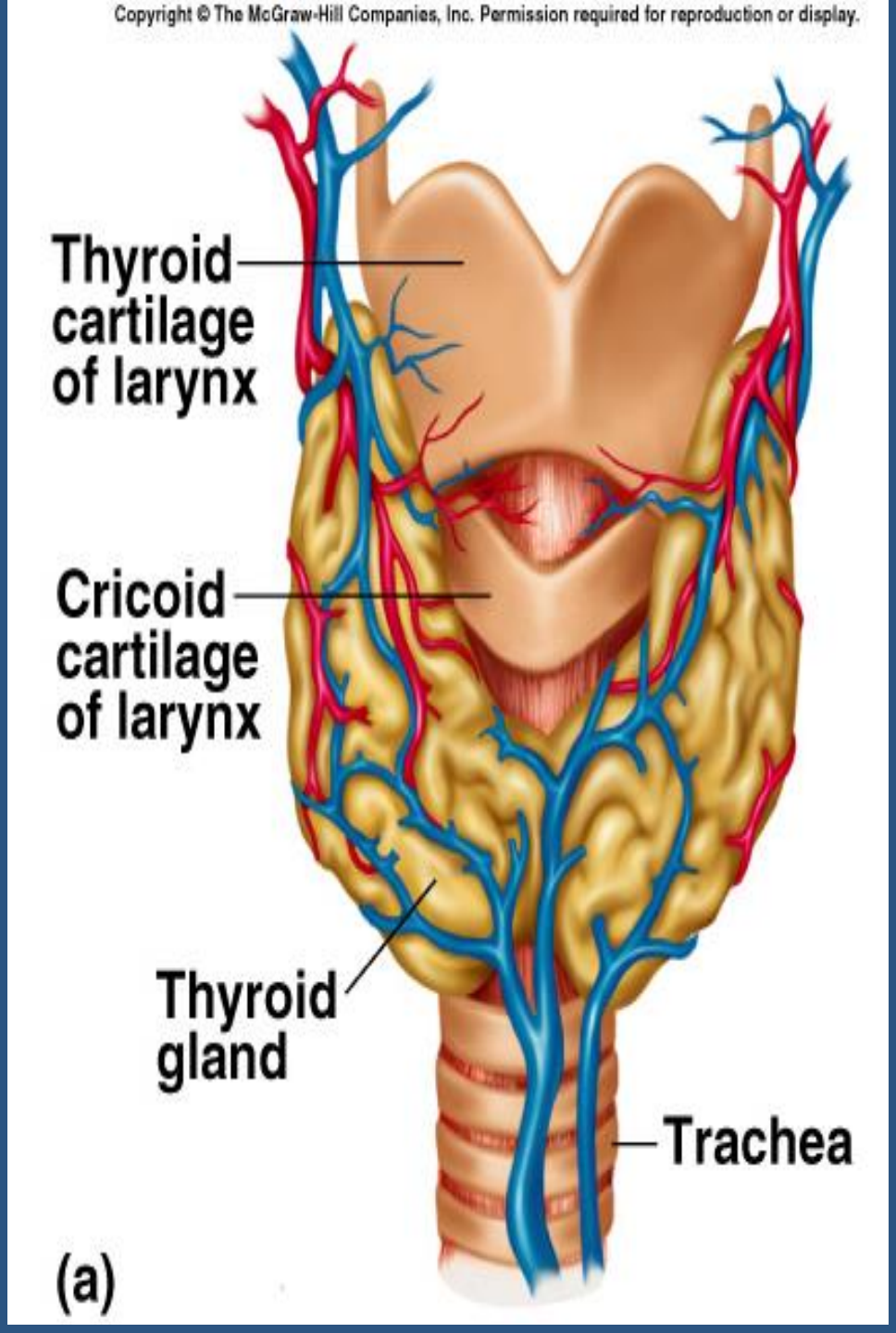
THE THYROID GLAND

DR. ABDULMAJEED AL-DREES

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



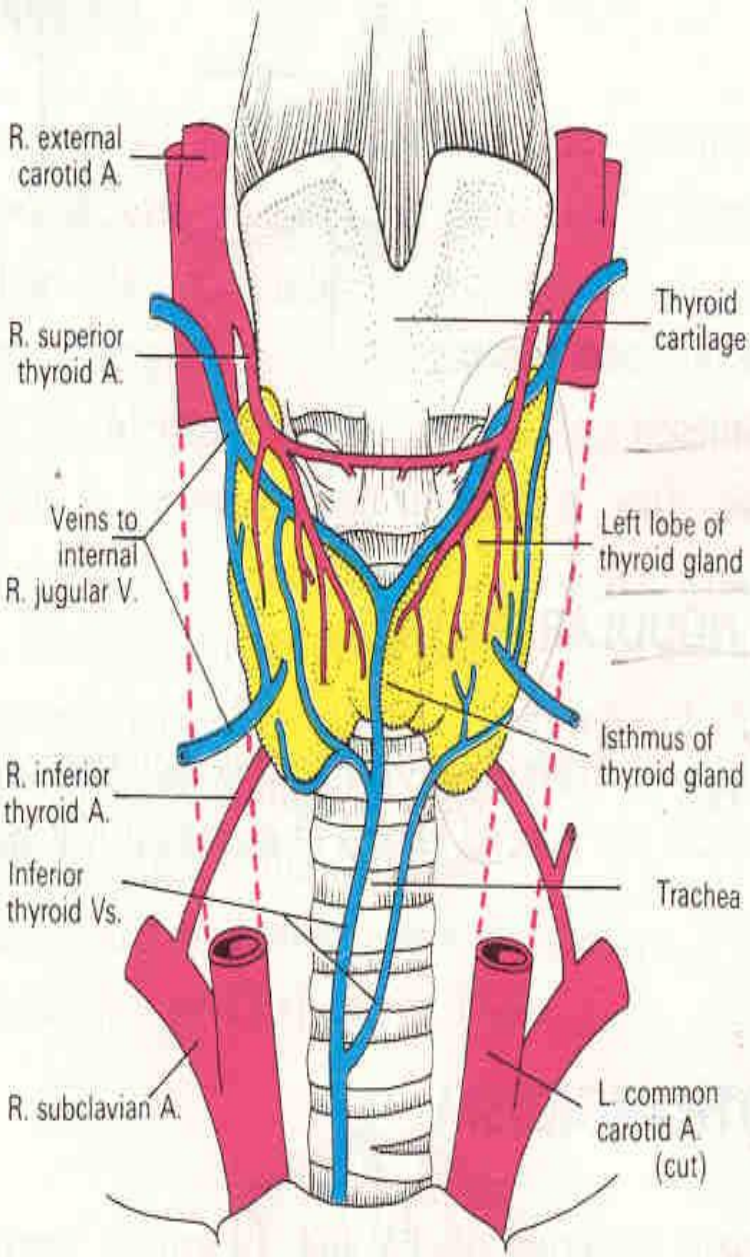
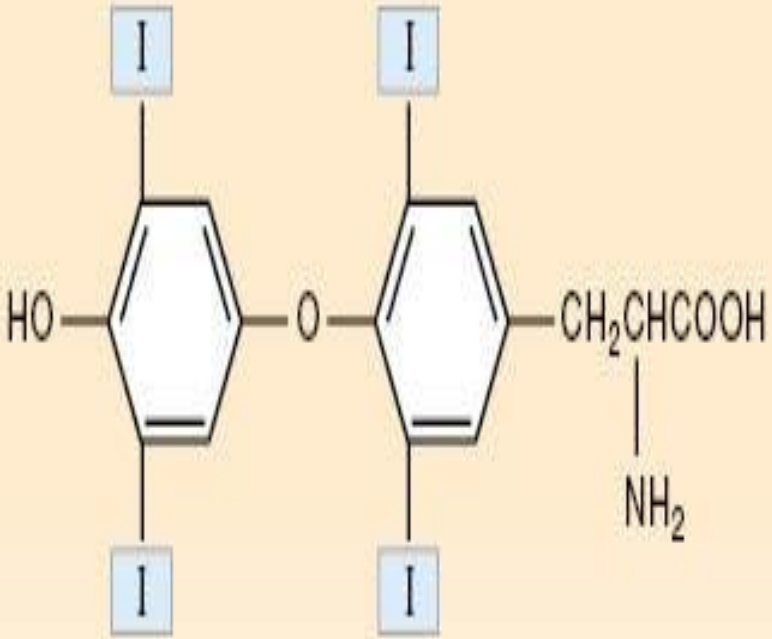


Figure 14:8 Position of thyroid gland and associated structures.

