart rate.
- d) increase stroke volume.

i.e.  $\beta$ -blocker (propranolol) is used in treatment of hyperthyroidism.

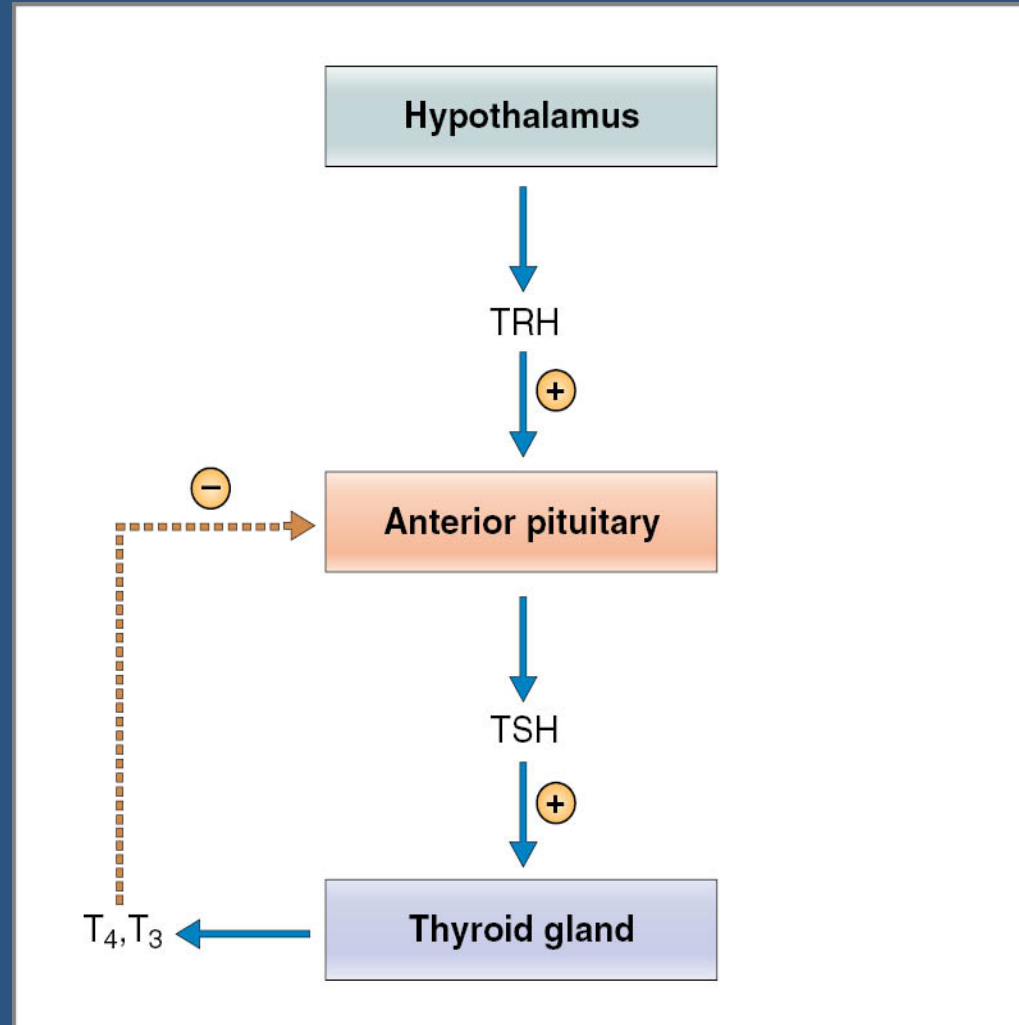
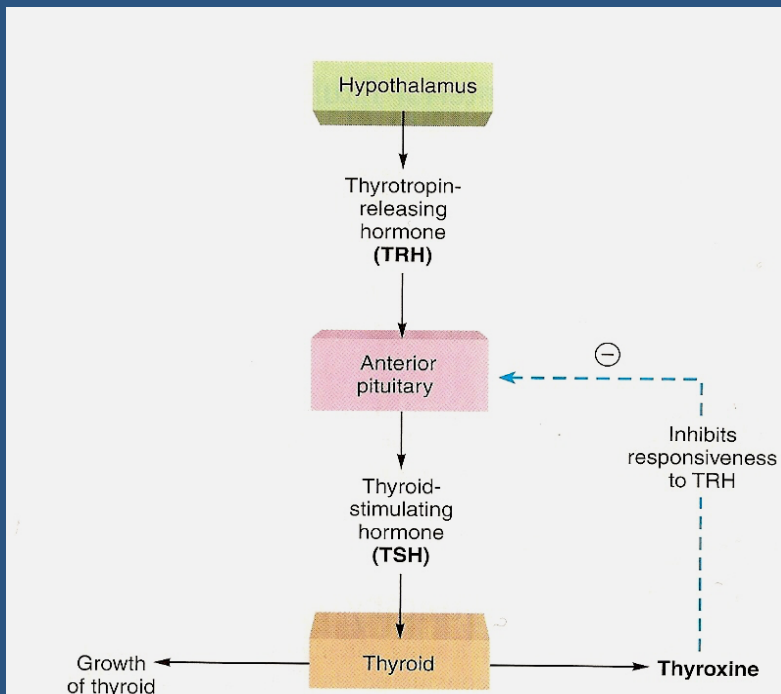
# ACTIONS OF THYROID HORMONES

