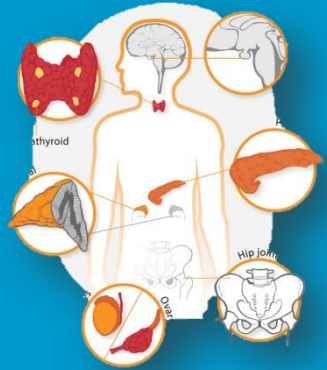


[lecture 2]

# Thyroid Hormones and Thermogenesis



Endocrine system



## The Objectives

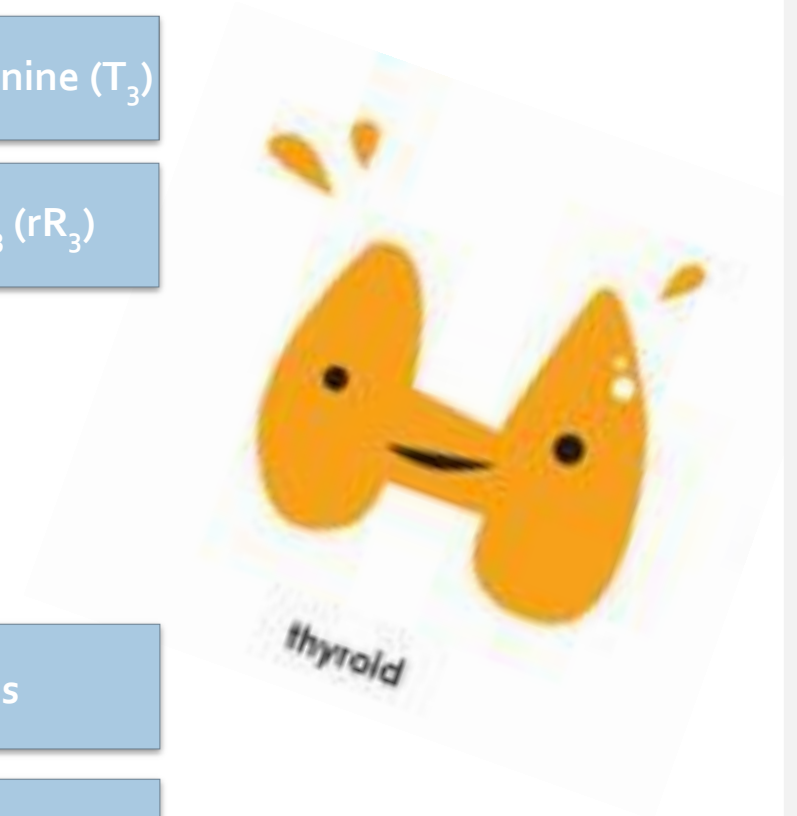
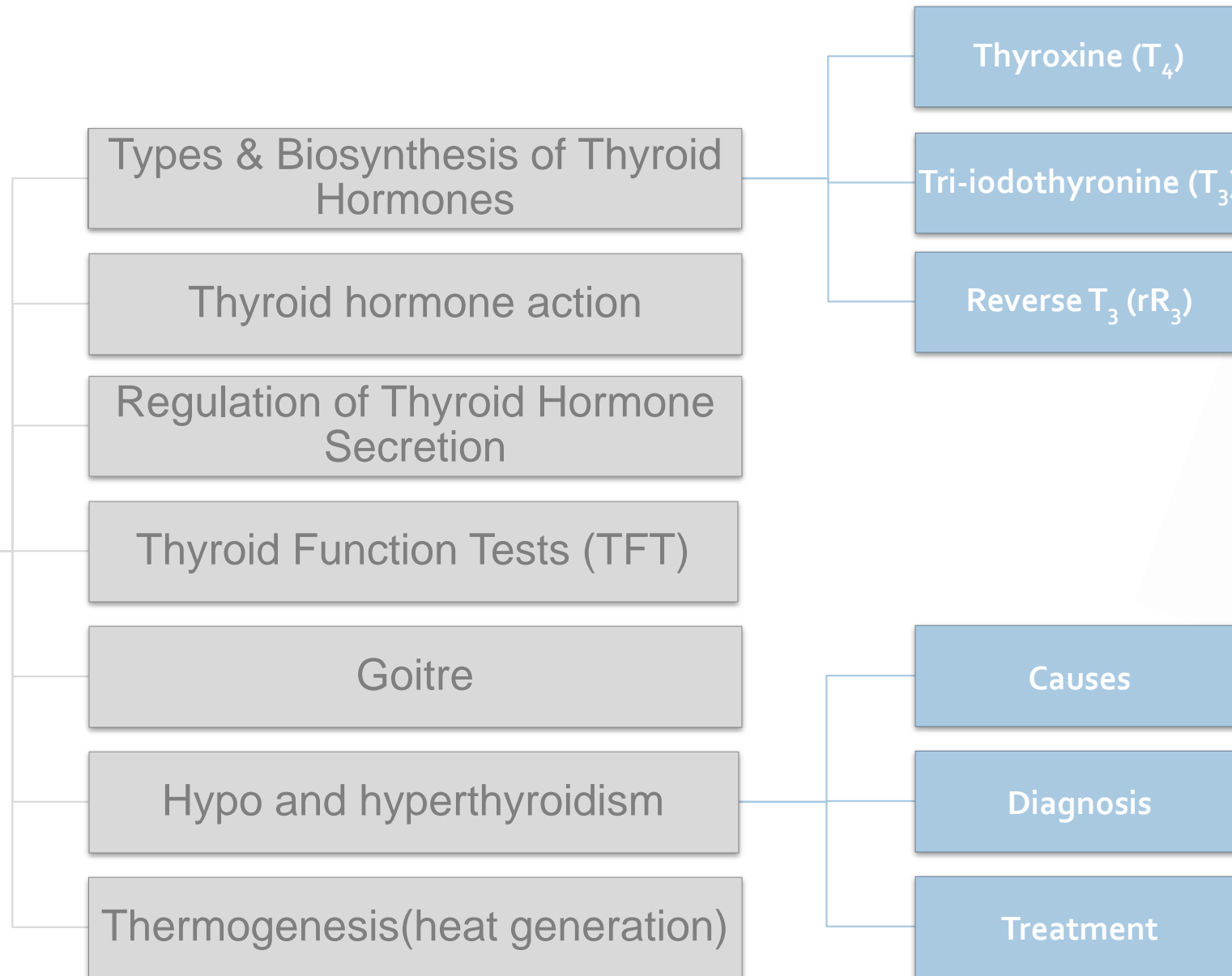
- Types and biosynthesis of thyroid hormones
- Thyroid hormone action
- Regulation of thyroid hormones
- Thyroid function tests
- Goitre
- Hypo and hyperthyroidism
  - Causes
  - Diagnosis
  - Treatment
- Thermogenesis