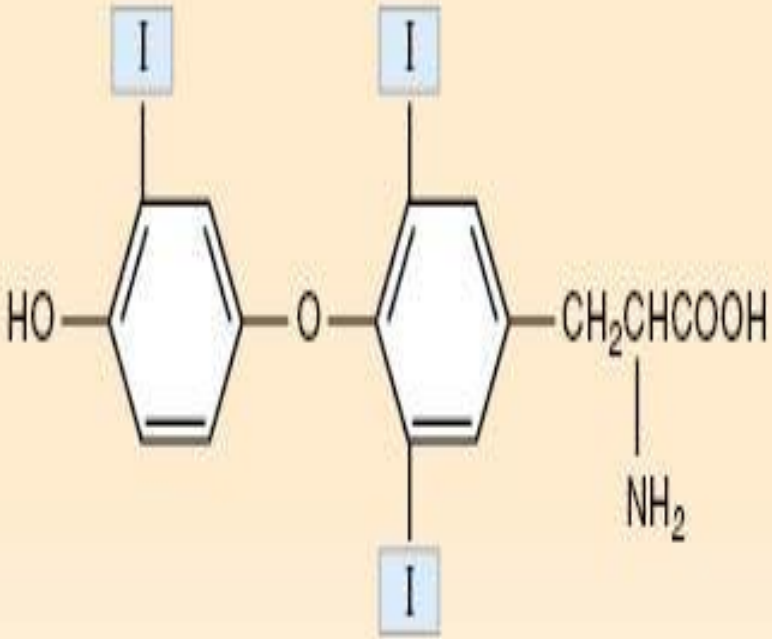
HORMONES

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

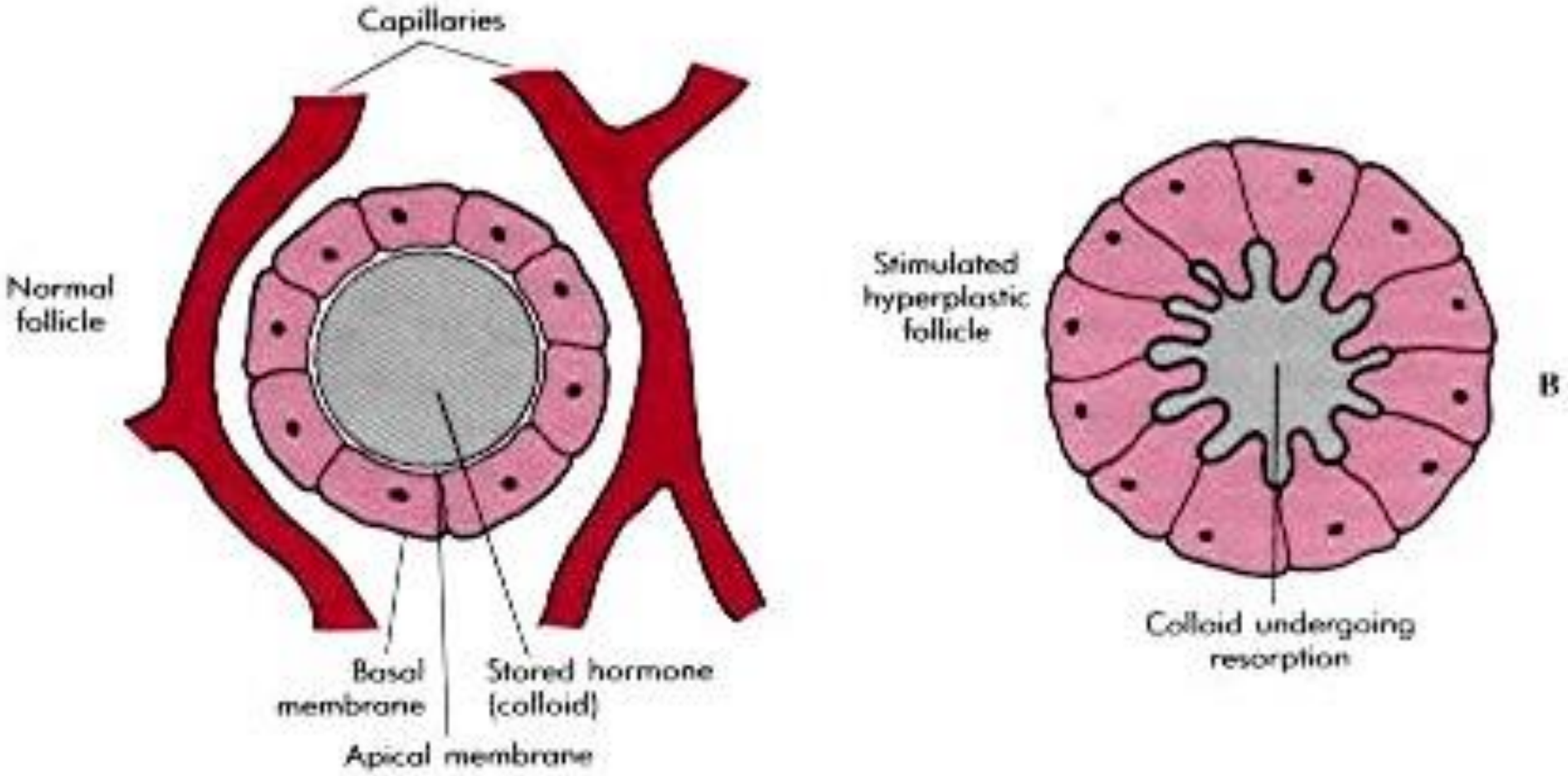
Thyroxine (T_4)



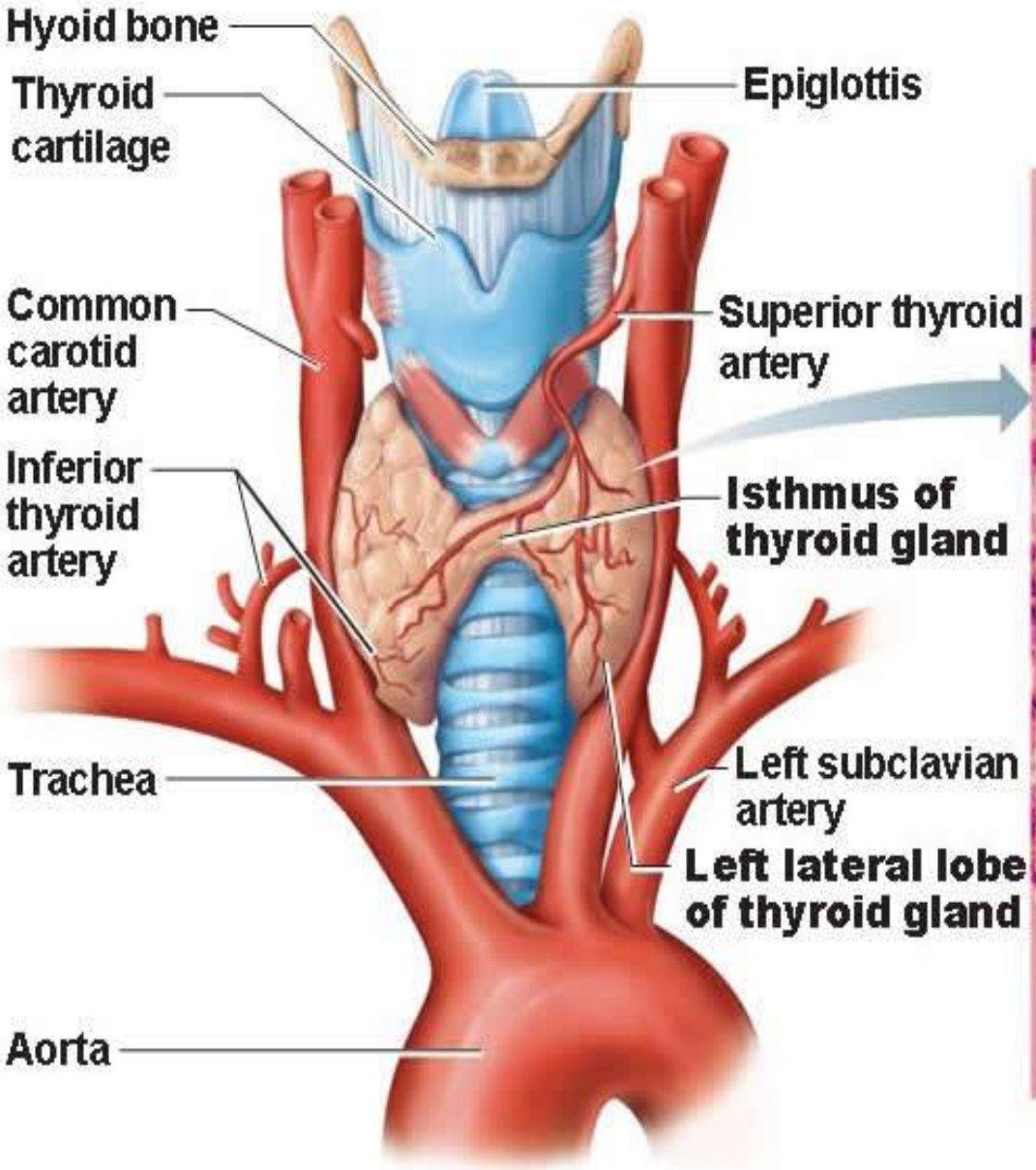
Triiodothyronine (T_3)



