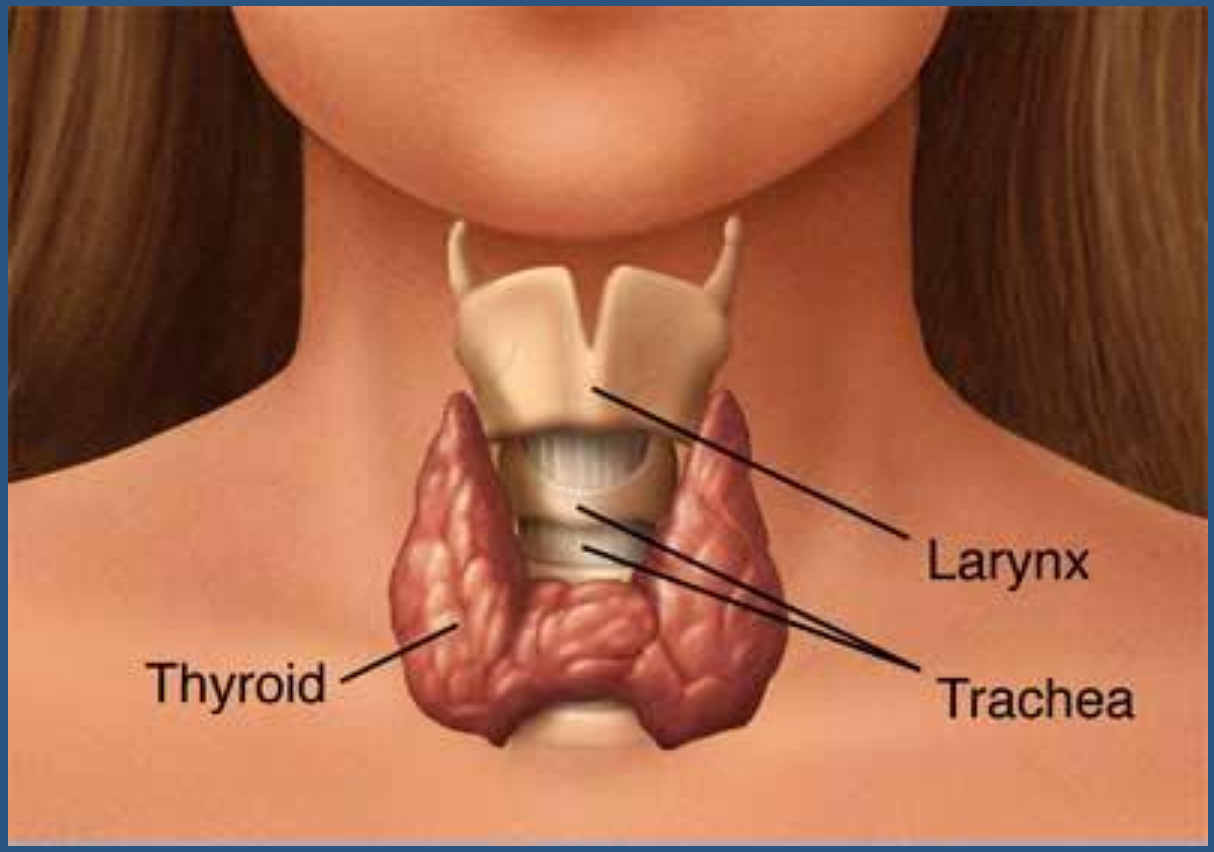
THE THYROID GLAND

DR. Nervana Bayoumy

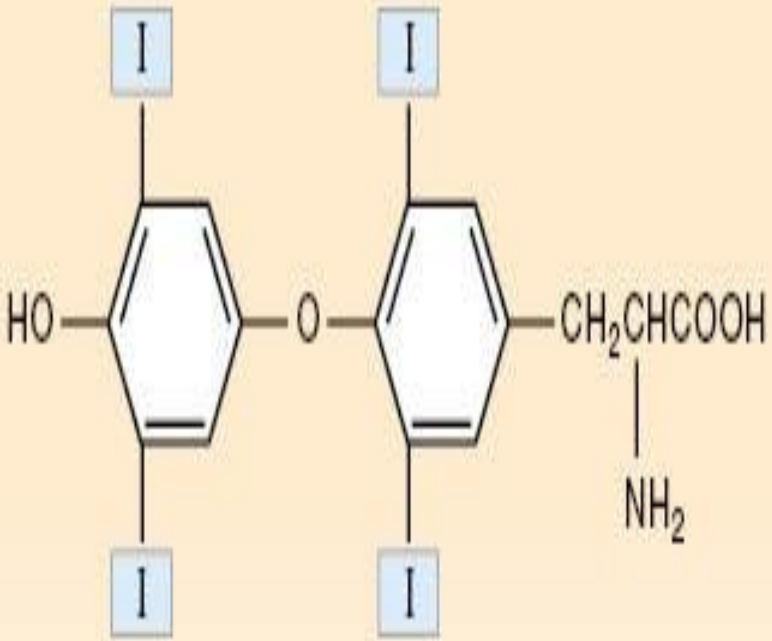

Larynx
Thyroid
Trachea

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

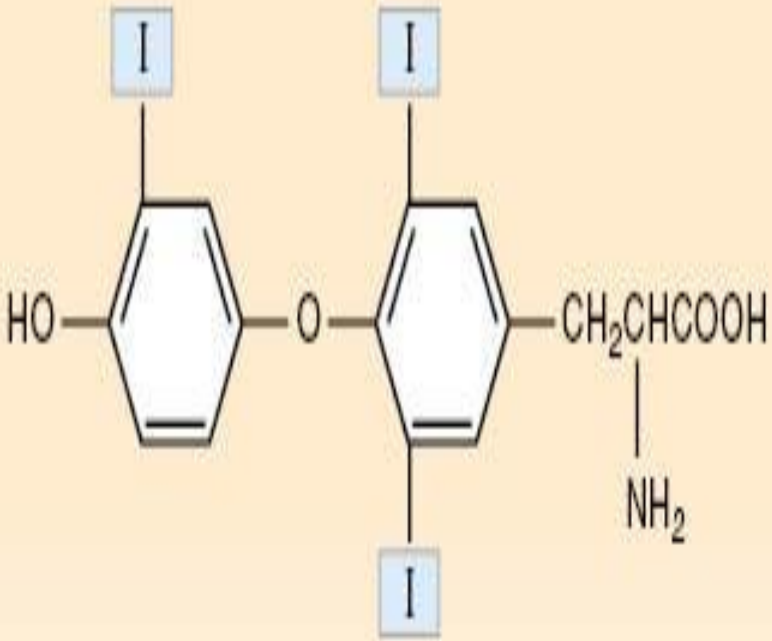
HORMONES

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

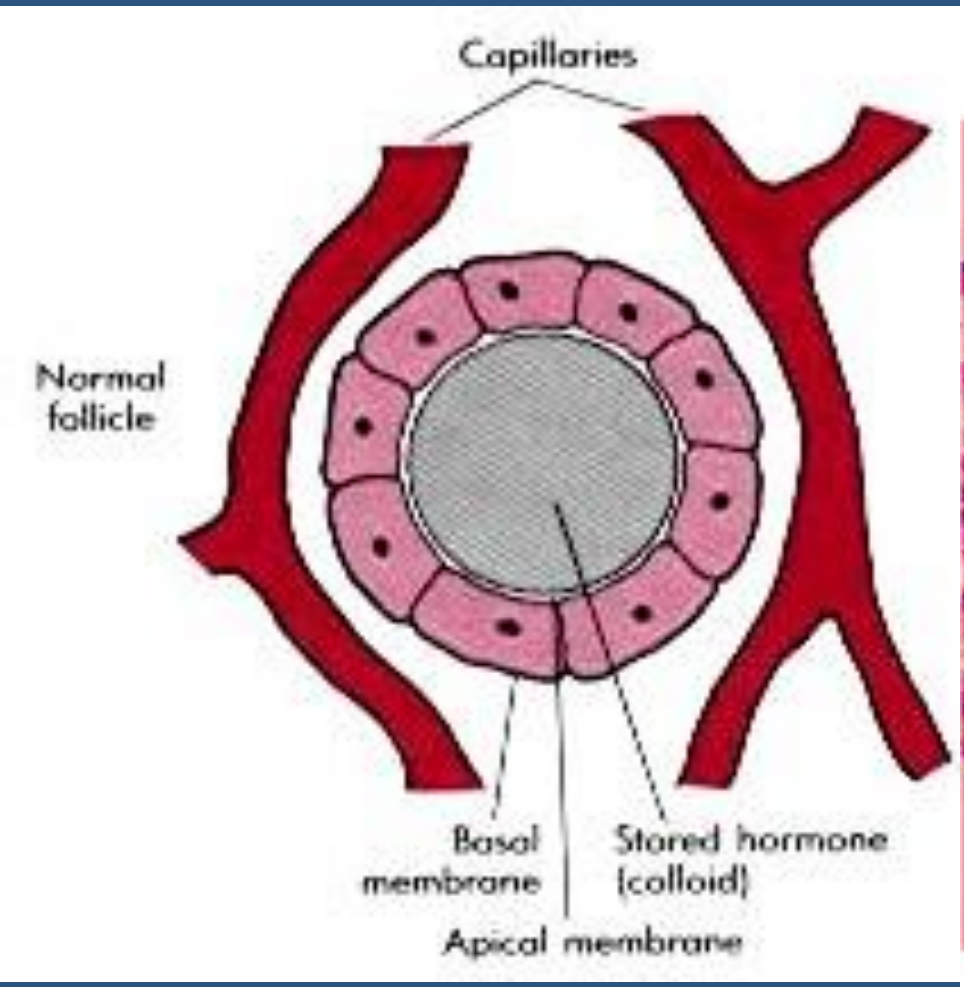
Thyroxine (T_4)