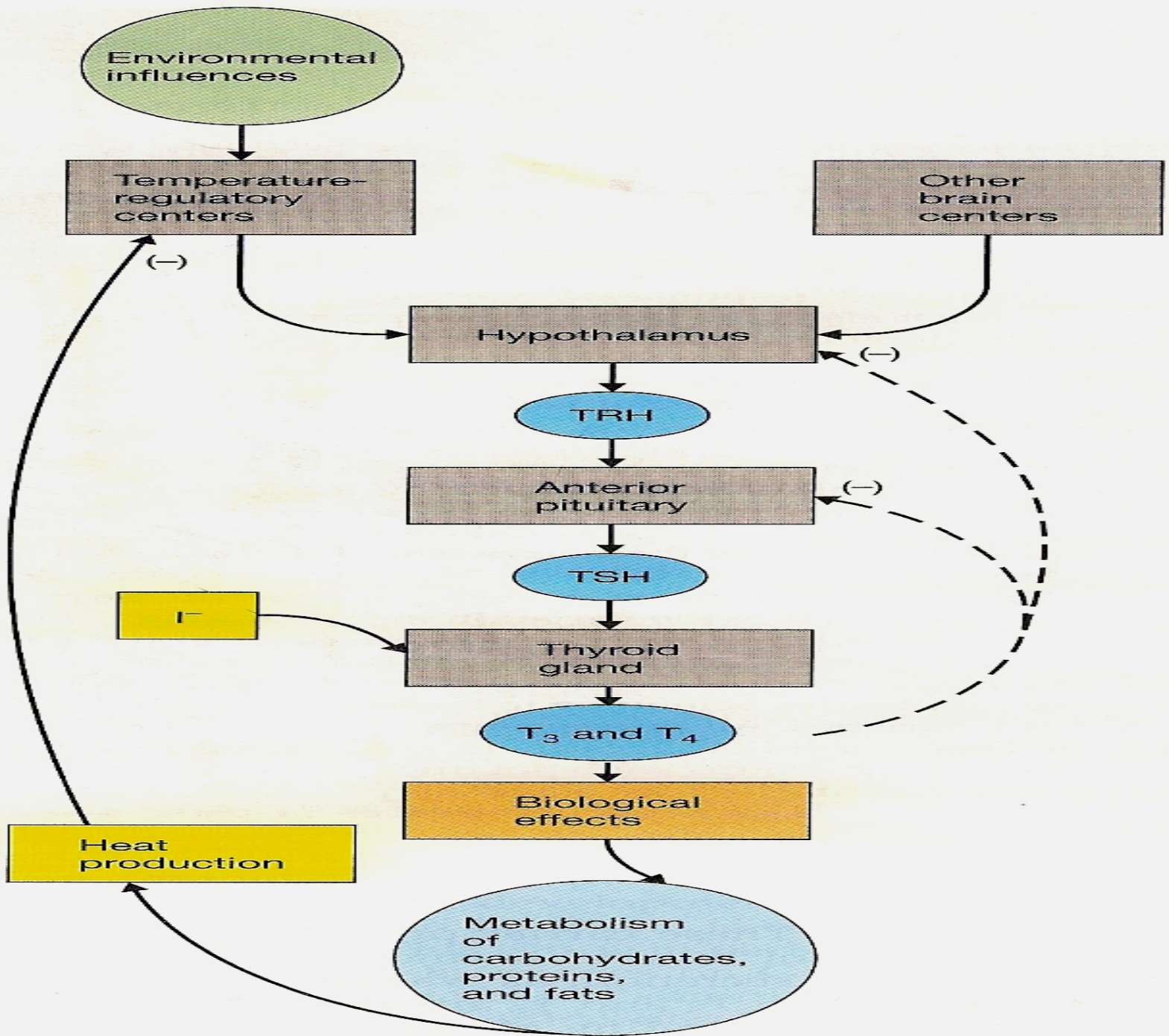
## Summary



# REGULATION OF HORMONES SECRETION

- It is regulated by the hypothalamic-pituitary axis.





# 1- Thyrotropin-releasing hormone (TRH):

- Tripeptide.
- Paraventricular nuclei of the hypothalamus.
- Act on the thyrotrophs of the anterior pituitary
- Transcription and secretion of TSH.
- Phospholipid second messenger system.

## 2- Thyroid-stimulating hormone (TSH):

- Glycoprotein.
- Anterior pituitary.
- Regulate metabolism , secretion and growth of thyroid gland (trophic effect).



# Action of TSH

- 1- Increase proteolysis of the thyroglobulin.
- 2- Increase pump activity.
- 3- Increase iodination of tyrosine.
- 4- Increase coupling reaction.
- 5- Trophic effect.

- TSH secretion started at 11-12 of gestational weeks.

- TSH + receptor → activation of adenylyl cyclase via Gs protein → ↑cAMP → ↑activation of protein kinase → multiple phosphorylation → secretion and thyroid growth.

## **Table 9-8** Factors Affecting Thyroid Hormone Secretion

### **Stimulatory Factors**

TSH

Thyroid-stimulating immunoglobulins

Increased TBG levels (e.g., pregnancy)

### **Inhibitory Factors**

I<sup>-</sup> deficiency

Deiodinase deficiency

Excessive I<sup>-</sup> intake (Wolff-Chaikoff effect)

Perchlorate; thiocyanate (inhibit Na<sup>+</sup>-I<sup>-</sup> cotransport)