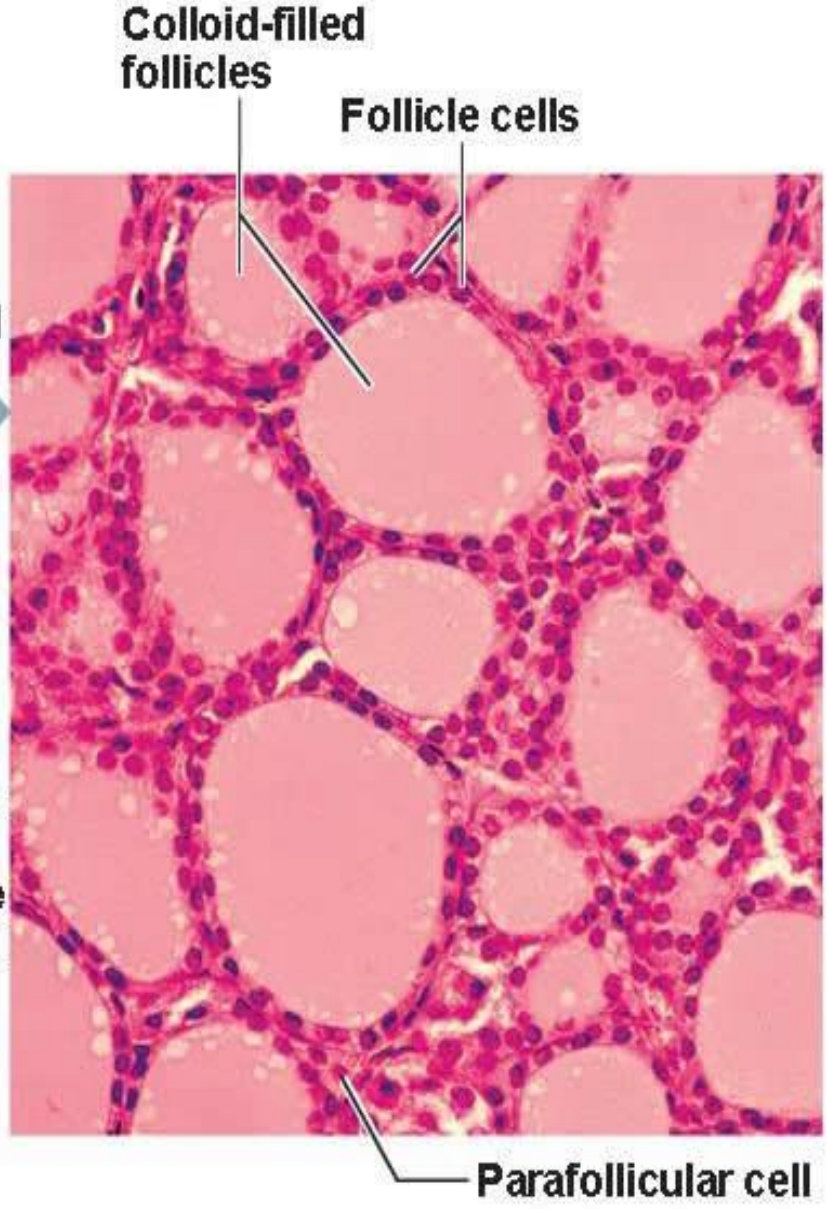
SYNTHESIS



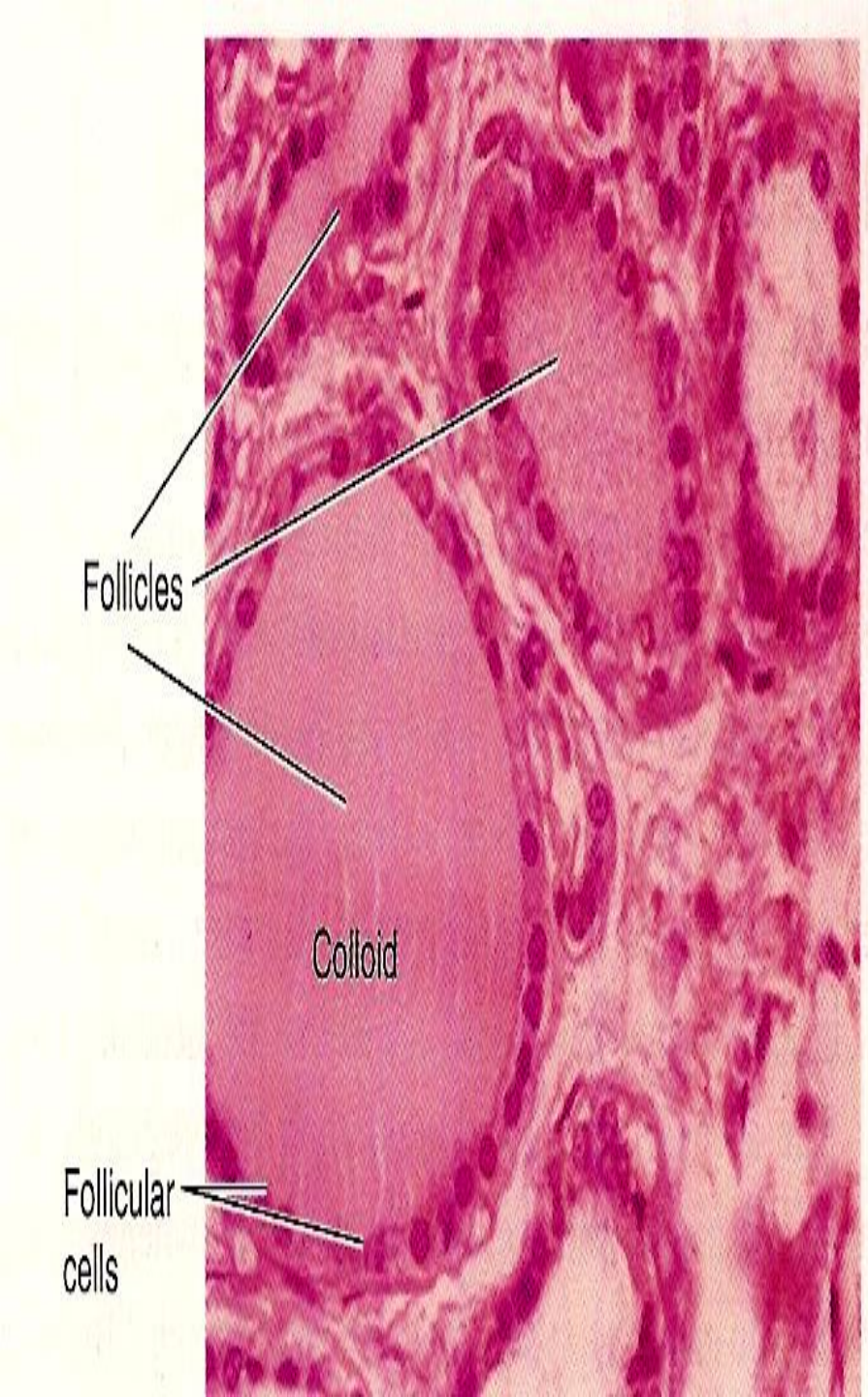
■ Fig. 49-1 **A,** Photomicrograph of thyroid gland follicle. **B,** Schematic drawing of normal thyroid gland follicle and a follicle stimulated by thyrotropin. Note change in shapes from cuboidal to columnar, relocation of nuclei to base of cells, and scalloped appearance of follicle lumen.

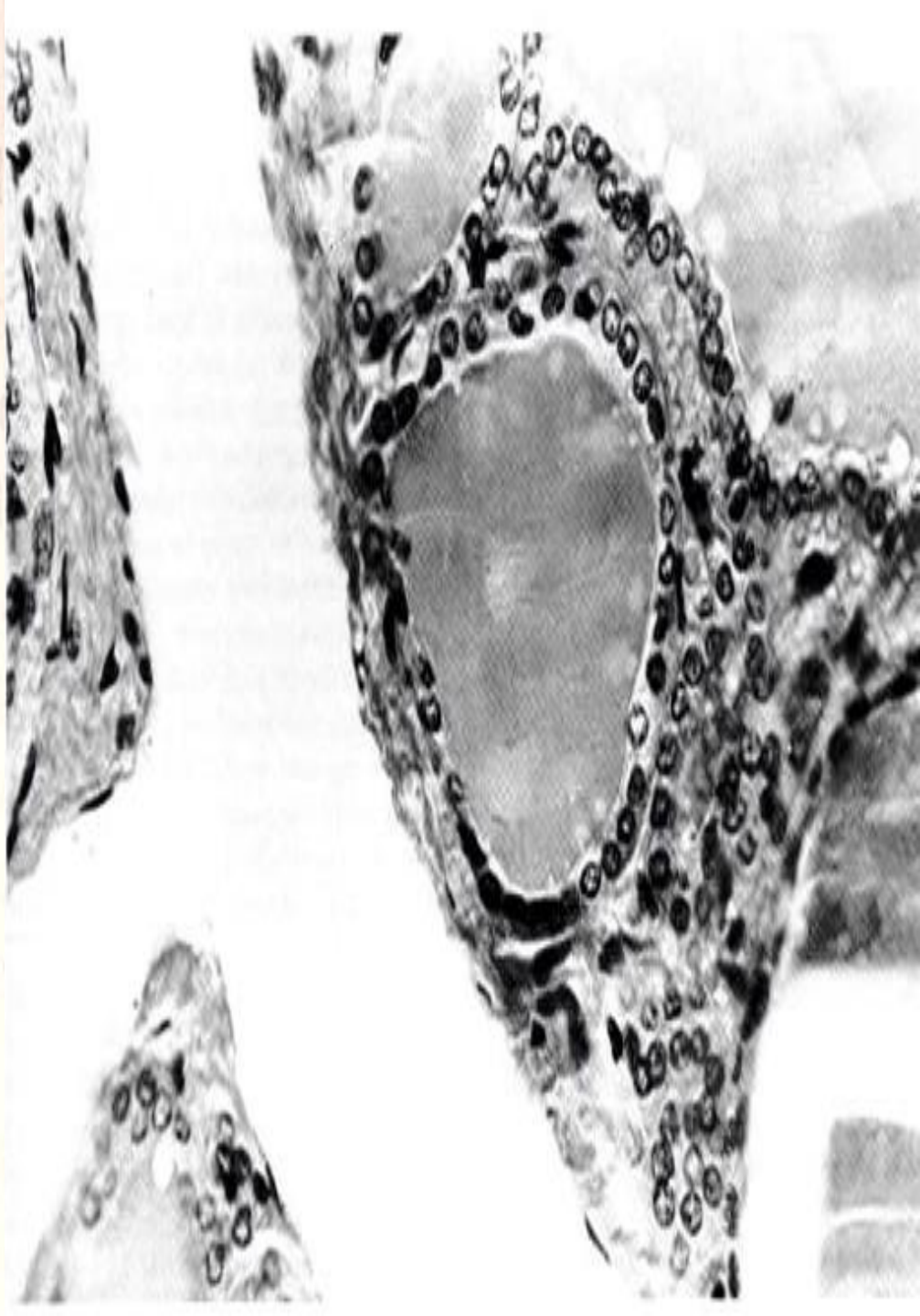


(a) Gross anatomy of the thyroid gland, anterior view



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


Follicles
Colloid
Follicular cells



THREE UNIQUE FEATURES

1- Contains a large amount of iodine.

- supplied in diet.

- 1mg/week.

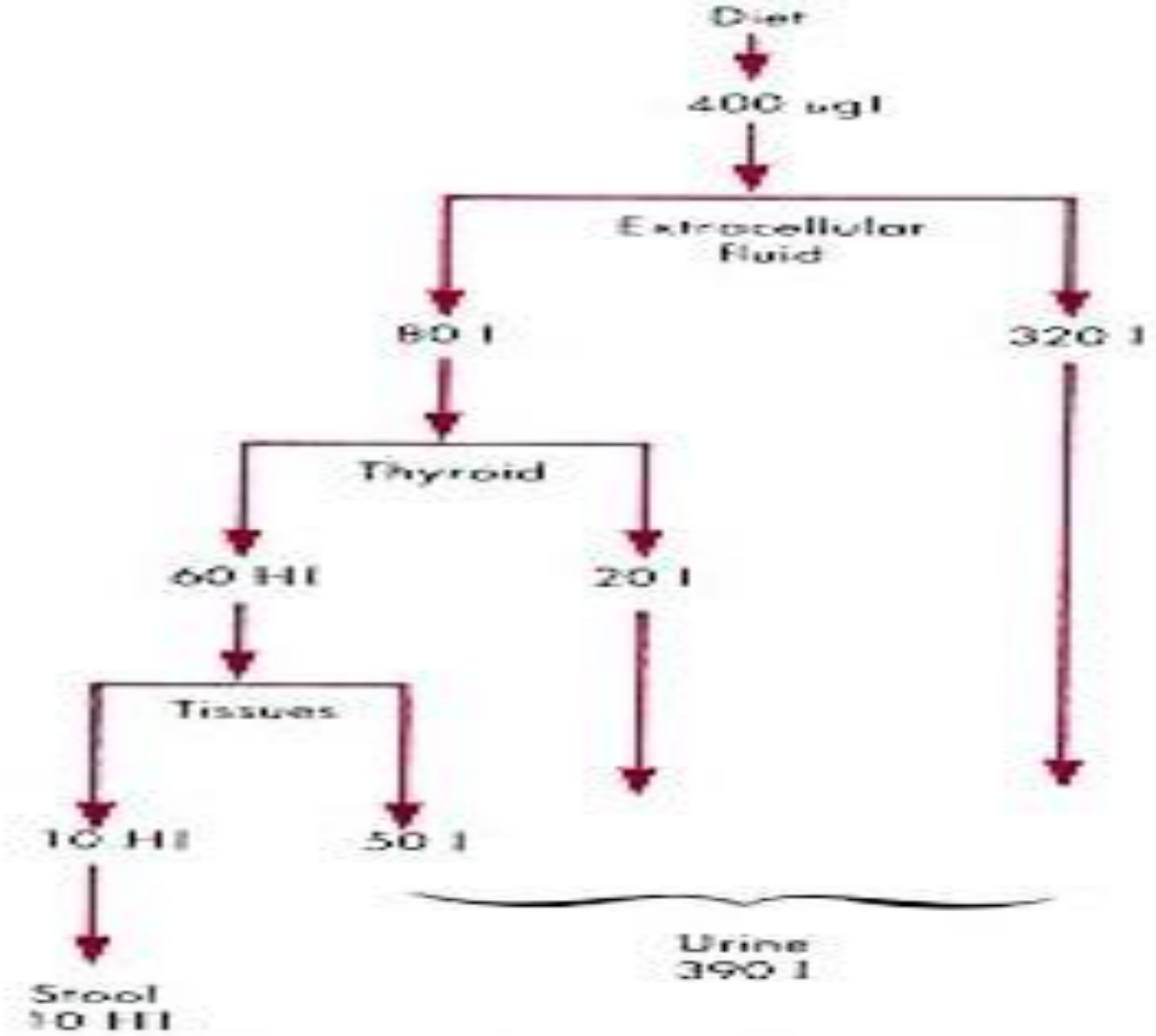


Fig. 49-2 Average daily iodide turnover in humans (United States). Note that 20% of the intake is taken up by the thyroid gland and 15% turns over in hormone synthesis and disposal. The unneeded excess is excreted in the urine. *I*, Iodide; *HI*, hormonal iodide.

2- Synthesis is partially intracellular and partially extracellular.

3- T4 is the major product.

STEPS IN BIOSYNTHESIS

1- THYROGLOBULIN FORMATION AND TRANSPORT:

- 140 tyrosine.

- Rough endoplasmic reticulum and Golgi apparatus.

2- IODIDE PUMP OR IODIDE TRAP:

- Active transport

- Wolff-chaikoff effect.

- Ratio of concentration from 30-250 times.

- It is stimulated by TSH.

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.
  MIT DIT
- - Remain attached to thyroglobulin until the gland stimulated to secret.