Red =  
Important

Blue =  
explain

Green =  
addition  
notes

# Mind Map



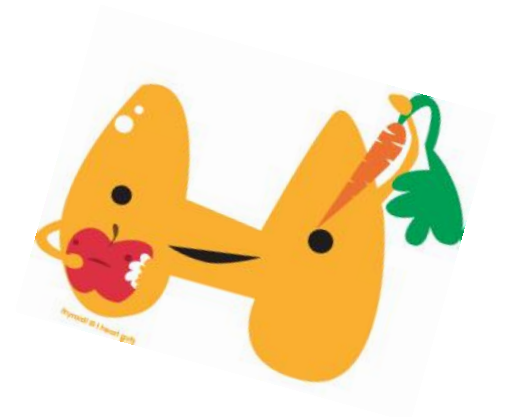
# Types & Biosynthesis of Thyroid Hormones

- ❖ Thyroxine ( $T_4$ ) and tri-iodothyronine ( $T_3$ )
- ❖ Synthesized in the thyroid gland by:
  - Iodination
  - Coupling of two tyrosine molecules
  - Attaching to thyroglobulin protein
- ❖ Thyroid gland mostly secretes  $T_4$
- ❖ Peripheral tissues (liver, kidney, etc.) de-iodinate  $T_4$  to  $T_3$  (active form)
- ❖  $T_3$  is the more biologically active form
- ❖  $T_4$  can be converted to  $rT_3$  (reverse  $T_3$ ) – inactive form ( $rT_3$  will be disturbed in non-thyroidal disease ).
- **Thyroxin Binding globulin** (TBG)-bound (70%)
- Albumin-bound (25%)
- Transthyretin (prealbumin)-bound (5%)
- ❖ The unbound (free) form of  $T_4$  and  $T_3$  are biologically active
- ❖ Plasma [ $T_4$ ]:100 nmol/L
- ❖ Plasma [ $T_3$ ]:2 nmol/L
- ❖ **Thyroid hormones has tyrosine amino acid**

Don't confuse between Thyroglobulin protein which is present in thyroid gland carrying T hormones and Thyroxin Binding globulin the transporter in the blood

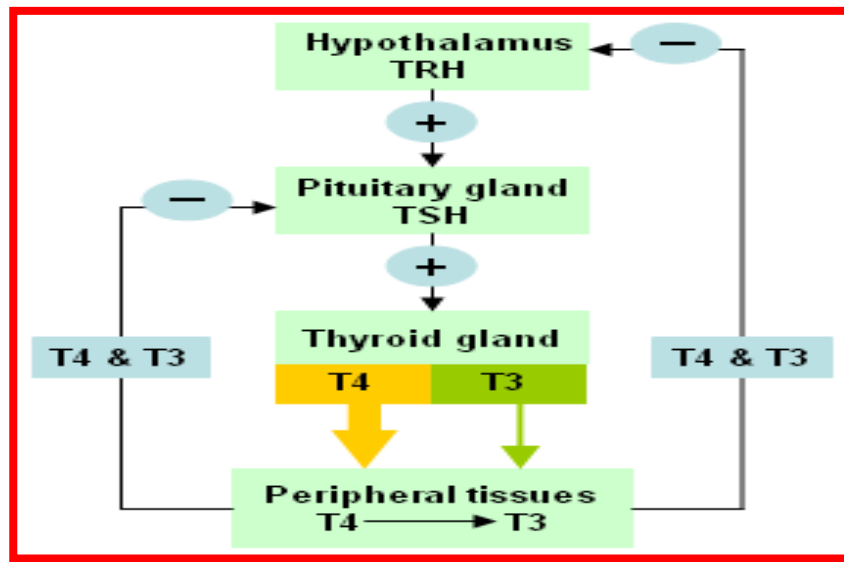
## Thyroid hormone action

- ❖ **Essential for normal maturation and metabolism of all body tissues**
- ❖ Affects the rate of protein, carbohydrate and lipid metabolism
- ❖ Regulates hermogenesis
- ❖ Untreated congenital hypothyroidism → **permanent brain damage**
- ❖ Hypothyroid children have:
  - delayed skeletal maturation → **short stature**
  - **delayed puberty**
- ❖ Hypothyroid patients have **high serum cholesterol** due to:
  - Down regulation of LDL receptors on liver cells
  - Failure of sterol excretion via the gut



# Regulation of Thyroid Hormone Secretion

- ❖ High thyroid hormone levels suppress TRH & TSH.
- ❖ Low thyroid hormone levels stimulate TRH & TSH to produce more hormone.
- ❖ The hypothalamic-pituitary-thyroid axis regulates thyroid secretion.
- ❖ The hypothalamus senses low levels of  $T_3/T_4$  and releases thyrotropin releasing hormone (TRH).
- ❖ TRH stimulates the pituitary to produce thyroid stimulating hormone (TSH).
- ❖ TSH stimulates the thyroid to produce  $T_3/T_4$  until levels return to normal.
- ❖  $T_3/T_4$  exert negative feed back control on the hypothalamus and pituitary.
- ❖ Controlling the release of both TRH and TSH.