Propylthiouracil (inhibits peroxidase enzyme)

Decreased TBG levels (e.g., liver disease)

# DISEASES OF THE THYROID GLAND

DR ABDULMAJEED AL-DREES

# **HYPERTHYROIDISM**

- Over activity of the thyroid gland.
- Women : men ratio (8:1).
- activity of gland :
  - a)- 5- 10 times increase in secretion.
  - b)- 2-3 times increase in size.

# CAUSES

## 1- Graves' disease :

- an autoimmune disorder.
- increased circulating level of thyroid-stimulating immunoglobulins ( TSI).
- 95%.
- 4 – 8 times more common in women than men.

## **2- Thyroid gland tumor:**

- 95% is benign.
- 5% is malignant.
- history of head and neck irradiation and family history.

## **3- Exogenous T3 and T4:**

( rarely cause)

## **4- Excess TSH secretion:**

- diseases of the hypothalamus ( TRH).
- diseases of the pituitary ( TSH).



# DIAGNOSIS

## ■ Symptoms:

1- Goiter in 95%.

2- skin:

- smooth, warm and moist.
- heat intolerance, night sweating.

### **3- musculo skeletal:**

- Muscle atrophy.

### **4- Neurological:**

- tremor.
- enhanced reflexes.
- irritability.

## **5- Cardiovascular:**

- increase heart rate.
- increase stroke volume.
- arrhythmias.
- hypertension.

## **6- G.I tract:**

- weight loss.
- diarrhea.

## **7- Renal function:**

- ↑ glomerular filtration rate.