5- COUPLING REACTION:

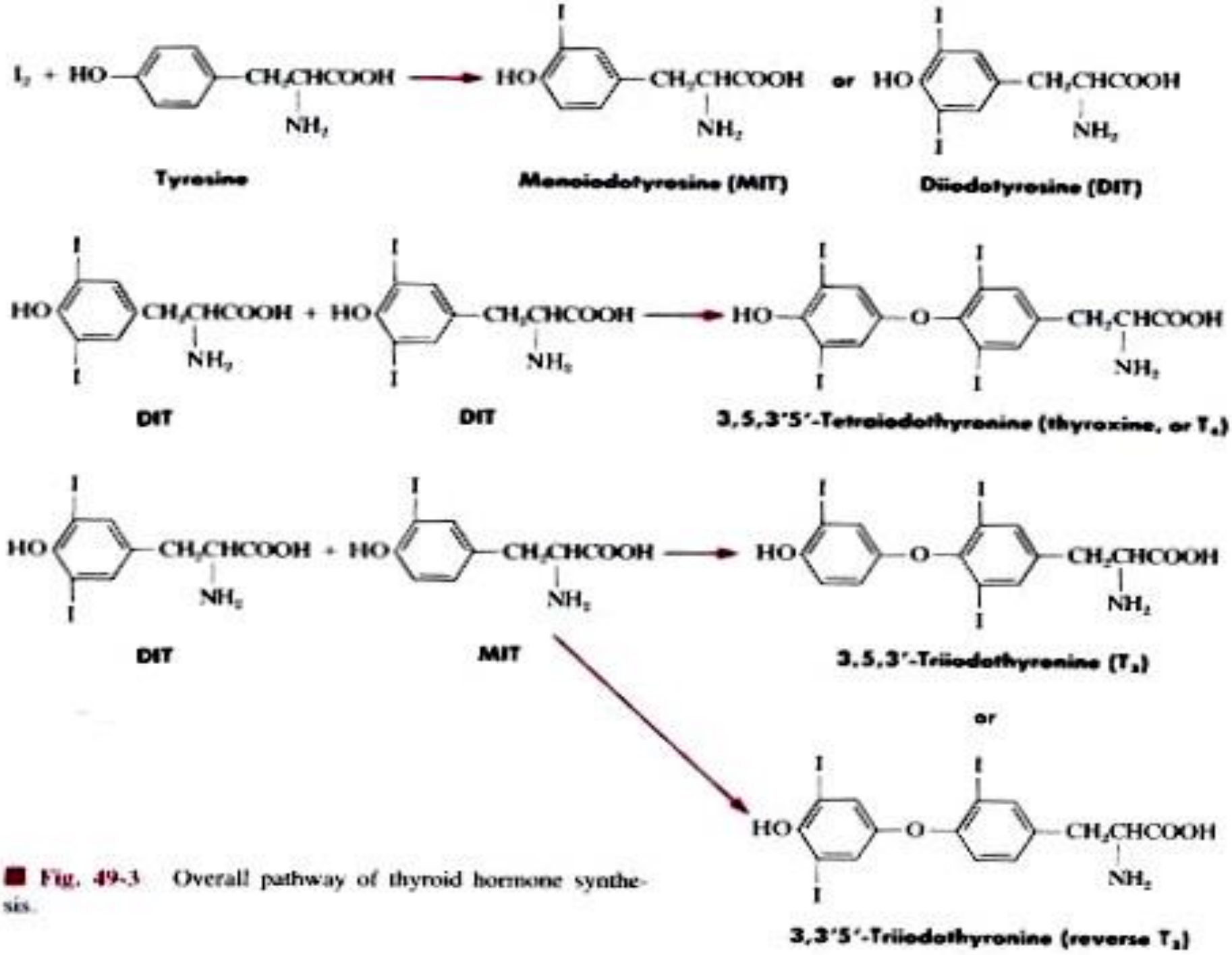
DIT + DIT → T_4 (faster)

DIT + MIT → T_3

- Catalyzed by thyroid peroxidase.

- It is stored as colloid.

- Is sufficient for **2-3 months.**



■ Fig. 49-3 Overall pathway of thyroid hormone synthesis.

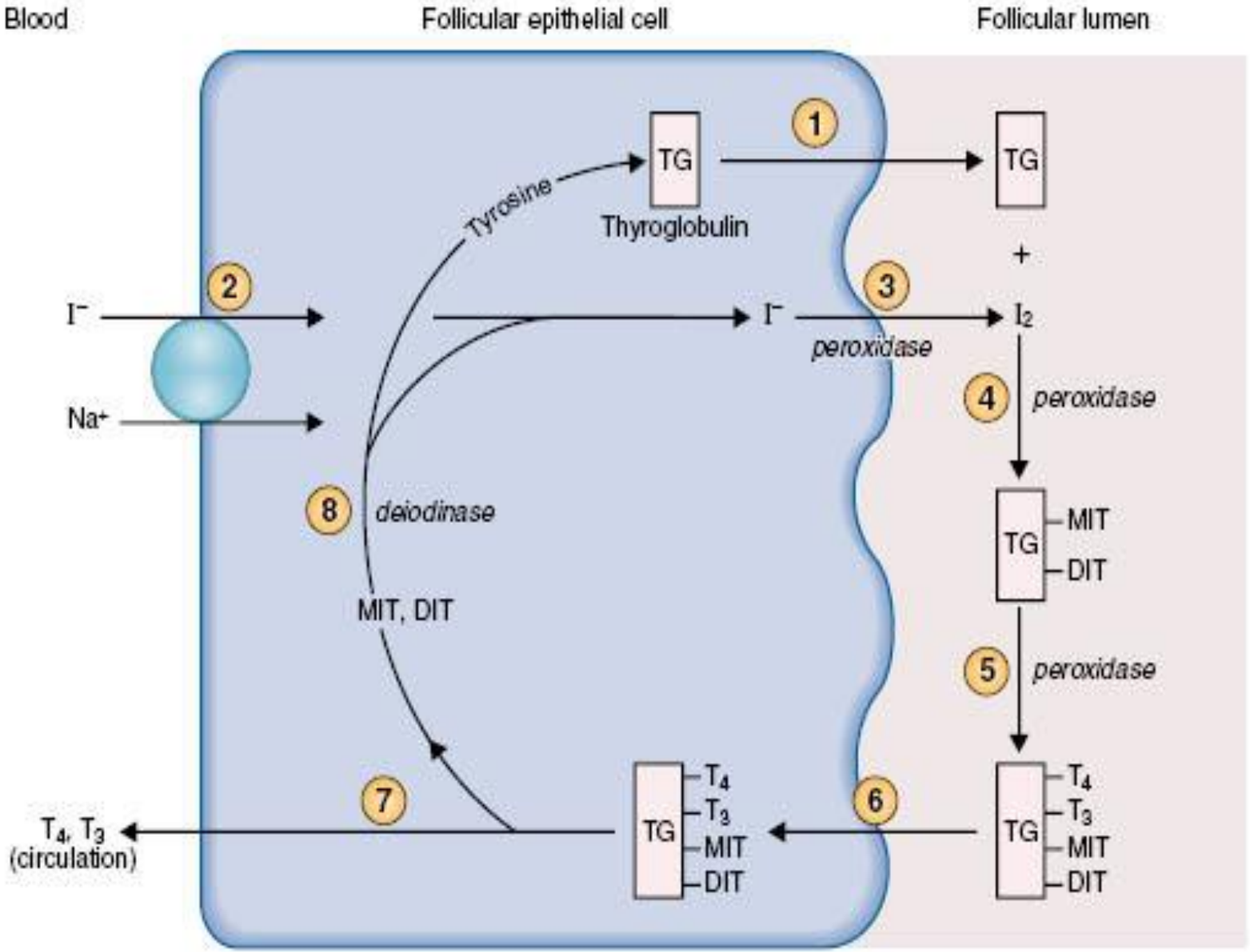
6- Endocytosis of thyroglobulin.

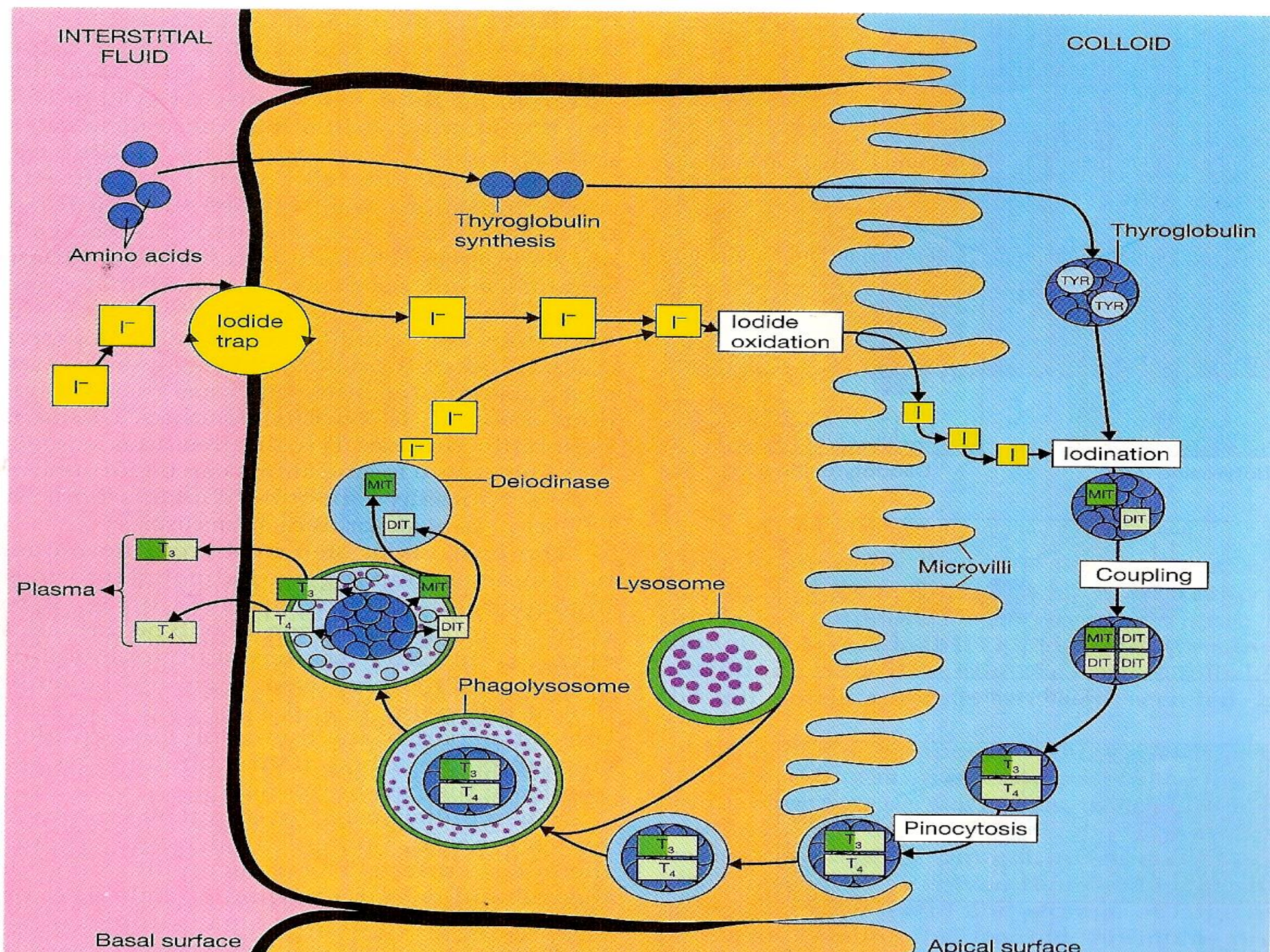
7- Fusion of lysosomes immediately with the vesicles.