# Thyroid Function Tests (TFT)

## Thyroid Function Tests (TFT)

### TSH measurement:

- Indicates thyroid status
- Sensitive, **first-line test**

### Total $T_4$ or free $T_4$ :

- Indicates thyroid status
- **Monitors thyroid treatment** (both anti-thyroid and thyroid supplement treatment)
- During the early treatment of hyperthyroidism, TSH may take up to 8 weeks to adjust to new level during treatment. ( **due to this, we cant use TSH measurement in monitoring treatment until it back to normal and** )
- Some labs only measure TSH as first-line test

### Total $T_3$ or free $T_3$ :

- Rise in  $T_3$  is independent of  $T_4$
- In some patients only  $T_3$  rises ( $T_4$  is normal):  **$T_3$  toxicosis**
- For earlier identification of  $T_3$  thyrotoxicosis

### Antibodies:

- Diagnosis and monitoring of **autoimmune** thyroid disease (Hashimoto's thyroiditis); anti-thyroid peroxidase in hypothyroidism
- Diagnosis of Grave's disease: Antibodies against TSH receptors on thyroid cells.

# Goitre

❖ Enlarged thyroid gland

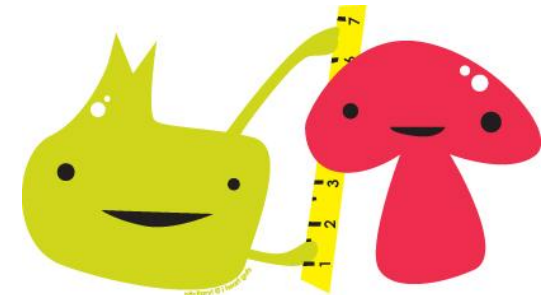
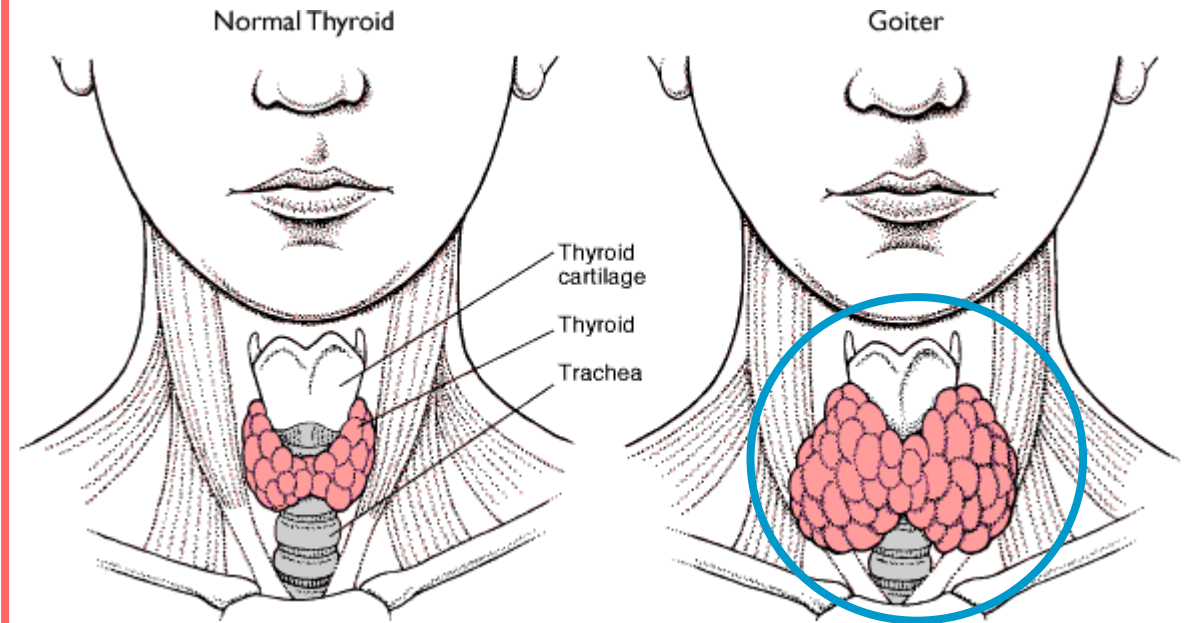
It is an anatomical definition rather than physiological