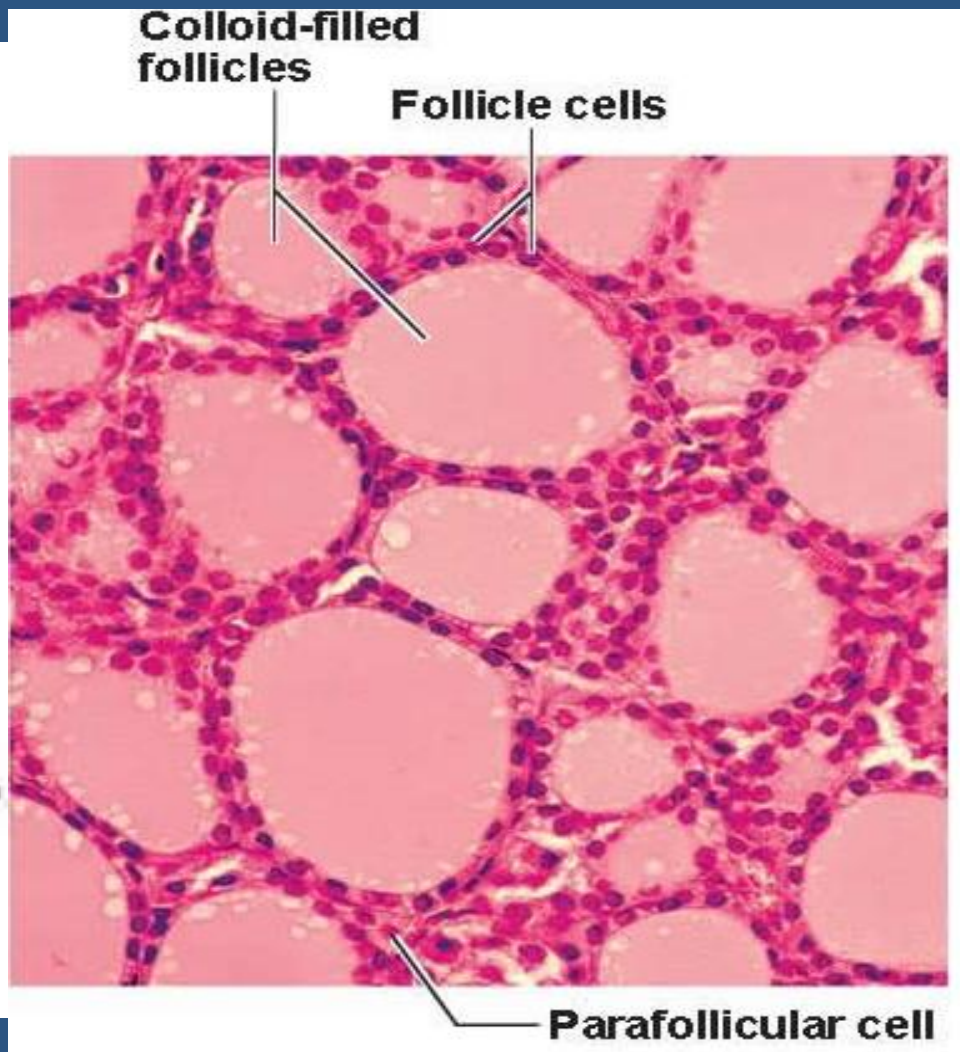


Triiodothyronine (T_3)



SYNTHESIS





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

THREE UNIQUE FEATURES

1- Contains a large amount of iodine.

- supplied in diet.

- 1mg/week.

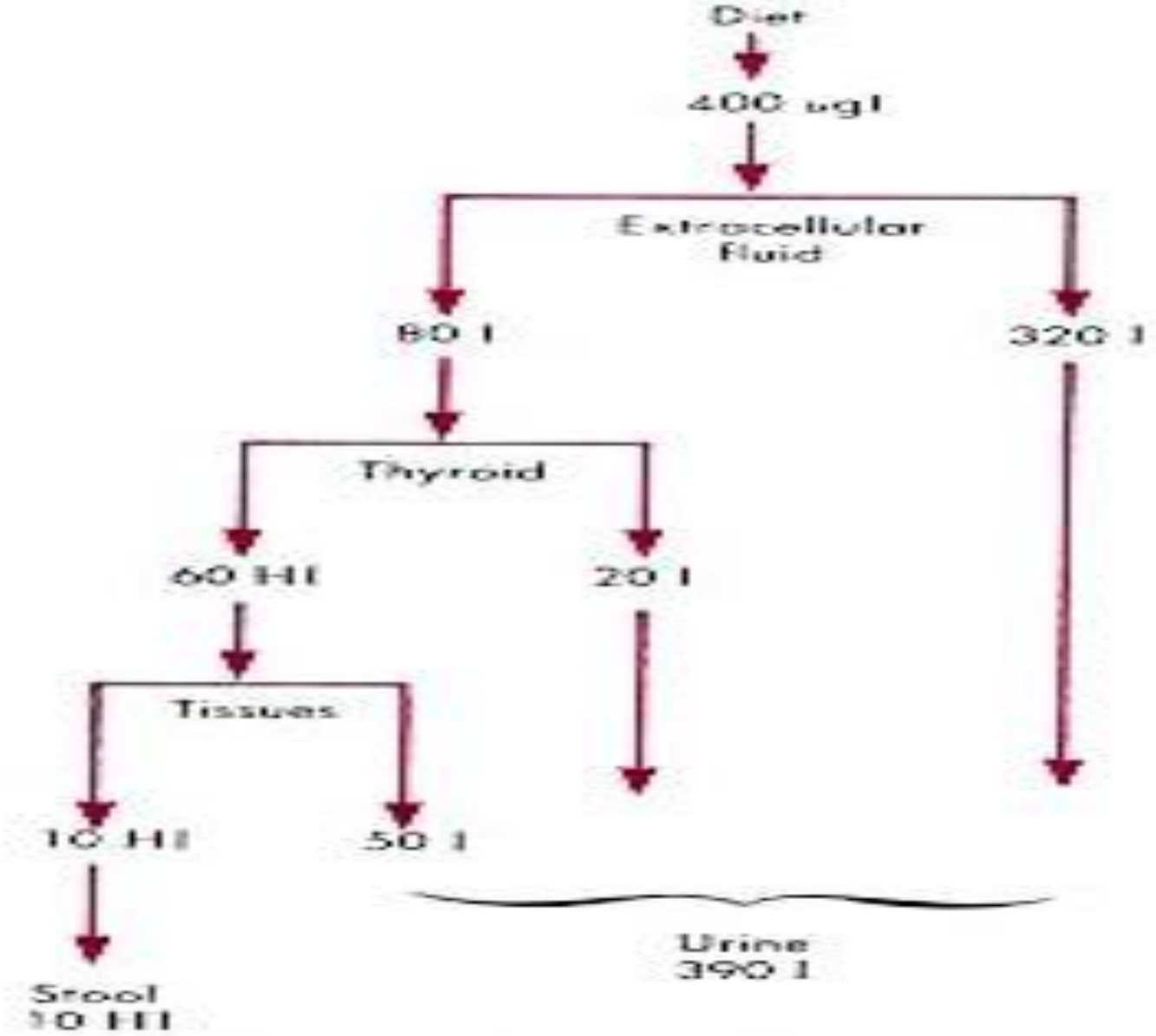
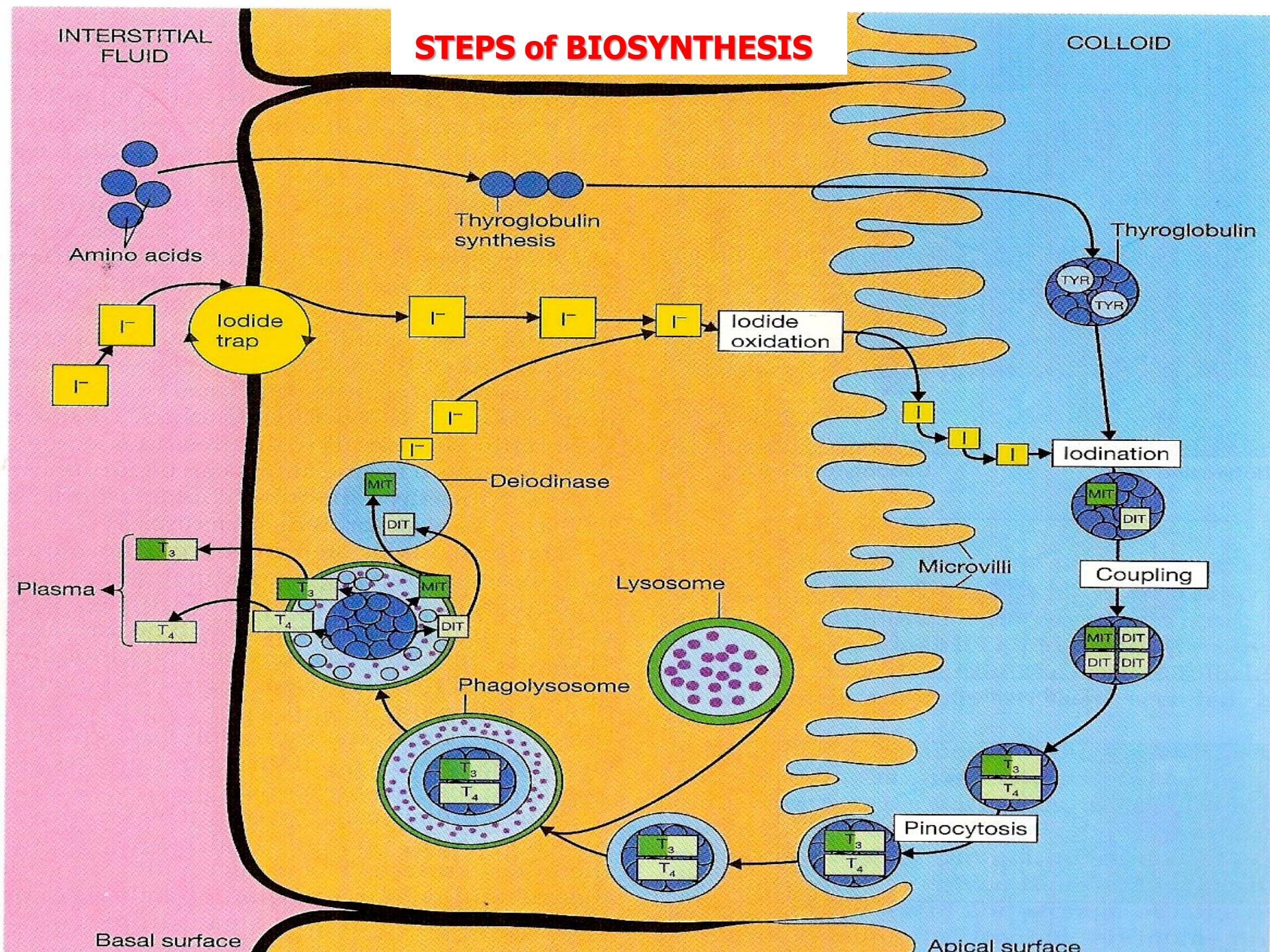