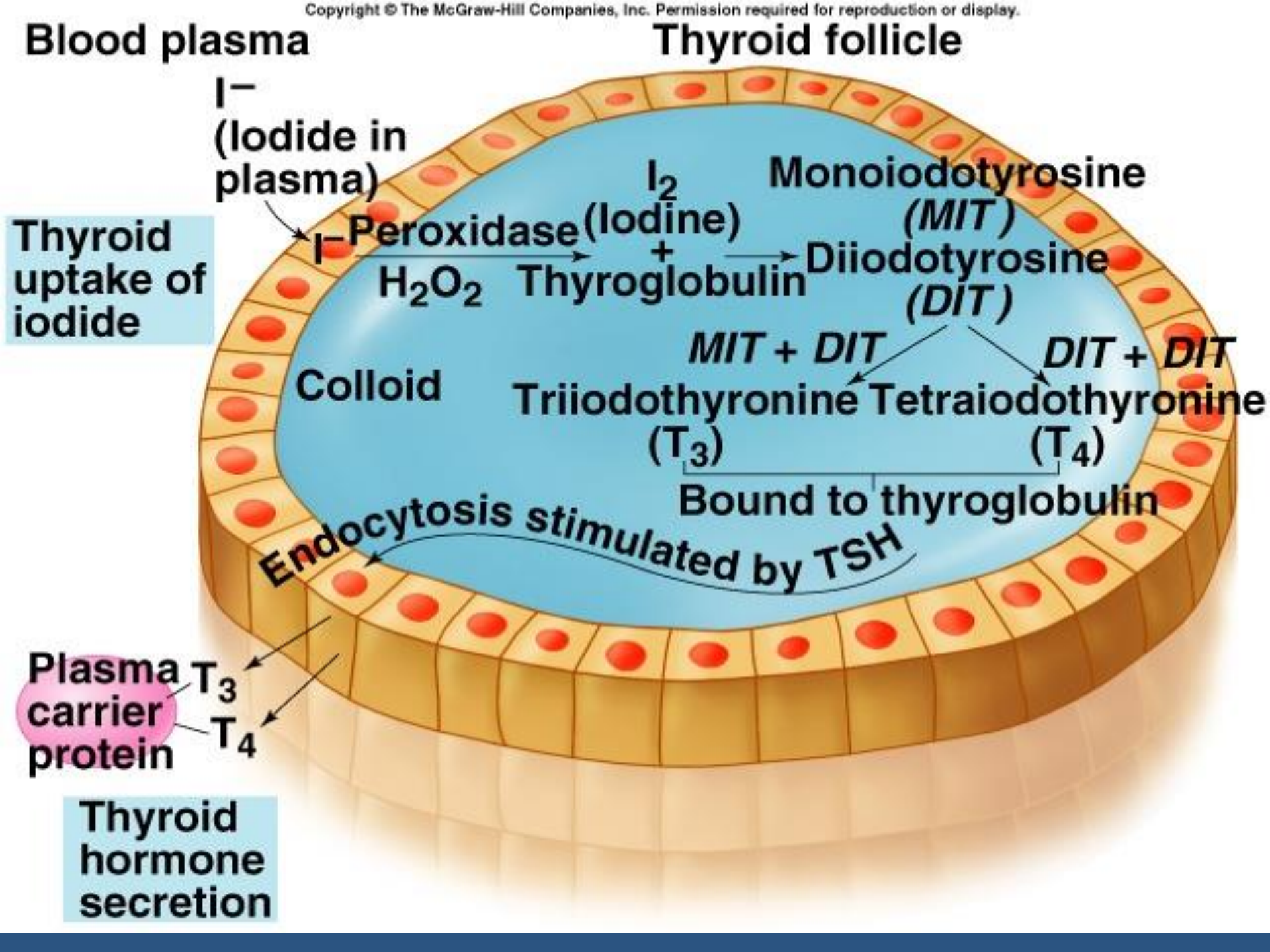
8- Hydrolysis of the peptide bond to release *DIT+MIT+T4+T3* from the thyroglobulin.

9- Delivery of T_4 and T_3 to the systemic circulation.

10- Deiodination of DIT and MIT by thyroid deiodinase.


Blood
Follicular epithelial cell
Follicular lumen
TG
Thyroglobulin
Tyrosine
1
TG
+
2
I⁻
3
I⁻
I₂
peroxidase
Na+
4
peroxidase
8
deiodinase
TG
MIT
DIT
MIT, DIT
5
peroxidase
7
6
T4
T3
MIT
DIT
T4, T3
(circulation)
TG
T4
T3
MIT
DIT
TG
T4
T3
MIT
DIT


INTERSTITIAL FLUID
COLLOID
Amino acids
Thyroglobulin synthesis
Thyroglobulin
TYR
TYR
I⁻
I⁻
Iodide trap
I⁻
I⁻
I⁻
Iodide oxidation
I
I
I
Iodination
I⁻
I⁻
MIT
DIT
Deiodinase
MIT
DIT
Coupling
Microvilli
Plasma
T3
T4
T3
T4
MIT
DIT
Lysosome
MIT
DIT
DIT
DIT
Phagolysosome
T3
T4
T3
T4
T3
T4
T3
T4
Pinocytosis
Basal surface
Apical surface



Event	Site	Enzyme	Inhibitor
1 Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 Na^+ - I^- cotransport	Basal membrane		Perchlorate, thiocyanate
3 Oxidation of $I^- \rightarrow I_2$	Apical (luminal) membrane	Peroxidase	PTU
4 Organification of I_2 into MIT and DIT	Apical membrane	Peroxidase	PTU
5 Coupling reaction of MIT and DIT into T_3 and T_4	Apical membrane	Peroxidase	PTU
6 Endocytosis of TG	Apical membrane		
7 Hydrolysis of T_4 and T_3; T_4 and T_3 enter circulation	Lysosomes	Proteases	
8 Deiodination of residual MIT and DIT Recycling of I^- and tyrosine	Intracellular	Deiodinase	

THYROID HORMONES IN THE CIRCULATION

1- Unbound:

Small amount

2- Bound:

- 70- 80% bound to thyroxine-binding globulin (TBG) synthesised in the liver.

- The reminder is bound to albumine.

In liver disease:

↓TBG → ↑T3 + T4 free level → inhibition of thyroid secretion.

In pregnancy:

↑estrogen → ↑TBG → ↓T3 + T4 free level → stimulation of thyroid secretion.

RELEASE OF T4 AND T3 TO THE TISSUES

1. **The release is slow because of the high affinity of the plasma binding proteins.**

   - ½ of T4 in the blood is released every 6 days.

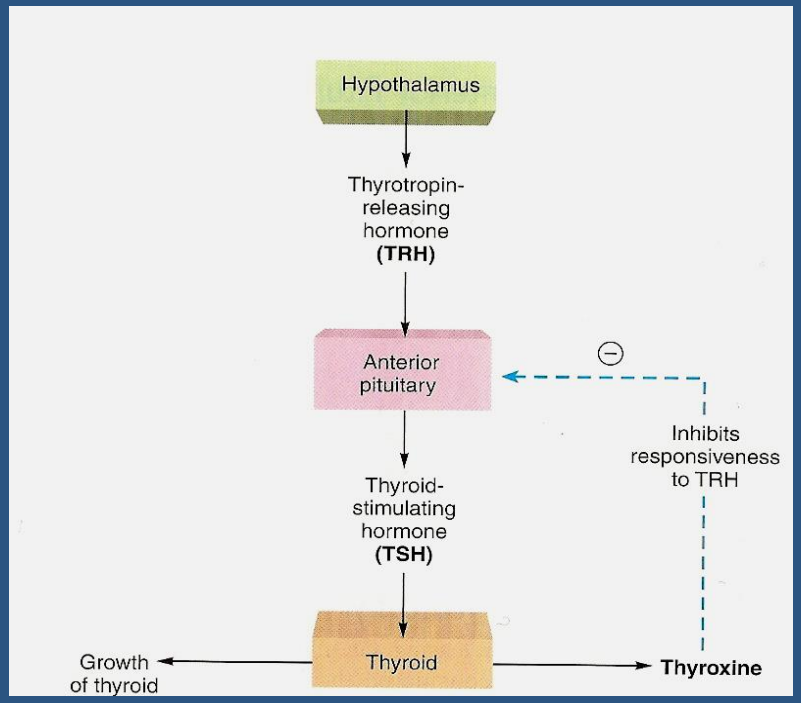
   - ½ of T3 in the blood is released every one day.

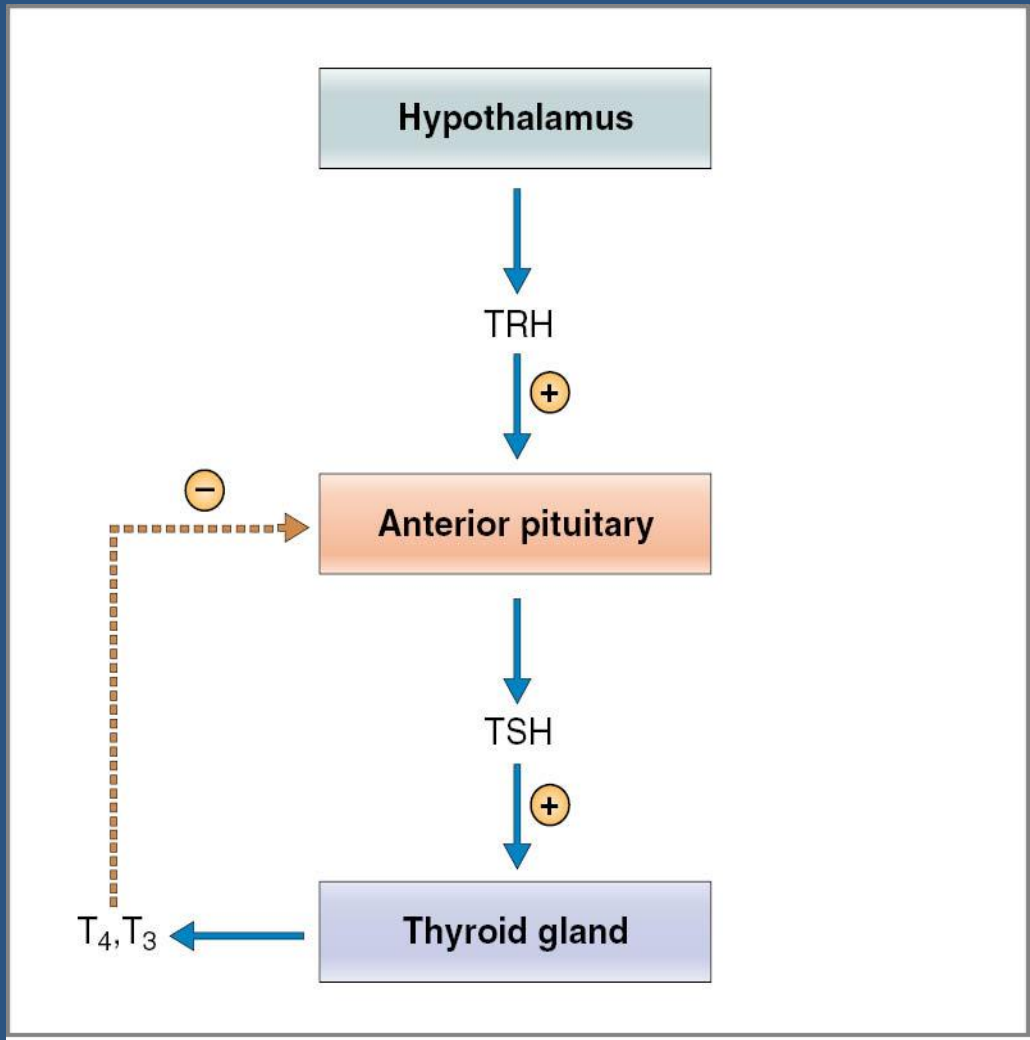
2- Stored in the targeted tissues .