## **8- Exophthalmos:**

- anxious staring expression.
- protrusion of eye balls.

## **9- Others:**

- menstrual cycle disturbance.



# INVESTIGATIONS

## 1- Serum T3, T4 measurement.

In primary hyperthyroidism:

high T3, T4 and low TSH .

In secondary hyperthyroidism:

high T3, T4 and high TSH.

# TREATMENT

## 1- Medical therapy:

e.g. propylthiouracil

- usually for 12-18 months course.
- with 3-4 monthly monitoring.

## **2- Surgery:**

- Subtotal thyroidectomy.

- **Indication for surgery:**

- a)- Relapse after medical treatment.

- b)- Drug intolerance.

- c)- Cosmetic.

- d)- Suspected malignancy.



# **HYPOTHYROIDISM**

Under activity of the thyroid gland

more in woman ( 30- 60 years).

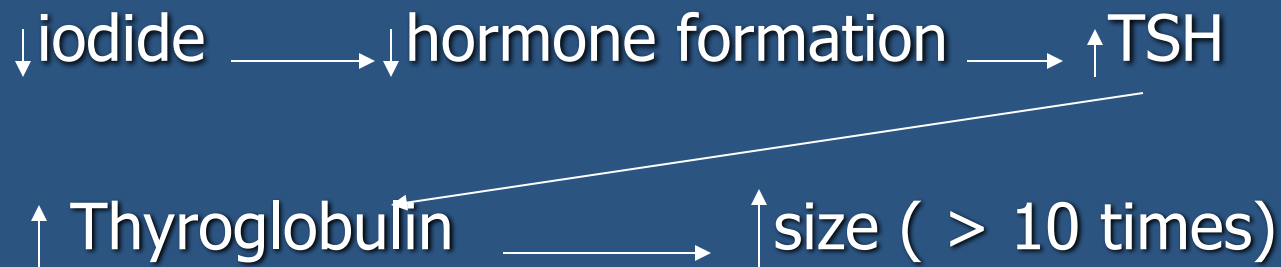
# CAUSES

## **1- inherited abnormalities of thyroid hormone synthesis :**

- peroxidase defect.
- Iodide trapping defect.
- thyroglobulin defect.

## 2- Endemic Colloid Goiter:

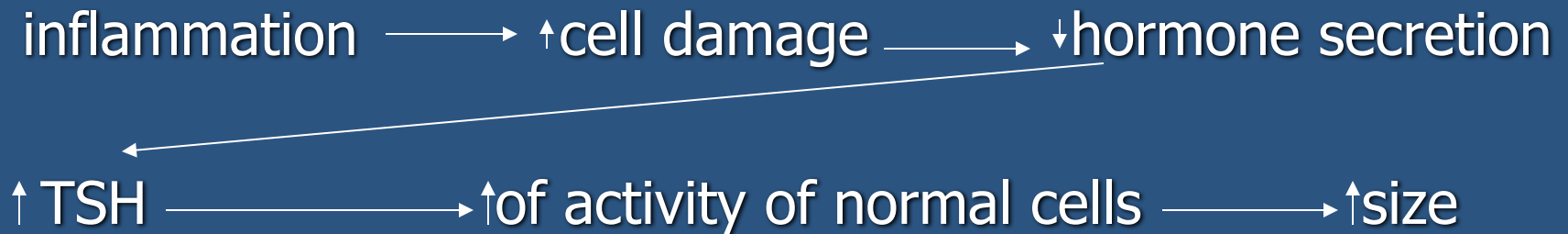
- before table salt.





### 3- Idiopathic Nontoxic Colloid Goiter:

- I intake is normal.
- thyroiditis?



4- Gland destruction (surgery).

5- Pituitary diseases or tumor.

6- Hypothalamus diseases or tumor.

# DIAGNOSIS

## 1- skin :

- dry skin.
- cold intolerance.

## 2- Musculo skeletal:

- ↑ muscle bulk.
- ↓ in skeletal growth.
- muscle sluggishness
- slow relaxation after contraction.

### **3- Neurological:**

- slow movement.
- impaired memory.
- decrease mental capacity.