Fig. 49-2 Average daily iodide turnover in humans (United States). Note that 20% of the intake is taken up by the thyroid gland and 15% turns over in hormone synthesis and disposal. The unneeded excess is excreted in the urine. *I*, Iodide; *HI*, hormonal iodide.

2- Synthesis is partially intracellular and partially extracellular.

3- T4 is the major product.

STEPS of BIOSYNTHESIS



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:

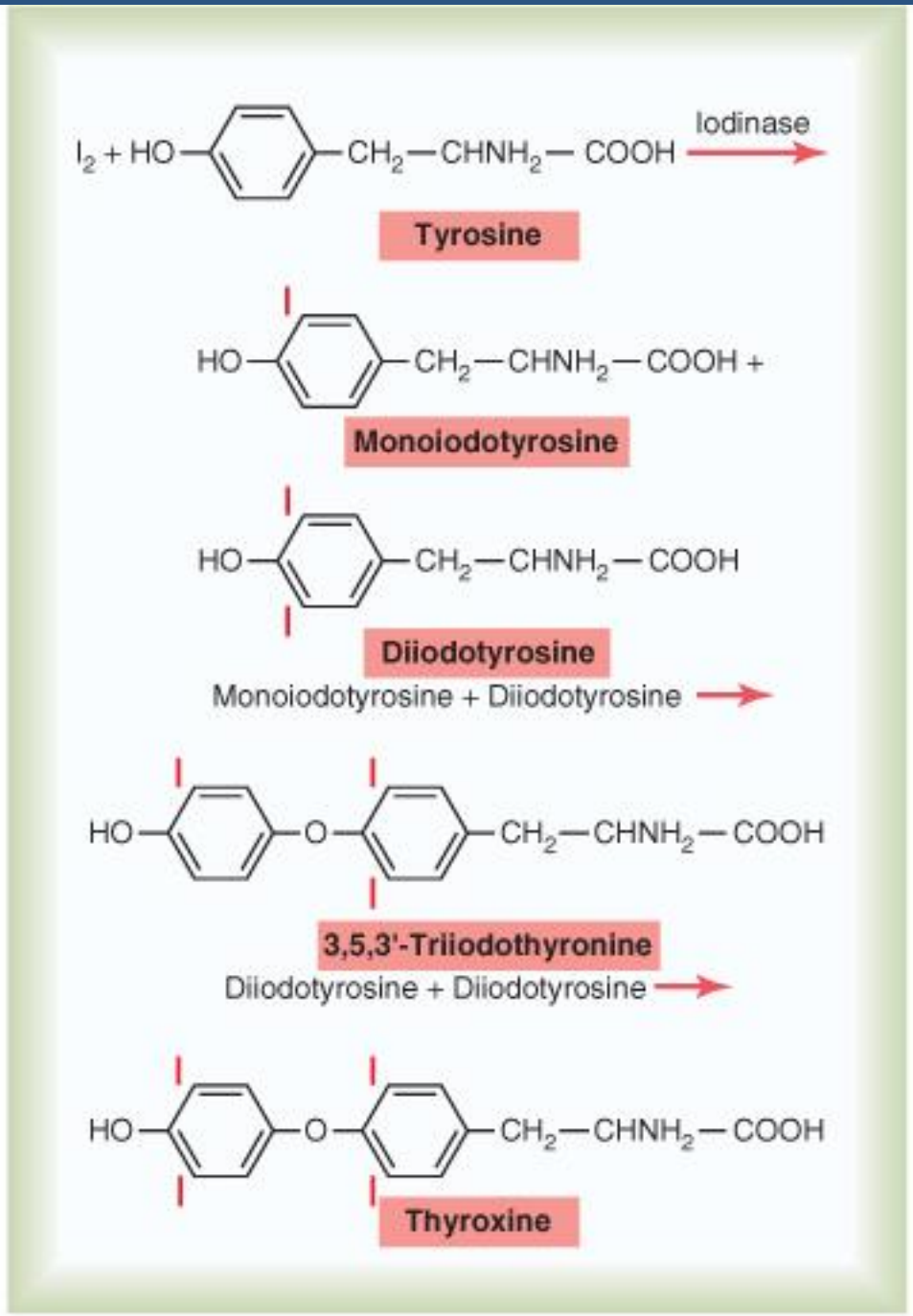
DIT + DIT ⟶ $T_{4\ (faster)}$

DIT + MIT ⟶ T_3

- Catalyzed by thyroid peroxidase.

- It is stored as colloid.

- Is sufficient for 2-3 months.