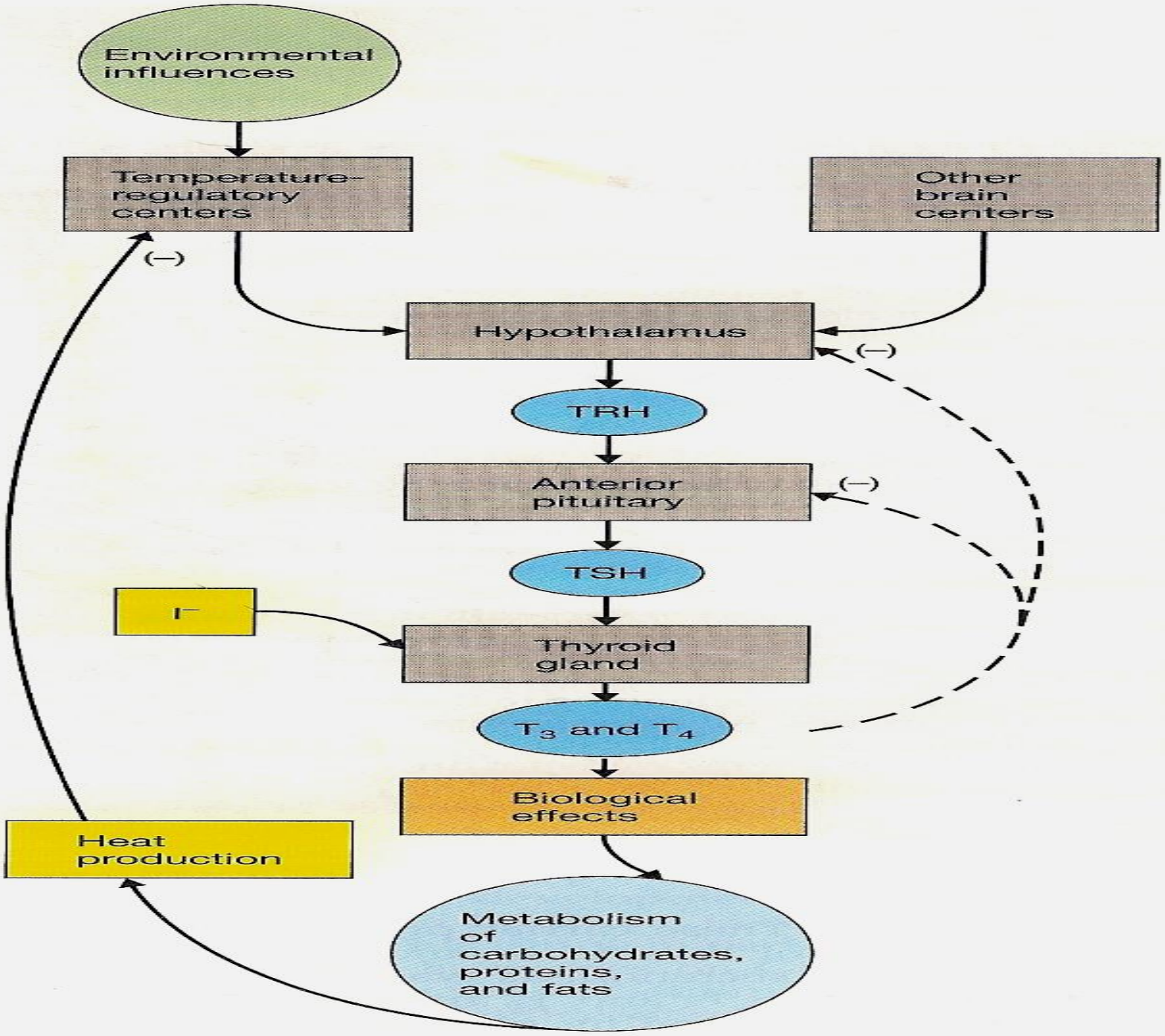
3- Enzyme 5- iodinase.

REGULATION OF HORMONES SECRETION

- **It is regulated by the hypothalamic-pituitary axis.**






Environmental influences
Temperature-regulatory centers
Other brain centers
(–)
Hypothalamus
(–)
TRH
Anterior pituitary
(–)
TSH
I⁻
Thyroid gland
T_3 and T_4
Biological effects
Heat production
Metabolism of carbohydrates, proteins, and fats

1- Thyrotropin-releasing hormone (TRH):

-Tripeptide.

- Paraventricular nuclei of the hypothalamus.

- Act on the thyrotrophs of the anterior pituitary

- Transcription and secretion of TSH.

2- Thyroid-stimulating hormone (TSH):

- Glycoprotein.

- Anterior pituitary.

- Regulate 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 11-13 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	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate; thiocyanate (inhibit Na^+-I^- cotransport)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

ACTION OF THYROID HORMONES

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

T3 + nuclear receptor → T3-receptor complex → 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 (stat of mental and physical rest 12-18 hours after a meal).

- Complete lack of thyroid hormones → ↓ 40% in BMR.

- Extreme increase of thyroid hormones → ↑ 60-100% 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 gastrointestinal tract.

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- NAPDH 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 out put up to 60%

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

1- Thyroid hormones potentiate the effect of catecholamine in the circulation ⟶ activation of β-adrenergic receptors.

2- Direct induction of:

a)- myocardial β-adrenergic receptors.

b)- sarcoplasmic reticulum.

c)- Ca+2 ATPase.

6- Effects on the CNS:

A)- perinatal period:

Thyroid hormones are essential for maturation of the CNS.

perinatal decrease of hormones secretion

↓

mental retardation

- Screening is necessary to introduce hormone replacement .

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 Autonomic nervous system:

Produced the same action as catecholamine's via

β-adrenergic receptors including:

a)- increase BMR.

b)- increase heat production.

c)- increase heart rate.

d)- increase stroke volume.

i.e. β-blocker (propranolol) is used in treatment of hyperthyroidism.

8- Effects on bone:

a)- promote bone formation.

b)- promote ossification.

c)- promote fusion of bone plate.

d)- promote bone maturation.

9- Effects on respiration:

1- increase ventilation rate.

2- increase dissociation of oxygen from Hb by increasing red cells 2,3-DPG (2,3 diphosphoglycerate).

10- Effects on the G.I tract:

1- increase appetite and food intake.

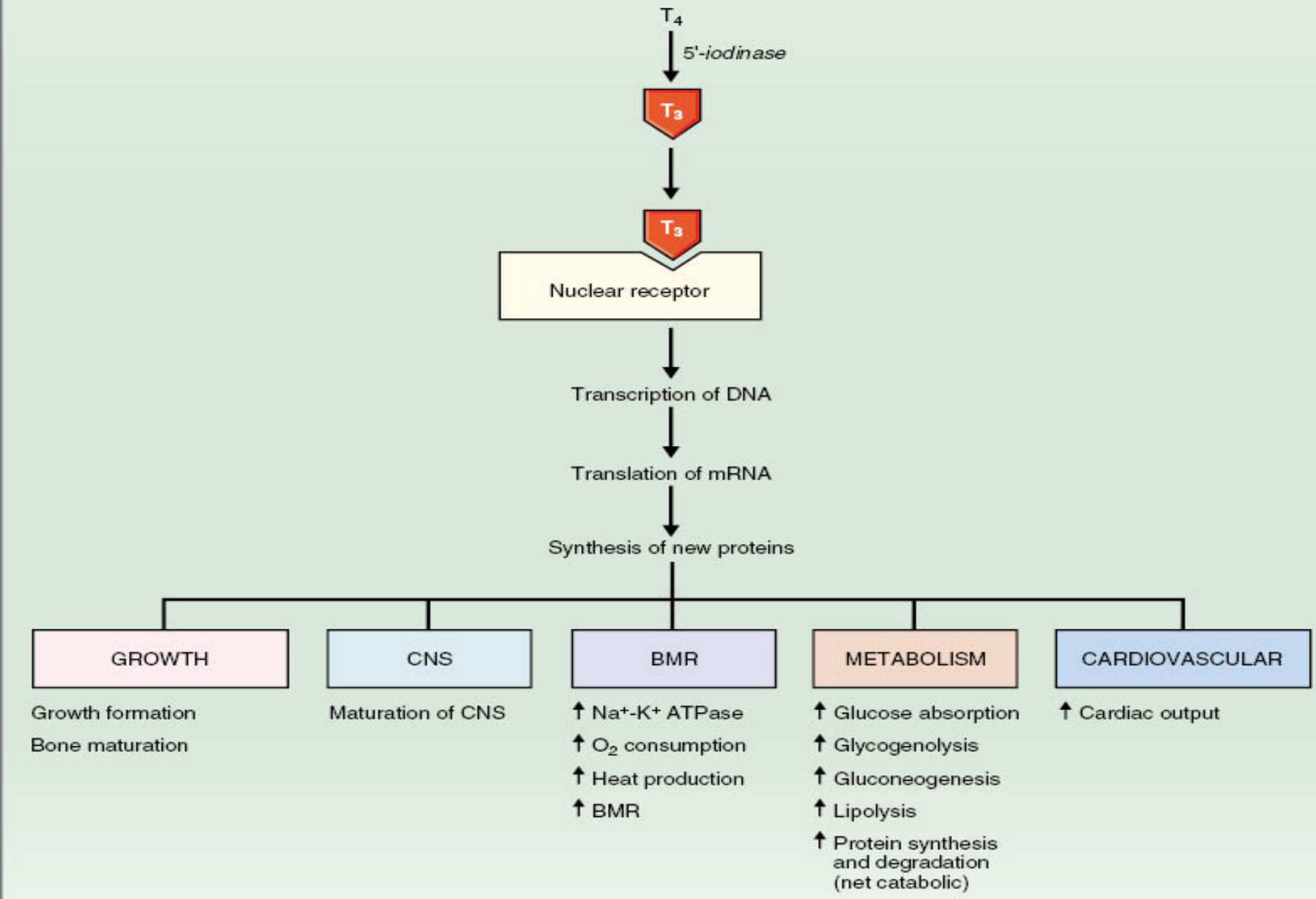
2- increase of digestive juices secretion.

3- increase of G.I tract motility.

excess secretion → diarrhea.

lack of secretion → constipation.

ACTIONS OF THYROID HORMONES



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.

- 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

S+s :

1- Goiter in 95%.

2- skin:

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

3- musculoskeletal:

-Muscle atrophy.

4- Neurological:

- tremor.
- enhanced reflexes.
- irritability.