### **4- Cardiovascular:**

- | blood volume.
- | heart rate
- ↓ stroke volume.



## **5- G.I tract:**

- constipation
- increase weight.

## **6- Renal function:**

- decrease glomerular filtration rate.

## 7- Myxoedema:

An edematous appearance through out body.

## 8- others:

- loss of libido.
- menstrual cycle disturbance.



# INVESTIGATIONS

**1- Serum T3,T4 are low.**

- TSH is elevated in primary.
- TSH is low in secondary hypothyroidism.

# TREATMENT

- **L- thyroxine**

- Starting dose is 25-50  $\mu\text{g}$ .
- Increase to 200  $\mu\text{g}$ .
- At 2-4 weeks period.

The first response seen is the weight loss.



**Table 9-9** Pathophysiology of Thyroid Hormones

	<b>Hyperthyroidism</b>	<b>Hypothyroidism</b>
<b>Symptoms</b>	<p>Increased basal metabolic rate</p> <p>Weight loss</p> <p>Negative nitrogen balance</p> <p>Increased heat production</p> <p>Sweating</p> <p>Increased cardiac output</p> <p>Dyspnea (shortness of breath)</p> <p>Tremor, muscle weakness</p> <p>Exophthalmos</p> <p>Goiter</p>	<p>Decreased basal metabolic rate</p> <p>Weight gain</p> <p>Positive nitrogen balance</p> <p>Decreased heat production</p> <p>Cold sensitivity</p> <p>Decreased cardiac output</p> <p>Hypoventilation</p> <p>Lethargy, mental slowness</p> <p>Drooping eyelids</p> <p>Myxedema</p> <p>Growth retardation</p> <p>Mental retardation (perinatal)</p> <p>Goiter</p>
<b>Causes</b>	<p>Graves' disease (increased thyroid-stimulating immunoglobulins)</p> <p>Thyroid neoplasm</p> <p>Excess TSH secretion</p> <p>Exogenous T<sub>3</sub> or T<sub>4</sub> (factitious)</p>	<p>Thyroiditis (autoimmune or Hashimoto's thyroiditis)</p> <p>Surgery for hyperthyroidism</p> <p>I<sup>-</sup> deficiency</p> <p>Congenital (cretinism)</p> <p>Decreased TRH or TSH</p>
<b>TSH Levels</b>	<p>Decreased (feedback inhibition of T<sub>3</sub> on the anterior lobe)</p> <p>Increased (if defect is in anterior pituitary)</p>	<p>Increased (by negative feedback if primary defect is in thyroid gland)</p> <p>Decreased (if defect is in hypothalamus or anterior pituitary)</p>
<b>Treatment</b>	<p>Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis)</p> <p>Thyroidectomy</p> <p><sup>131</sup>I<sup>-</sup> (destroys thyroid)</p> <p>β-Adrenergic blocking agents (adjunct therapy)</p>	<p>Thyroid hormone replacement therapy</p>

# CRETINISM

Extreme hypothyroidism during infancy and childhood (failure of growth).

# CAUSES

- 1- Congenital lack of thyroid gland (congenital cretinism).
- 2- Genetic deficiency leading to failure to produce hormone.
- 3- Iodine lack in the diet (endemic cretinism).



# SYMPTOMS

- 1- Infant is normal at birth but abnormality appears within weeks.
- 2- Protruding tongue.
- 3- Dwarf with short limbs.
- 4- Mental retardation.
- 5- Often umbilical hernia.
- 6- teeth.



***Cretinism*** (dwarf + mental retardation)



# TREATMENT

Changes are irreversible unless treatment is given early.





# Calculate your BMR:

**Men:**  $BMR = 66 + (13.7 \times \text{wt in kg}) + (5 \times \text{ht in cm}) - (6.8 \times \text{age in years})$

**Women:**  $BMR = 655 + (9.6 \times \text{wt in kg}) + (1.8 \times \text{ht in cm}) - (4.7 \times \text{age in years})$

## **Example:**

You are female

You are 30 years old

You are 5' 6 " tall (167.6 cm)

You weigh 120 lbs. (54.5 kilos)

Your BMR =  $655 + 523 + 302 - 141 =$  **1339 calories/day**