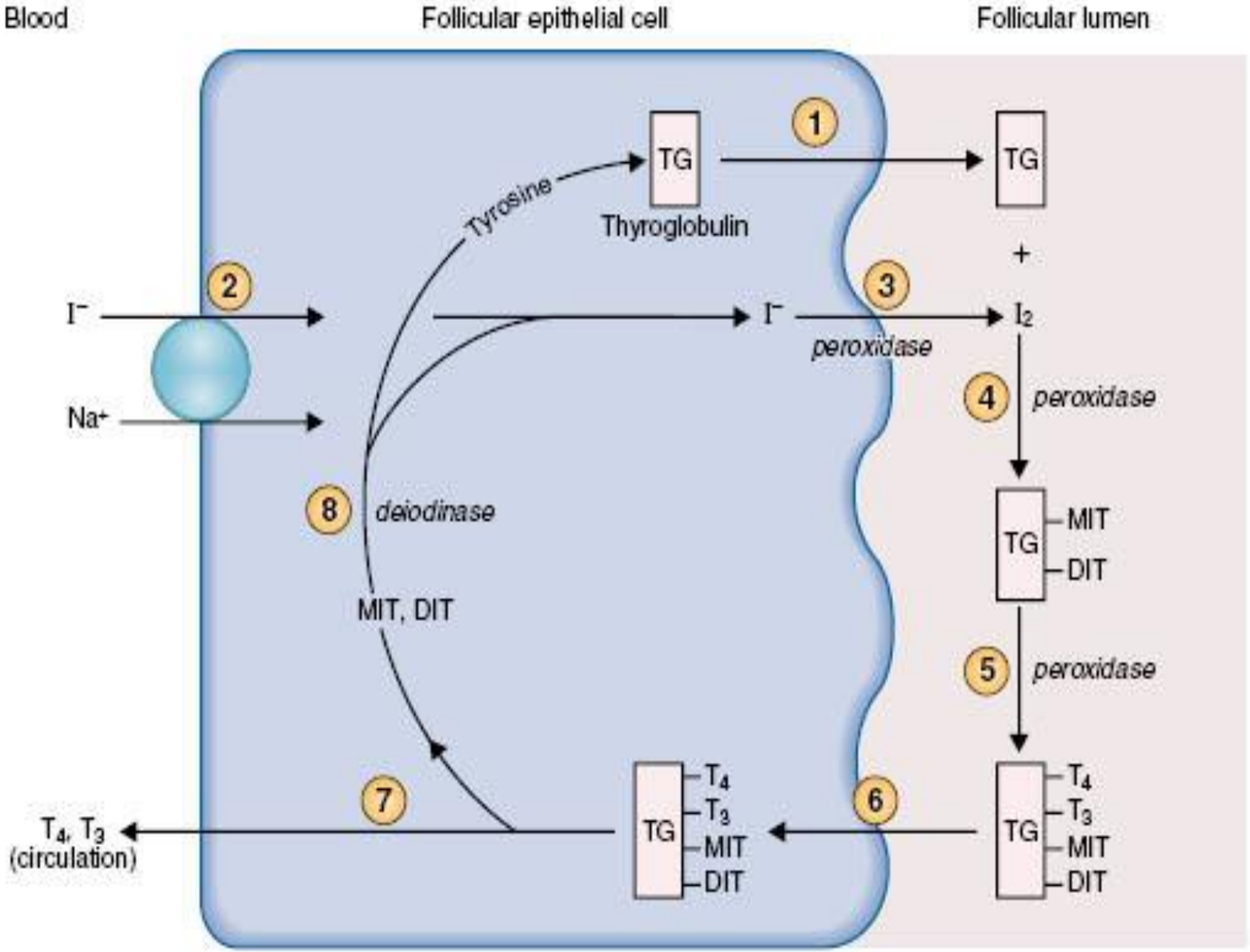
6- Endocytosis of thyroglobulin.

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
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

	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- Bound:

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

- The reminder is bound to albumin.

2- Unbound (Free):

0.03% of T_4

0.3% of T_3.

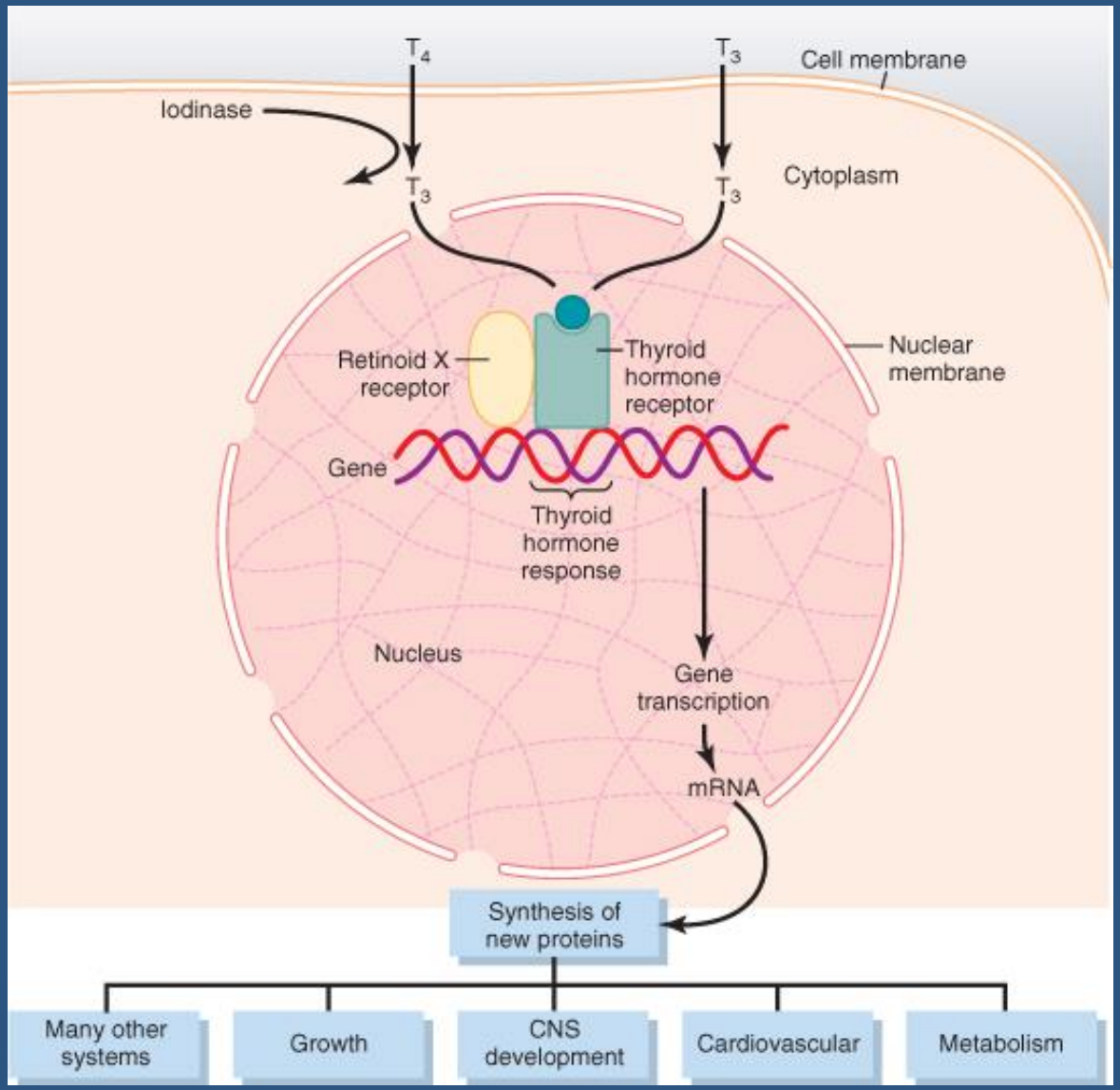
In hepatic failure:

↓ 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.

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

ACTION OF THYROID HORMONES *cont.*

1- Basal Metabolic Rate (BMR):

- Is the energy requirement under basal condition (mental and physical rest 12-18 hours after a meal).

- Complete lake of thyroid hormones → 40-50%↓ 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 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- 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 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 β-adrenergic receptors.

2- Direct induction of:

a) myocardial β-adrenergic receptors.

b) sarcoplasmic reticulum.

c) 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.

lake of secretion ⟶ constipation.

10- Effects on Autonomic nervous system:

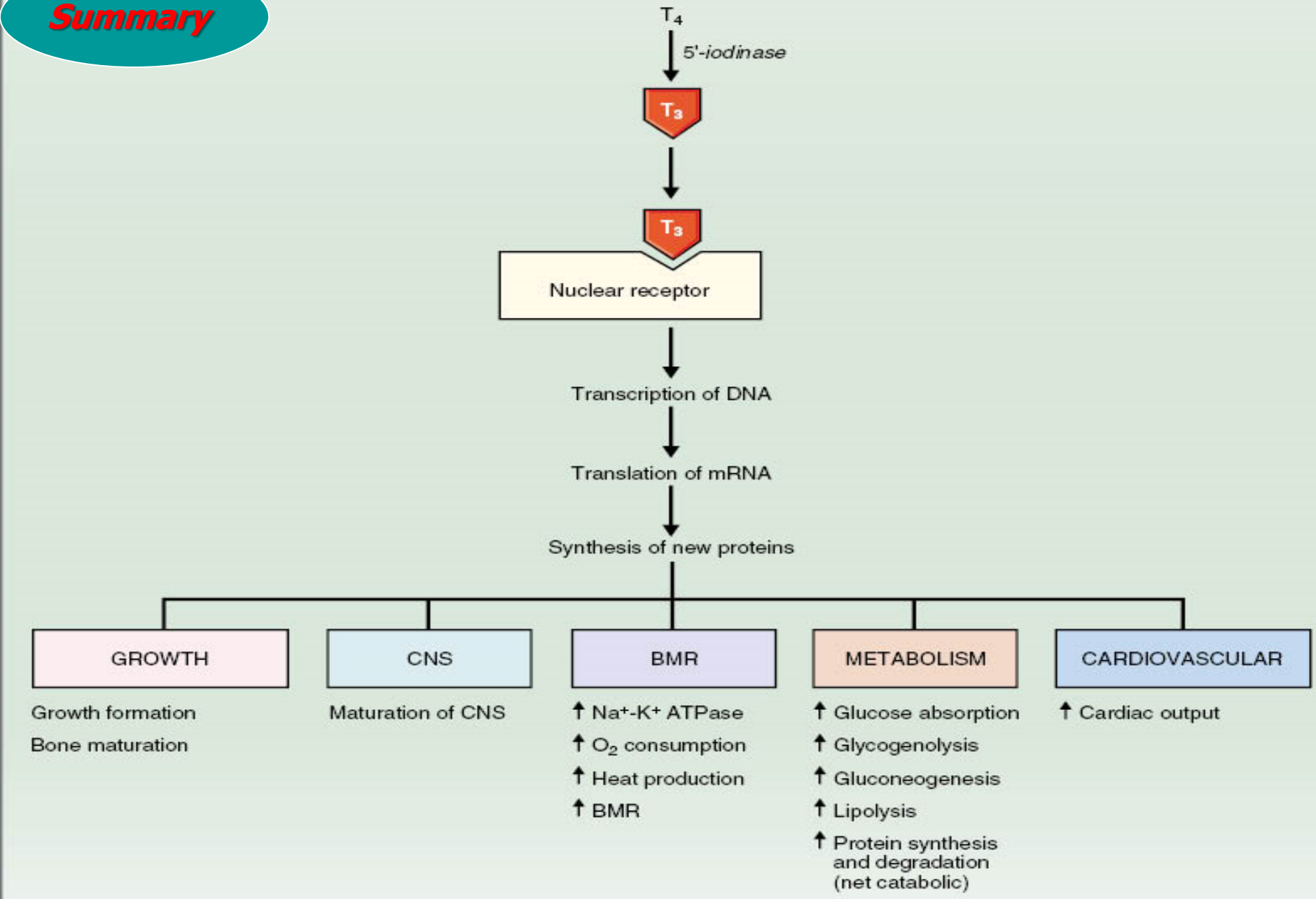
Produced the same action as *catecholamines* via β-adrenergic receptors including:

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.

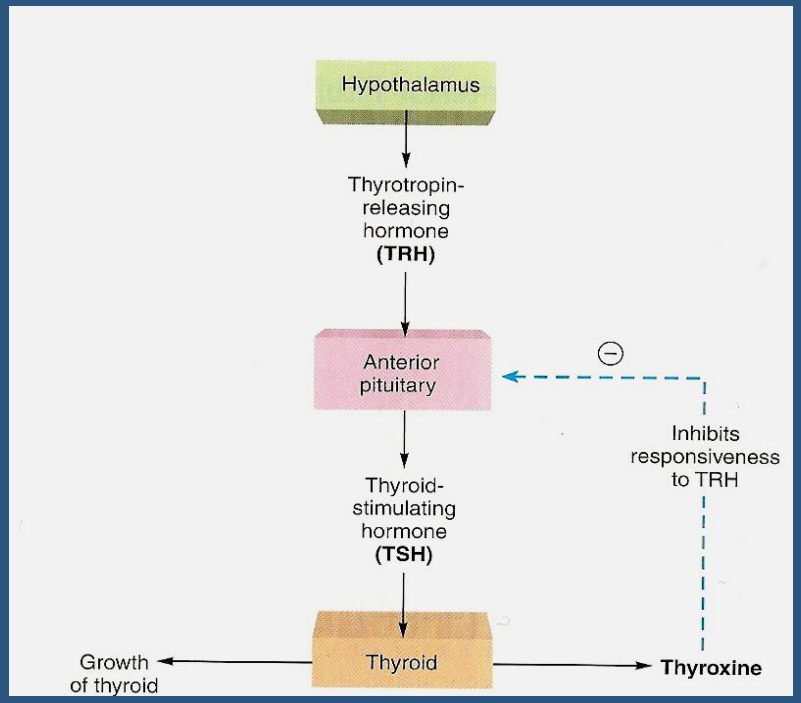
Summary

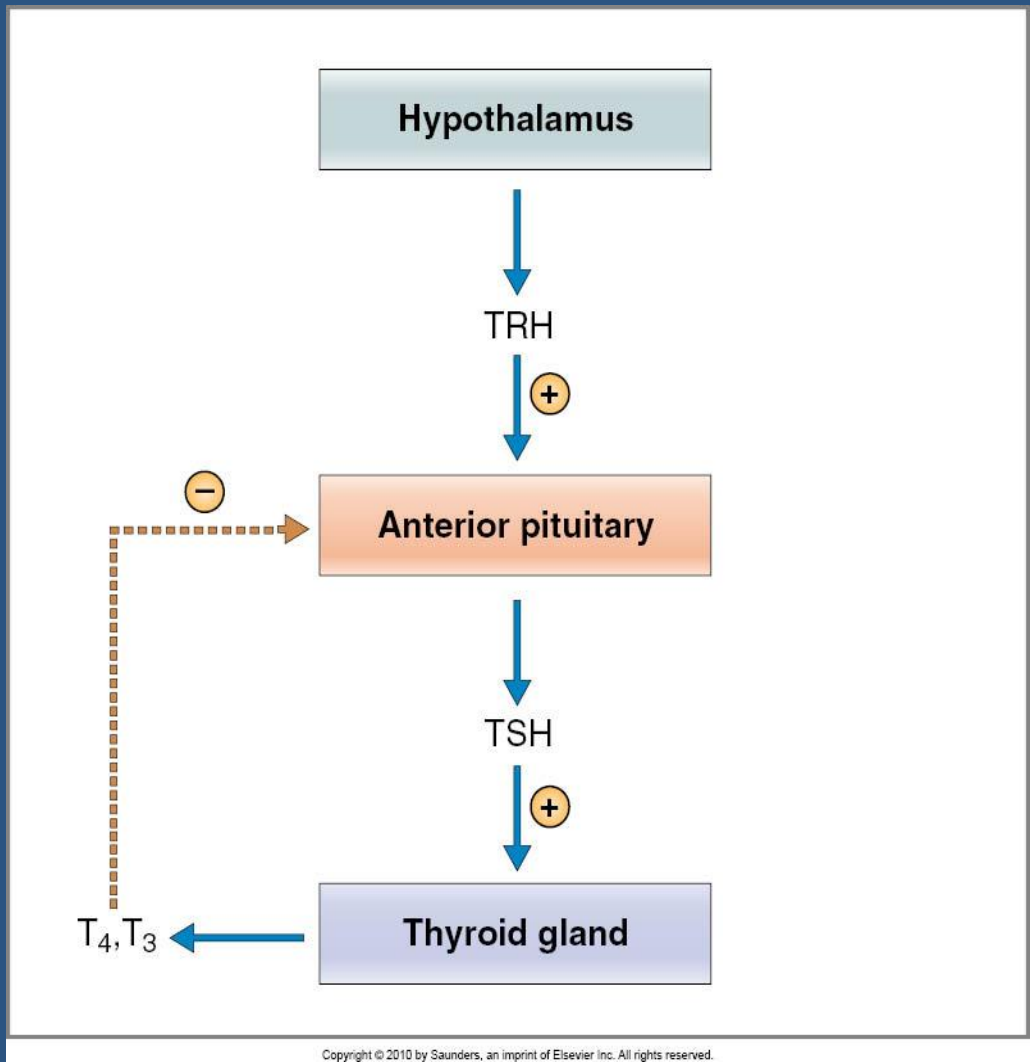
ACTIONS OF THYROID HORMONES

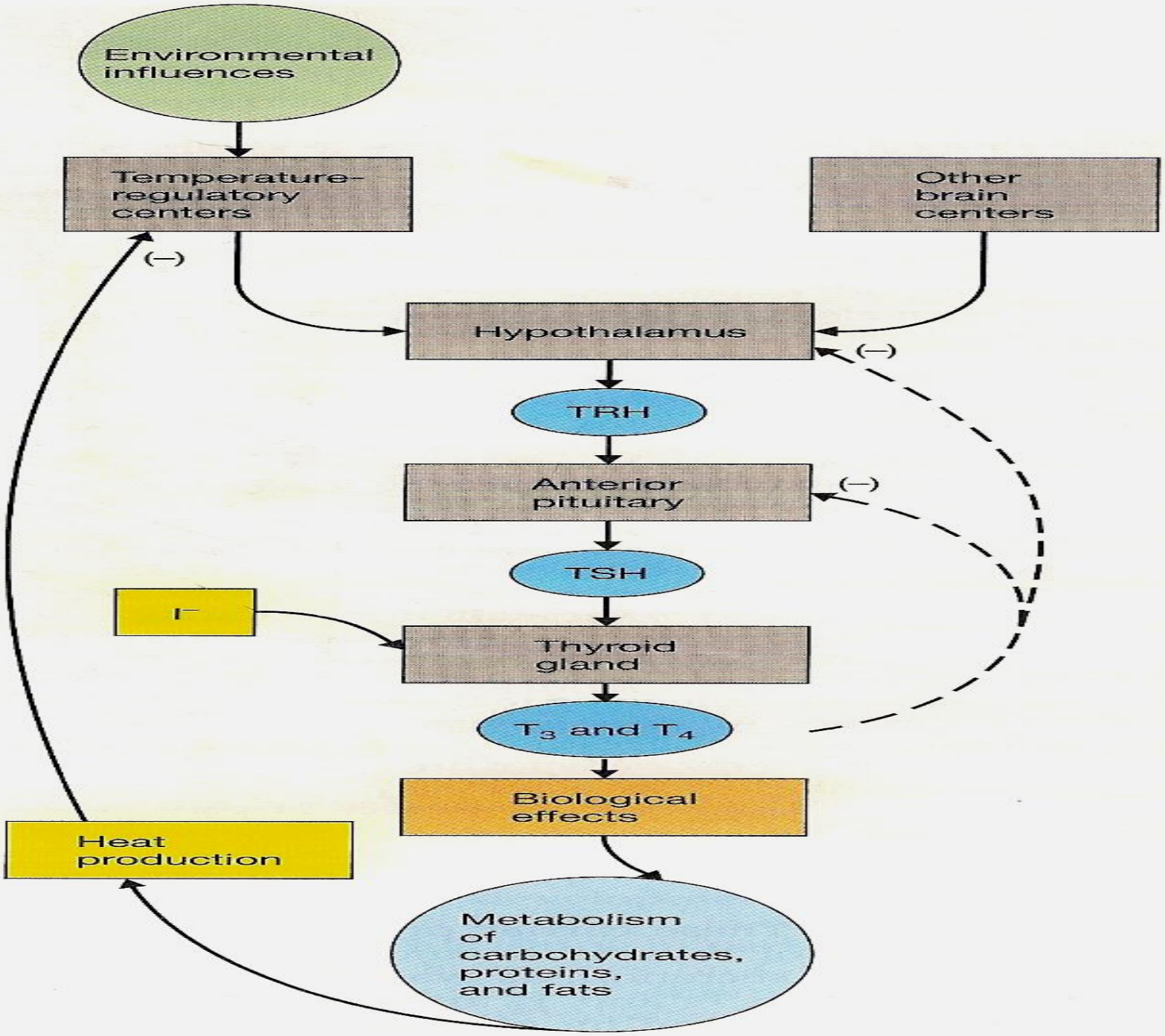


REGULATION OF HORMONES SECRETION

- 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.

- 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	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)