5- Cardiovascular:

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

6- G.I tract:

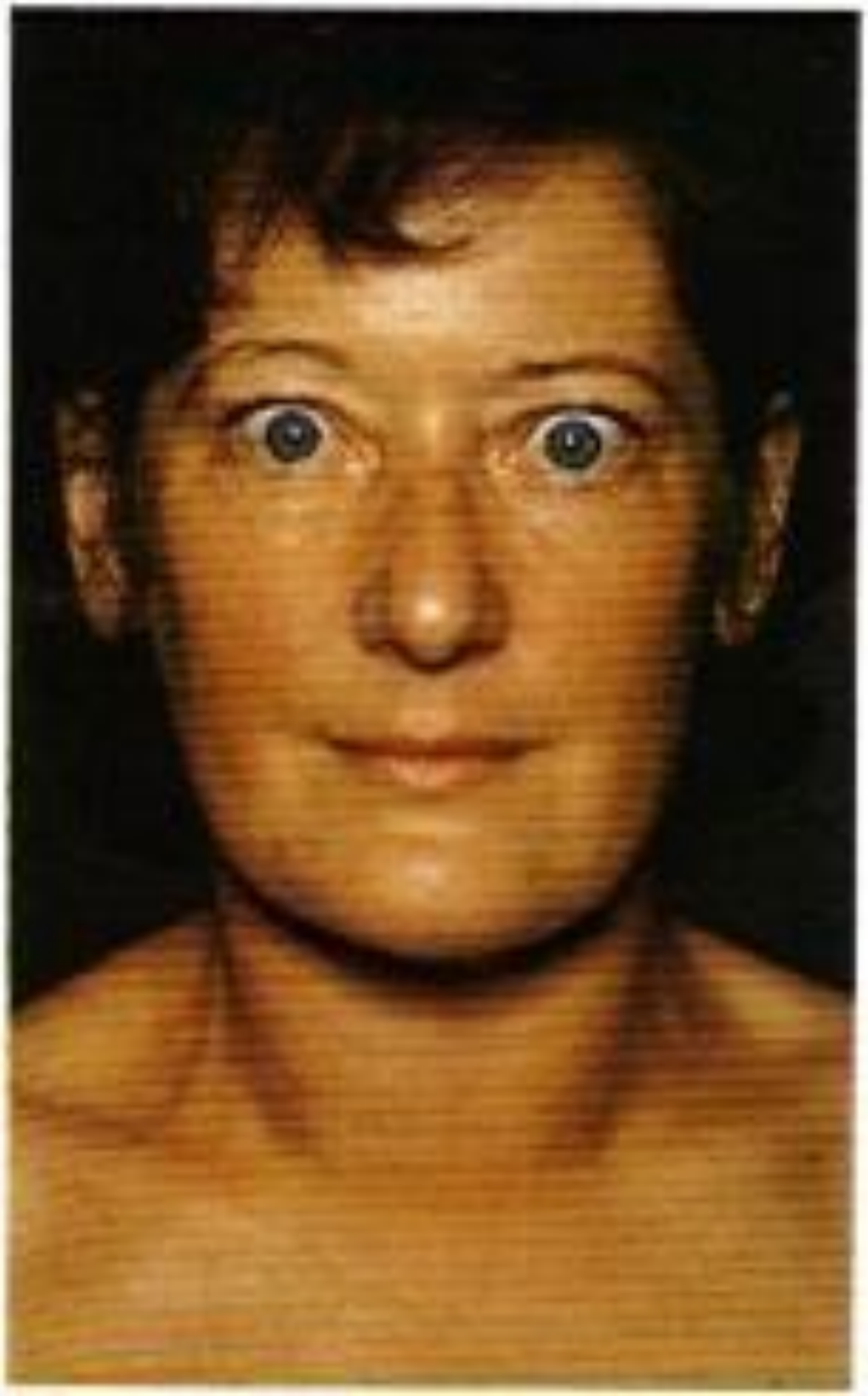
- weight loss.
- diarrhea.

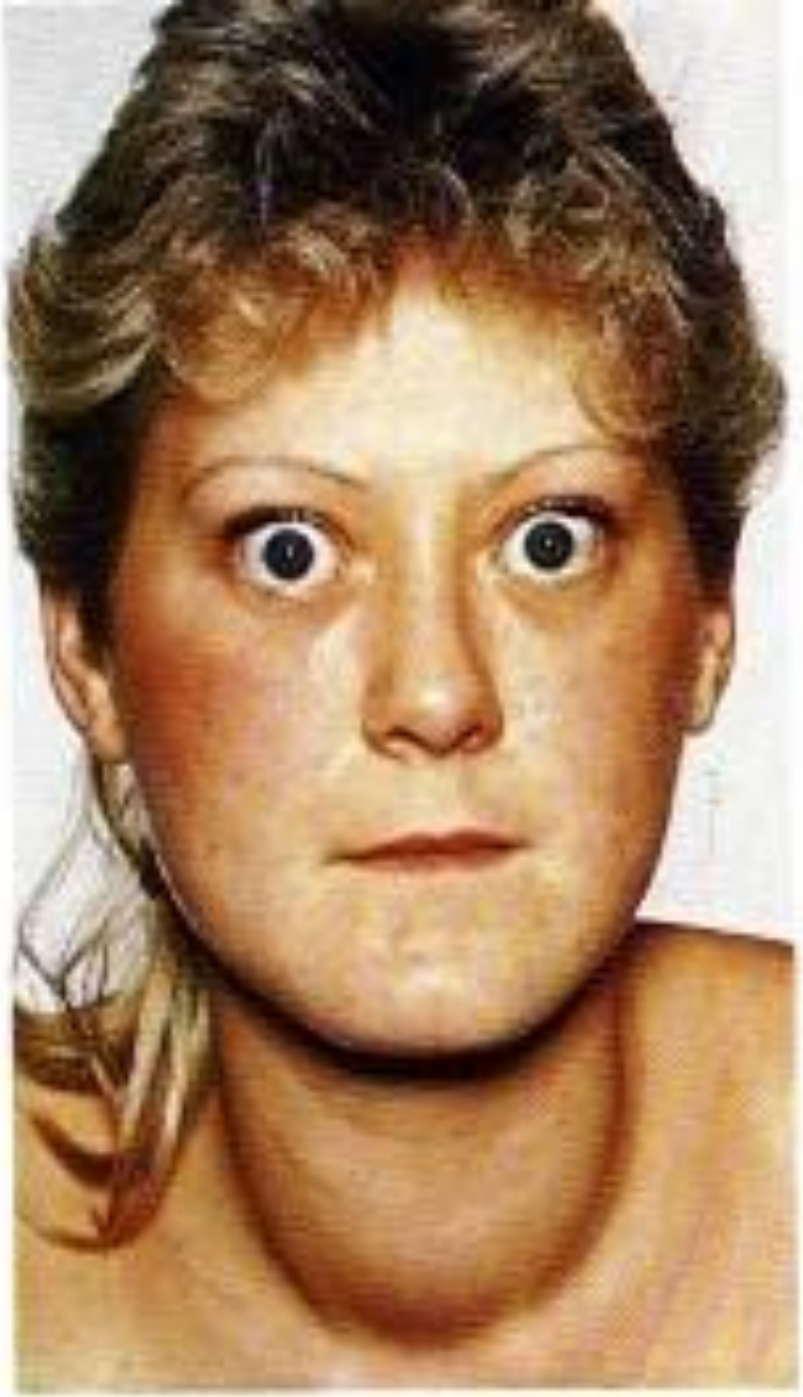
7- Exophthalmos:

- anxious staring expression.
- protrusion of eye balls.

8- Others:

- menstrual cycle disturbance.





INVESTIGATIONS

1- Serum T3, T4 ,TSH 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. propylthiourcal

- 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).

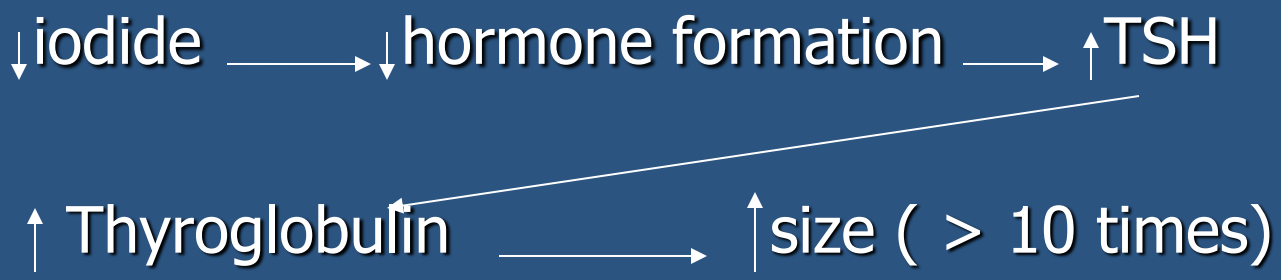
CAUSES

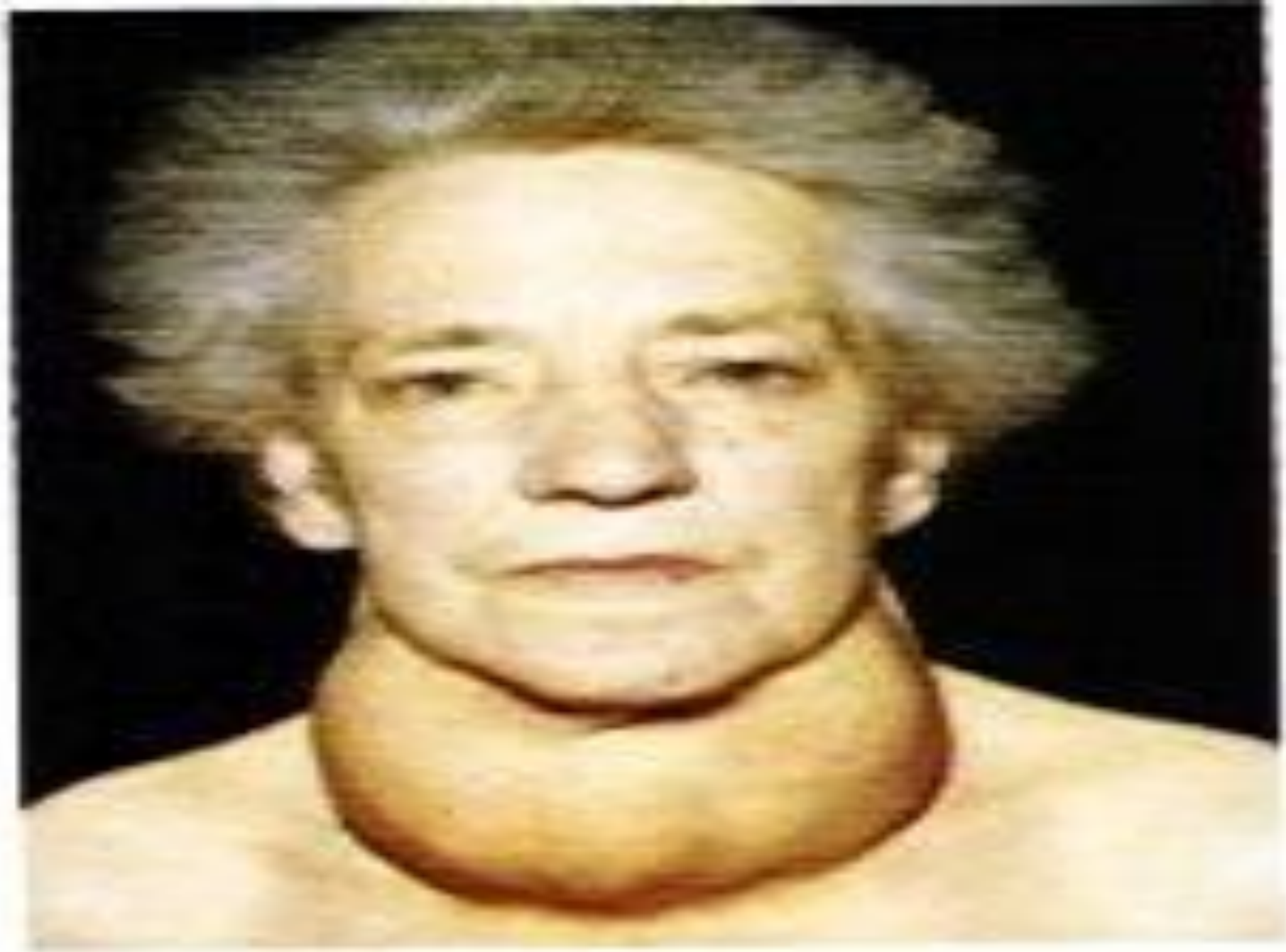
1- inherited abnormalities of thyroid hormone synthesis :