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:

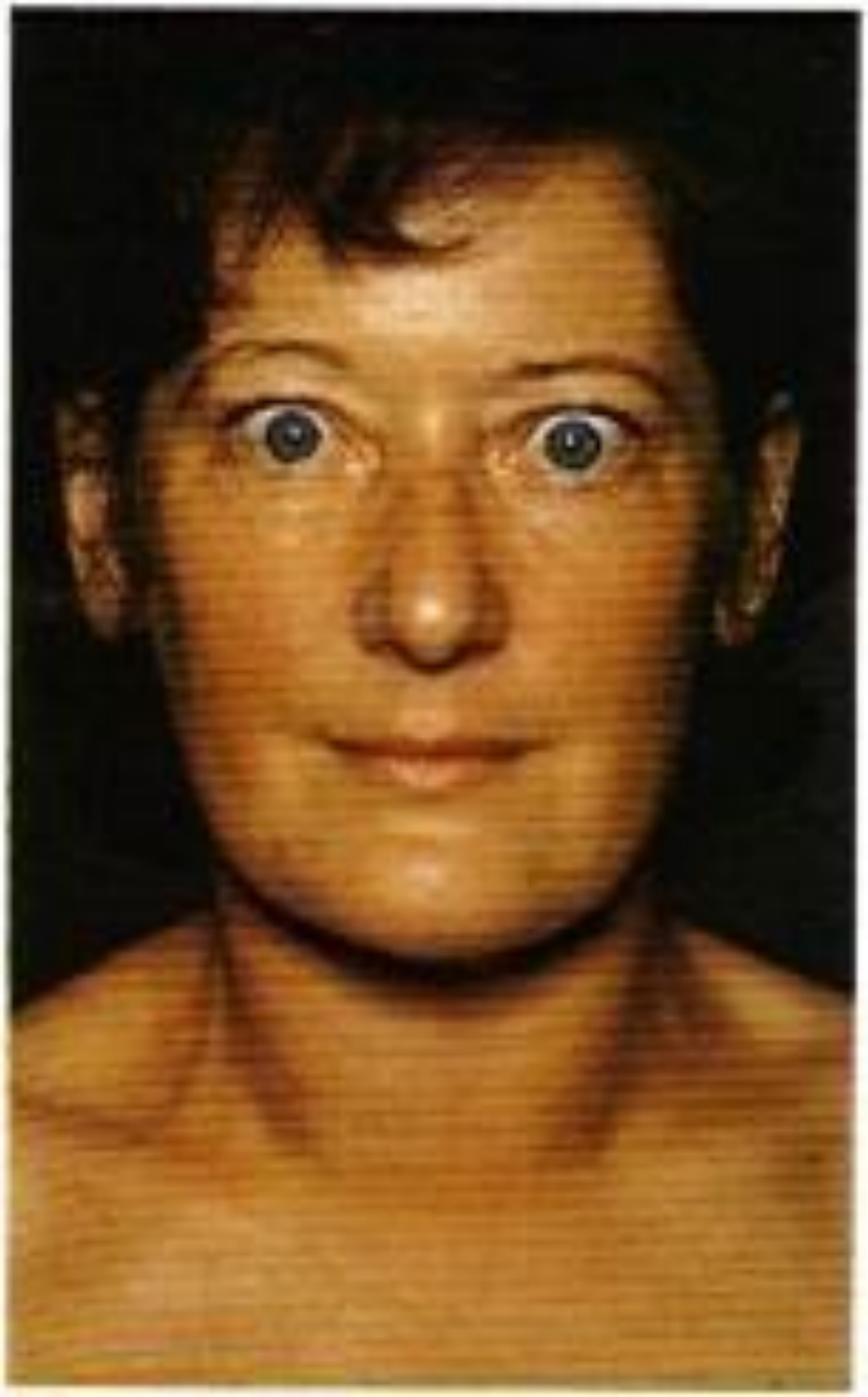
- ↑ glomerular filtration rate.

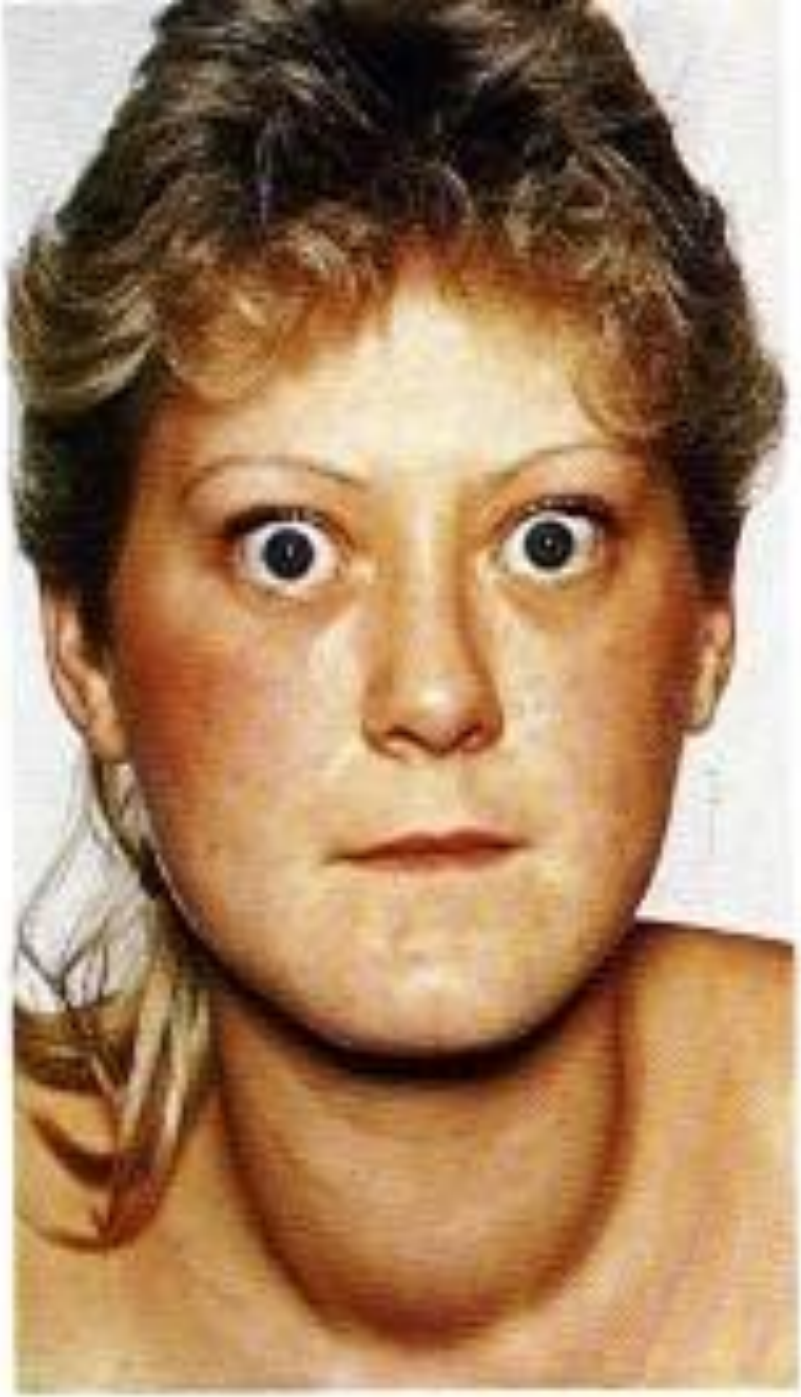
8- Exophthalmos:

- 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. propylthiourcal

- 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).

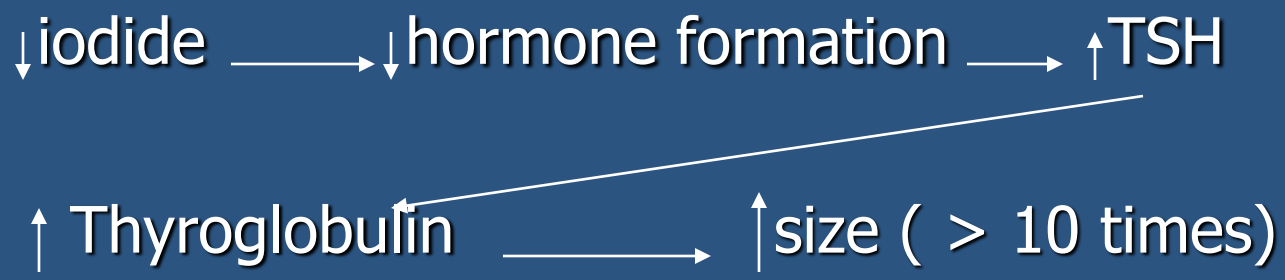
CAUSES

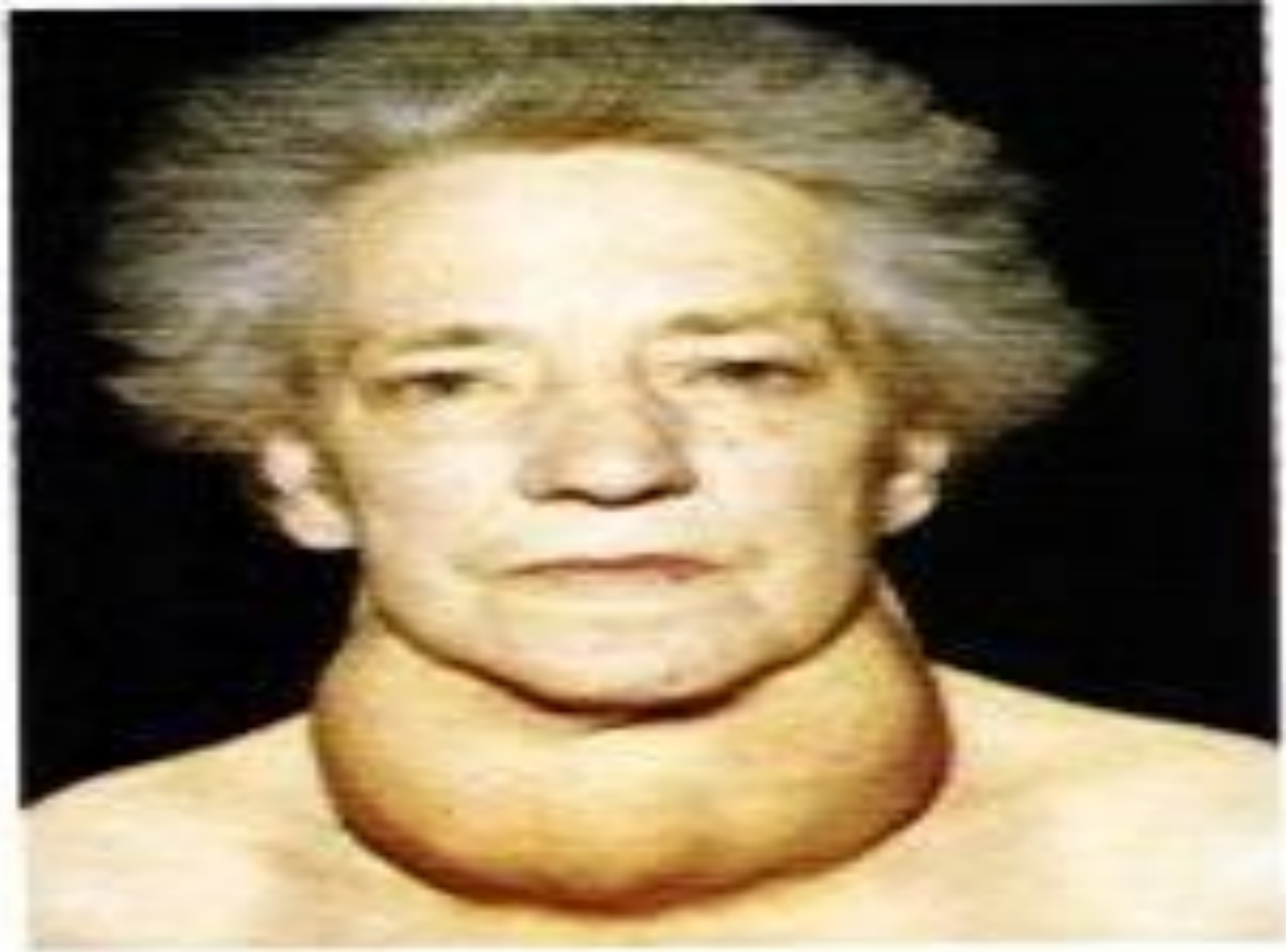
1- inherited abnormalities of thyroid hormone synthesis :

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

2- Endemic Colloid Goiter:

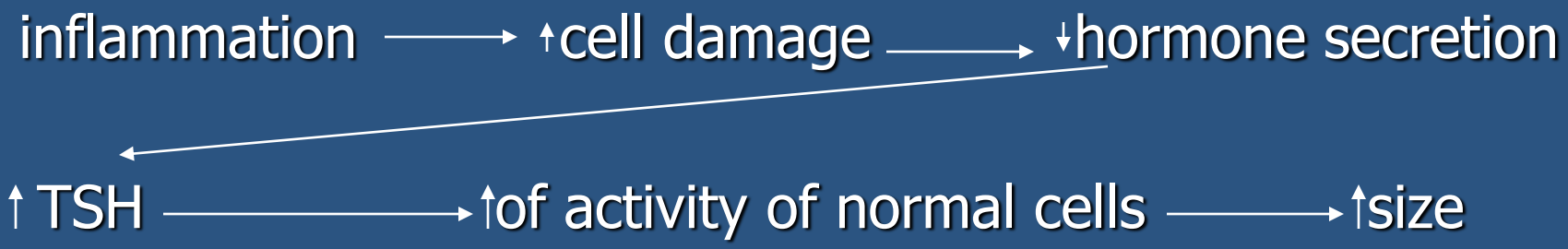
- before table salt.





3- Idiopathic Nontoxic Colloid Goiter:

- I 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
- 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:

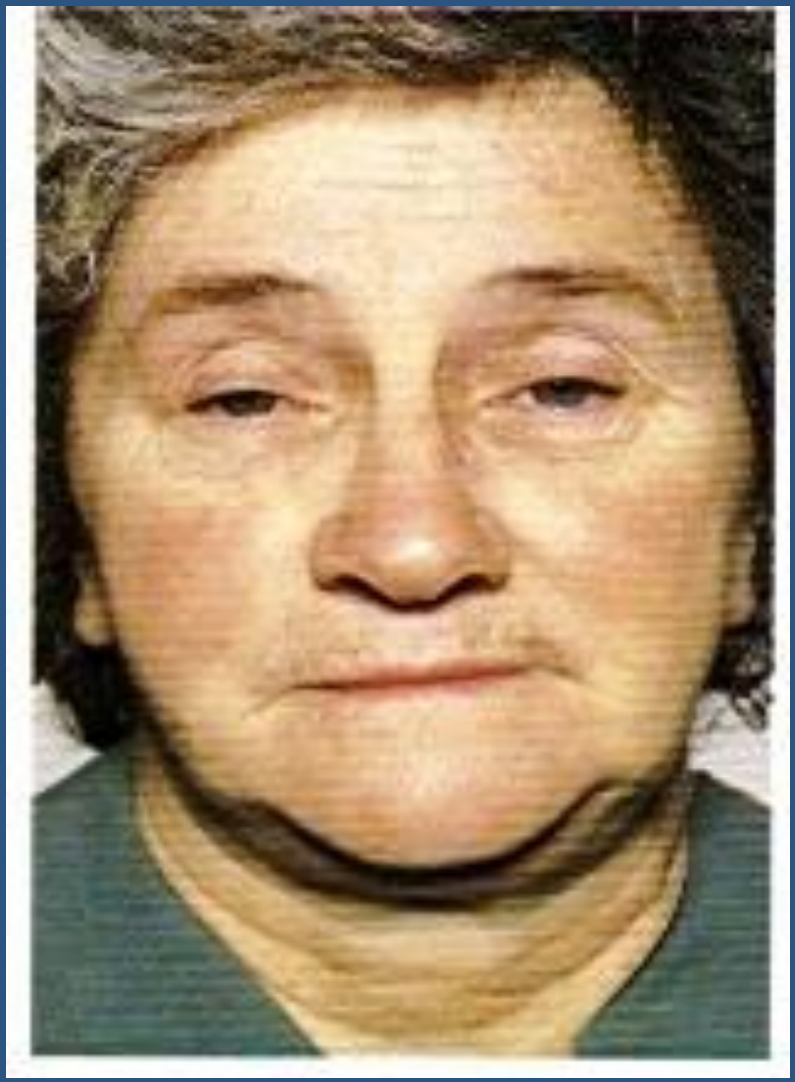
- constipation
- increase weight.