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

2- Endemic Colloid Goiter:

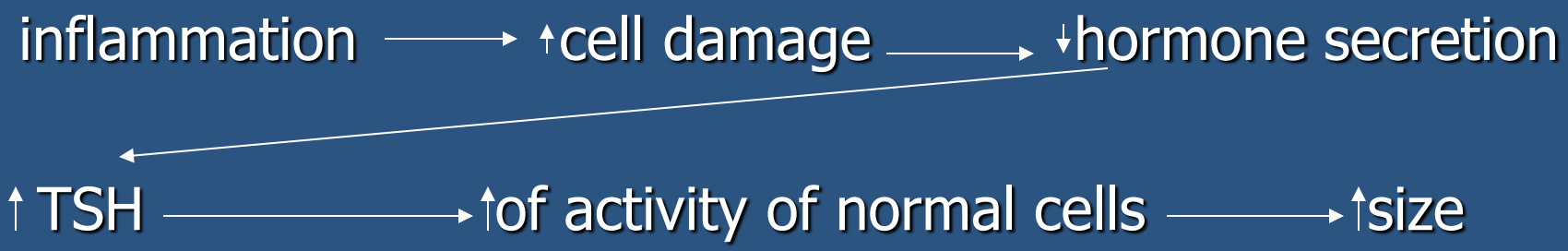
- **before table salt.**





3- Idiopathic Nontoxic Colloid Goiter:

- I in take 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

3- Neurological:

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

4- Cardiovascular:

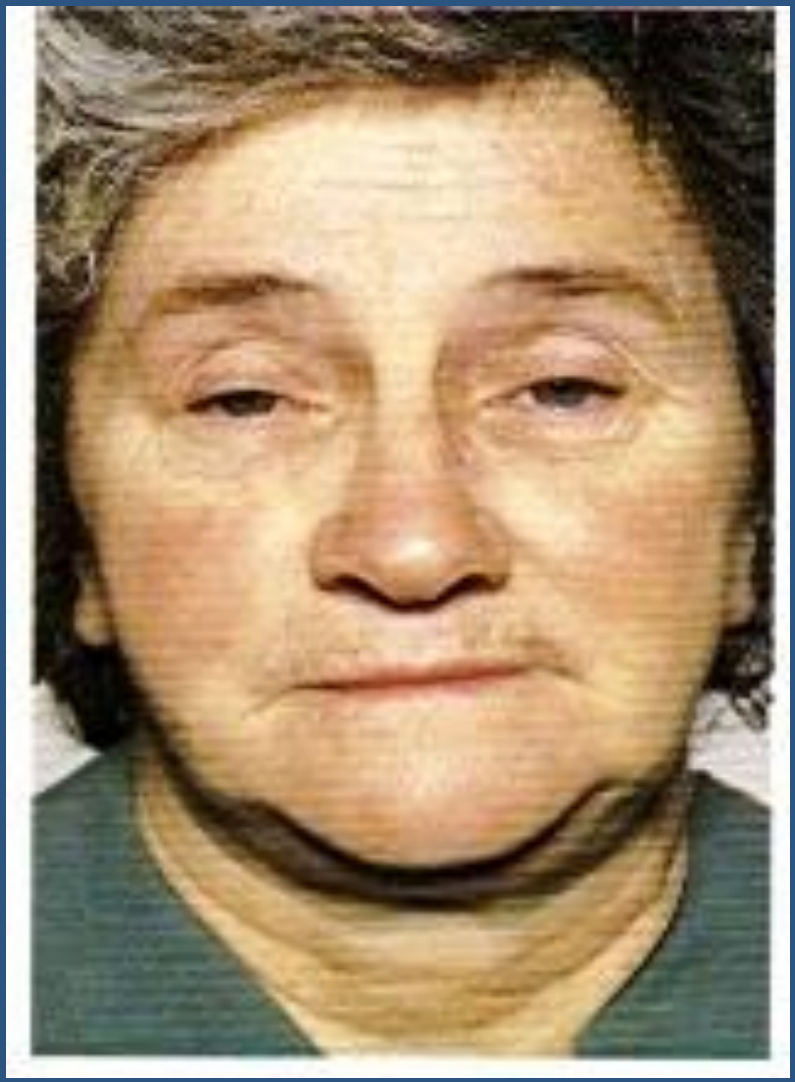
- heart rate
- stroke volume.

5- G.I tract:

- constipation
- increase weight.

6- Myxoedema:

An edematous appearance through out body.



7- 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 µg.
- - At 2-4 weeks period.

The first response seen is the weight loss.

Table 9-9 Pathophysiology of Thyroid Hormones

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate Weight loss Negative nitrogen balance Increased heat production Sweating Increased cardiac output Dyspnea (shortness of breath) Tremor, muscle weakness Exophthalmos Goiter	Decreased basal metabolic rate Weight gain Positive nitrogen balance Decreased heat production Cold sensitivity Decreased cardiac output Hypoventilation Lethargy, mental slowness Drooping eyelids Myxedema Growth retardation Mental retardation (perinatal) Goiter
Causes	Graves' disease (increased thyroid-stimulating immunoglobulins) Thyroid neoplasm Excess TSH secretion Exogenous T_3 or T_4 (factitious)	Thyroiditis (autoimmune or Hashimoto's thyroiditis) Surgery for hyperthyroidism I^- deficiency Congenital (cretinism) Decreased TRH or TSH
TSH Levels	Decreased (feedback inhibition of T_3 on the anterior lobe) Increased (if defect is in anterior pituitary)	Increased (by negative feedback if primary defect is in thyroid gland) Decreased (if defect is in hypothalamus or anterior pituitary)
Treatment	Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis) Thyroidectomy $^{131}I^-$ (destroys thyroid) β-Adrenergic blocking agents (adjunct therapy)	Thyroid hormone replacement therapy

CRETINISM

Extreme hypothyroidism during infancy and child hood (failure of growth).

CAUSES

1- Congenital lake of thyroid gland (congenital cretinism).

2- Genetic deficiency leading to failure to produce hormone.

3- Iodine lake in the diet (endemic cretinism).

SYMPTOMS

1- Infant is normal at birth but abnormality appears within weeks.

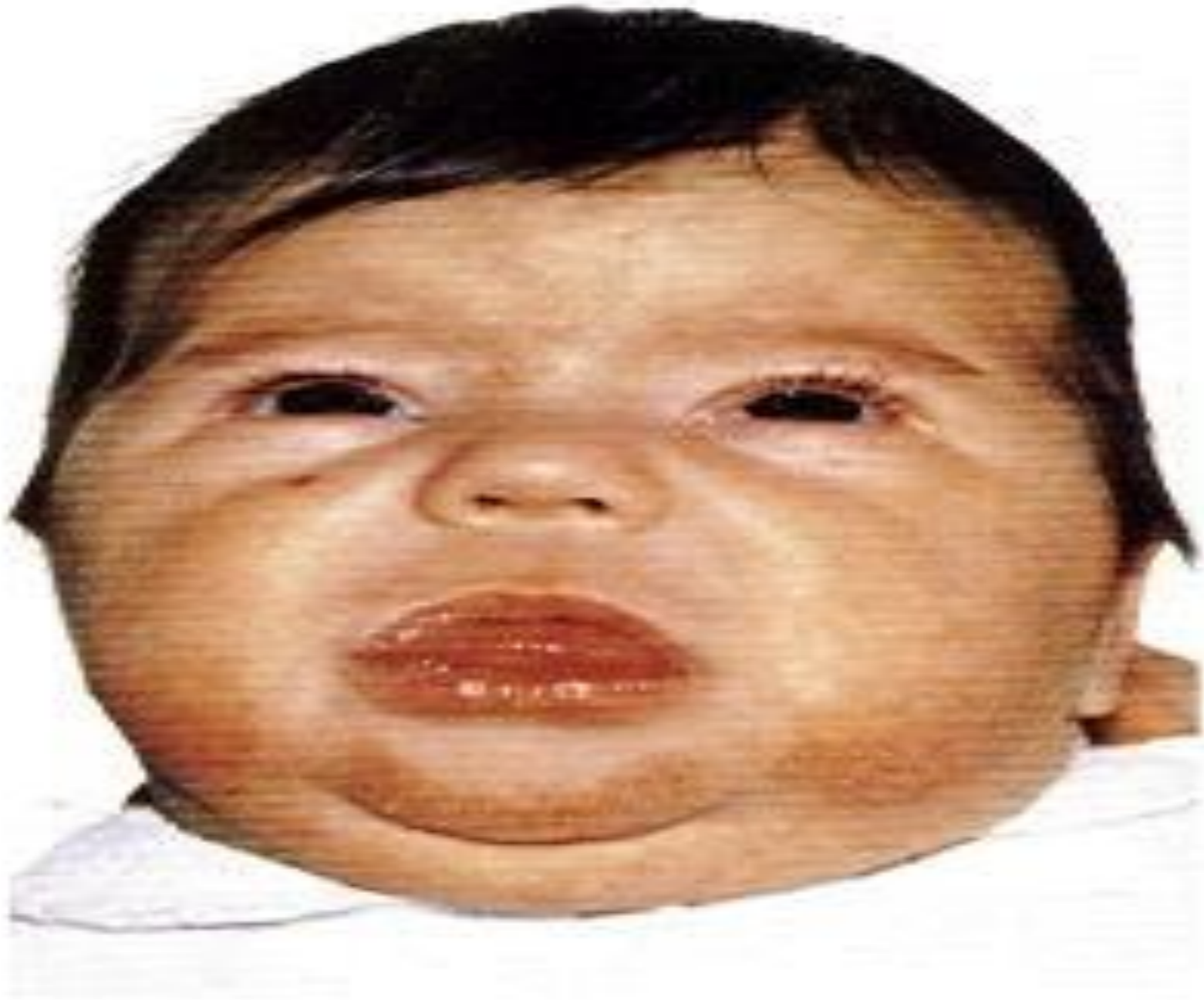
2- Protruding tongue.

3- Dwarf with short limbs.

4- Mental retardation.

5- Often umbilical hernia.

6- teeth.



TREATMENT

Changes are irreversible unless treatment is given early.


4'
3'6"
3'