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 µg.
- Increase to 200 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.

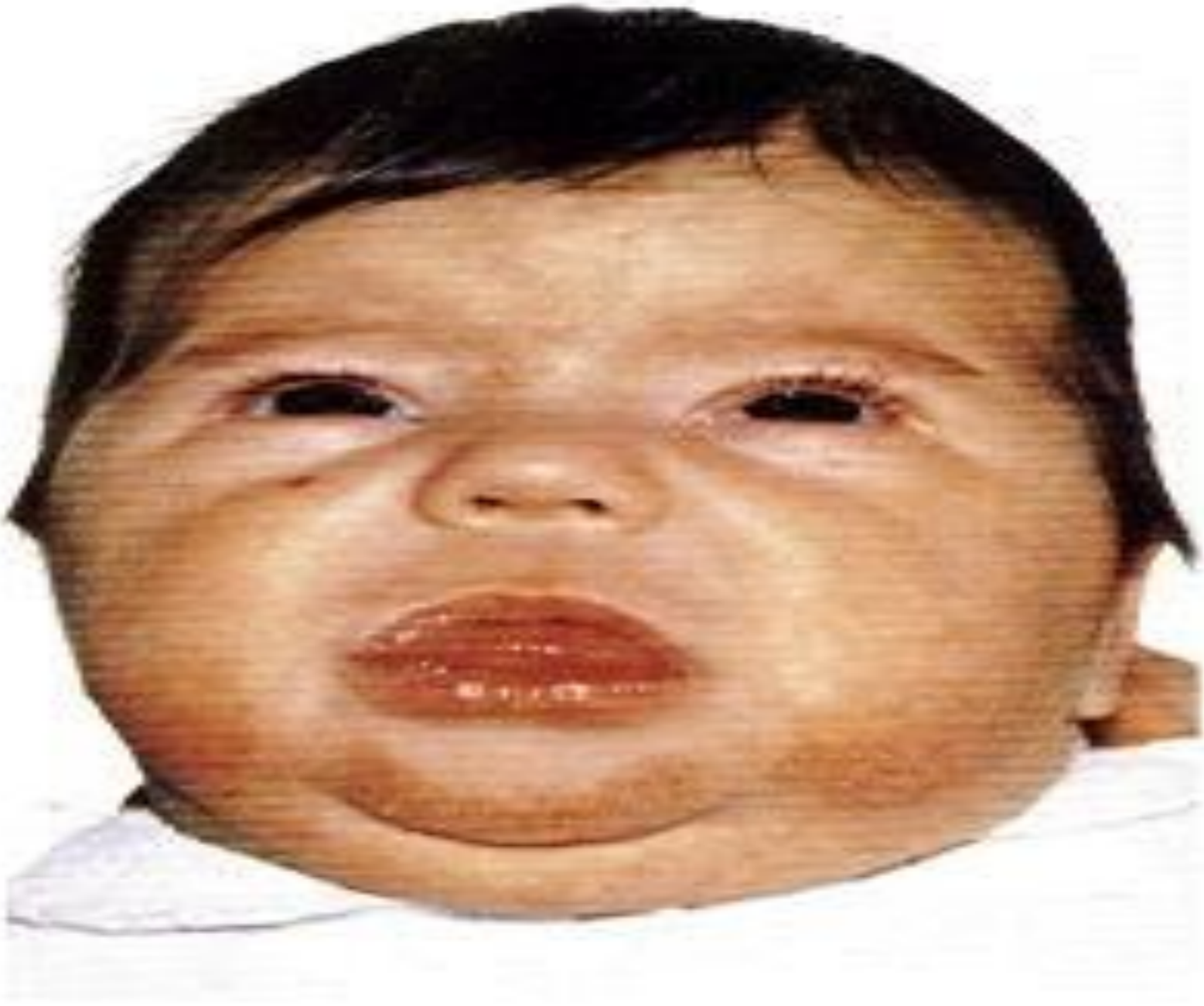
2- Protruding tongue.

3- Dwarf with short limbs.

4- Mental retardation.

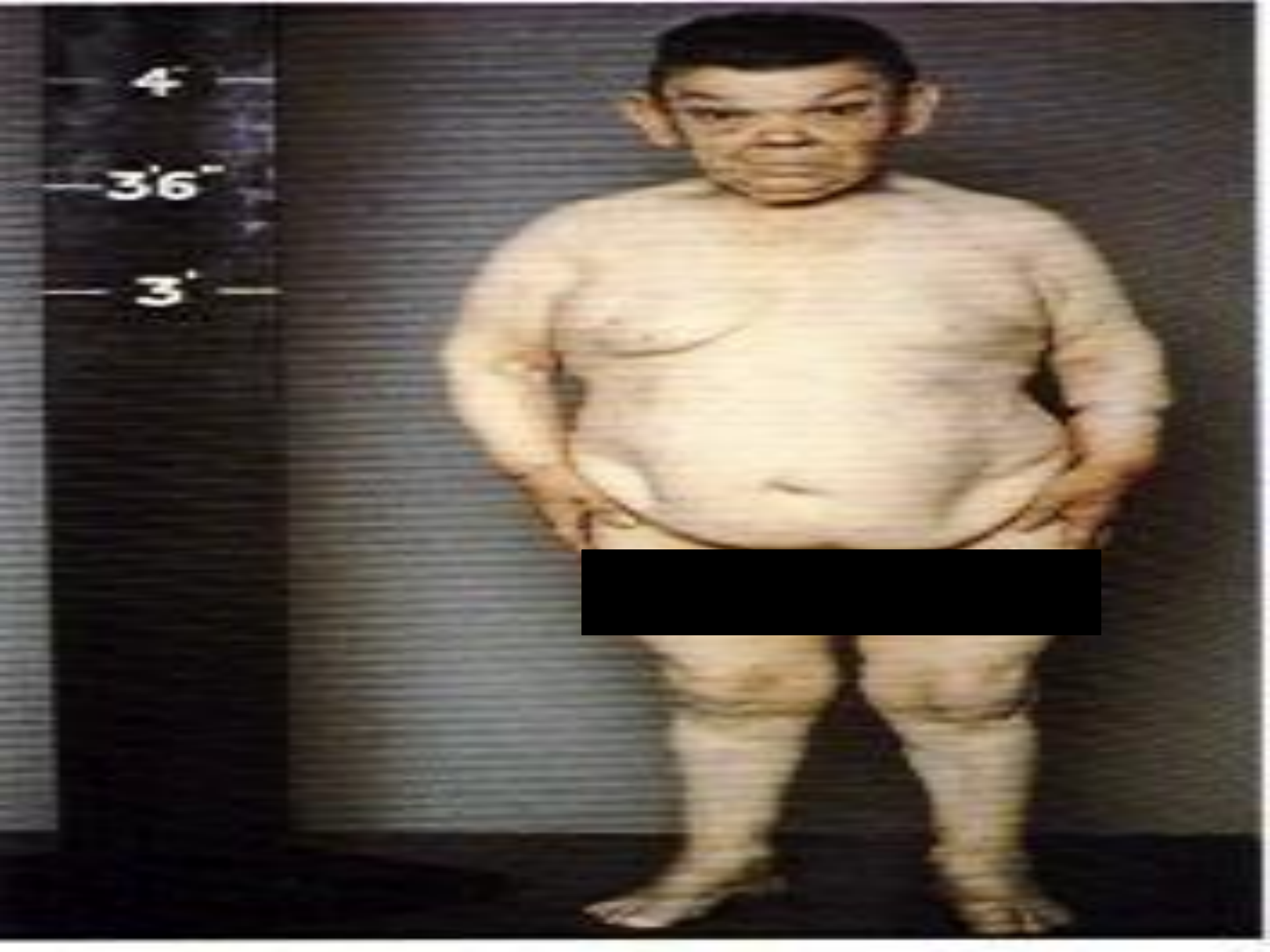
5- Often umbilical hernia.

6- teeth.



TREATMENT

Changes are irreversible unless treatment is given early.


4'
3'6"
3'

Calculate your BMR:

Men: BMR = 66 + (13.7 X wt in kg) + (5 X ht in cm) - (6.8 X age in years)

Women: BMR = 655 + (9.6 X wt in kg) + (1.8 X ht in cm) - (4.7 X 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**