Functionally; Goitre may be associated with:

- Hypofunction
- Hyperfunction
- Normal concentration of thyroid hormones (euthyroid)

## Causes:

- Iodine deficiency
- Selenium deficiency
- **Autoimmune:**
  - Hashimoto's thyroiditis (hypothyroidism)
  - Grave's disease (hyperthyroidism)
- Congenital hypothyroidism
- Thyroid cancer

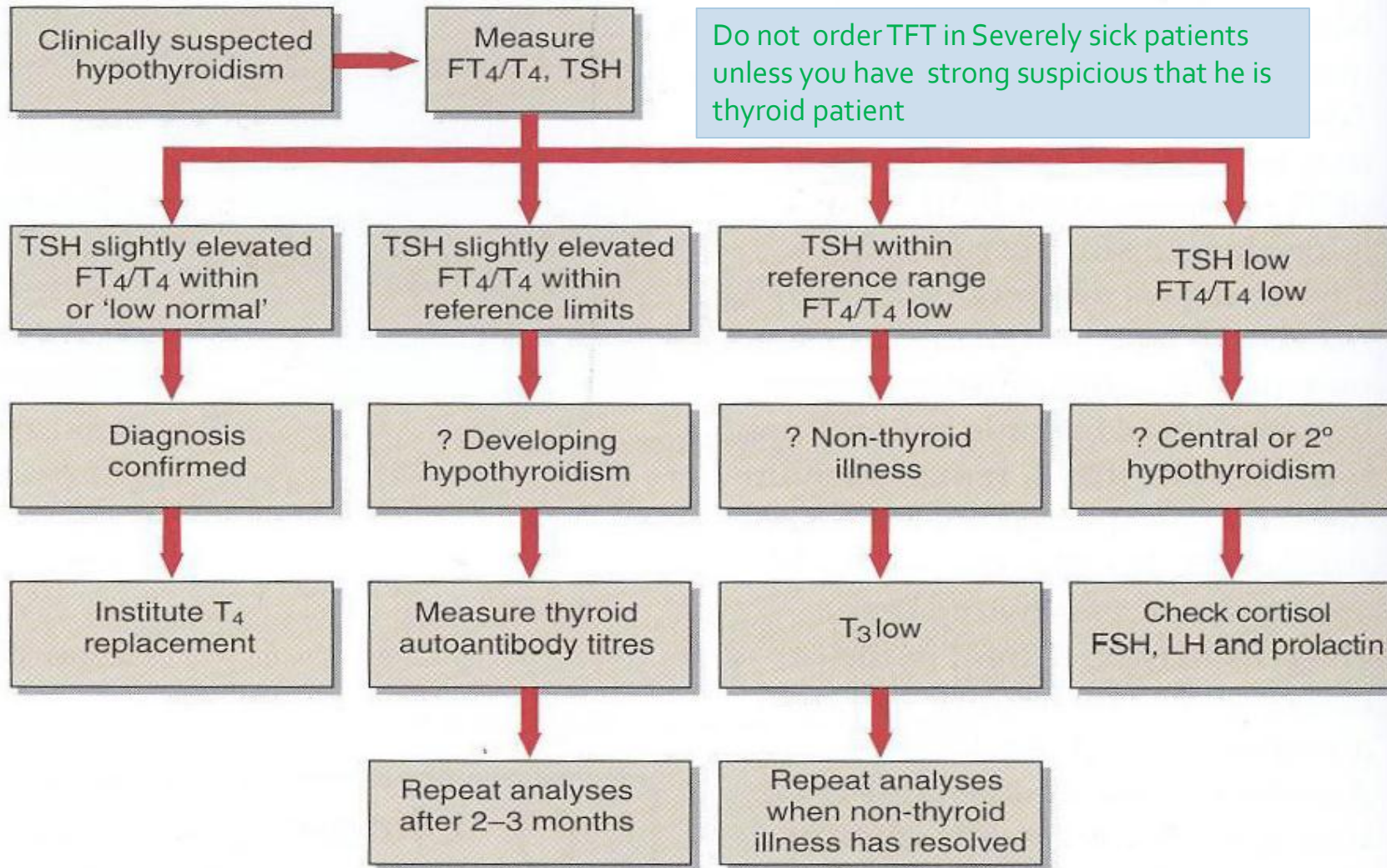


	Hypothyroidism	Hyperthyroidism
	<p>Deficiency of thyroid hormones</p> <p><b>Primary hypothyroidism:</b> Failure of thyroid gland (Elevated TSH )</p> <p><b>Secondary hypothyroidism:</b> Failure of the pituitary to secrete TSH (rare) Failure of the hypothalamic-pituitary-thyroid axis ( it affects adrenal ,FSH and LH also )</p>	<p><b>Primary</b> Over-activity of the thyroid gland → ↑secretion of thyroid hormones</p> <p>Tissues are exposed to ↑ levels of thyroid hormones (thyrotoxicosis)</p> <p><b>Secondary</b> to ↑ pituitary stimulation of the thyroid gland</p>
Causes	<ul style="list-style-type: none"> <li>• Hashimoto’s disease (autoimmune destruction of the thyroid gland )</li> <li>• Radioiodine or surgical treatment of hyperthyroidism (iatrogenic)</li> <li>• Drug effects (e.g. lithium and tyrosin kinase inhibitors)</li> <li>• TSH deficiency</li> <li>• Congenital defects</li> <li>• Severe iodine deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Grave’s disease</li> <li>• Toxic multinodular goitre</li> <li>• Thyroid adenoma</li> <li>• Thyroiditis (inflammation destruction )</li> <li>• Intake of iodine / iodine drugs</li> <li>• Excessive intake of T<sub>4</sub> and T<sub>3</sub> (iatrogenic) or (Factitious hyperthyroidism)</li> </ul>
Clinical features	<ul style="list-style-type: none"> <li>• Tiredness</li> <li>• Cold intolerance</li> <li>• Weight gain</li> <li>• Dry skin</li> </ul>	<ul style="list-style-type: none"> <li>•Weight loss with normal appetite</li> <li>•Sweating / heat intolerance</li> <li>•Fatigue</li> <li>•Palpitation / agitation, tremor</li> <li>•Angina, heart failure</li> <li>•Diarrhea</li> <li>•Eyelid retraction and lid lag</li> </ul>





# Hypothyroidism



## Non-thyroidal illness

- In some diseases, the normal regulation of TSH, T<sub>3</sub> and T<sub>4</sub> secretion and metabolism is disturbed.
- Most of T<sub>4</sub> is converted to rT<sub>3</sub> (inactive)
- Causing thyroid hormone deficiency
- TSH secretion is suppressed
- Secretion of T<sub>4</sub> and T<sub>3</sub> is decreased



Dr. reem said this diagram is not important , just read it

Fig. 1 Strategy for the biochemical investigation of suspected hypothyroidism.



# Hyperthyroidism

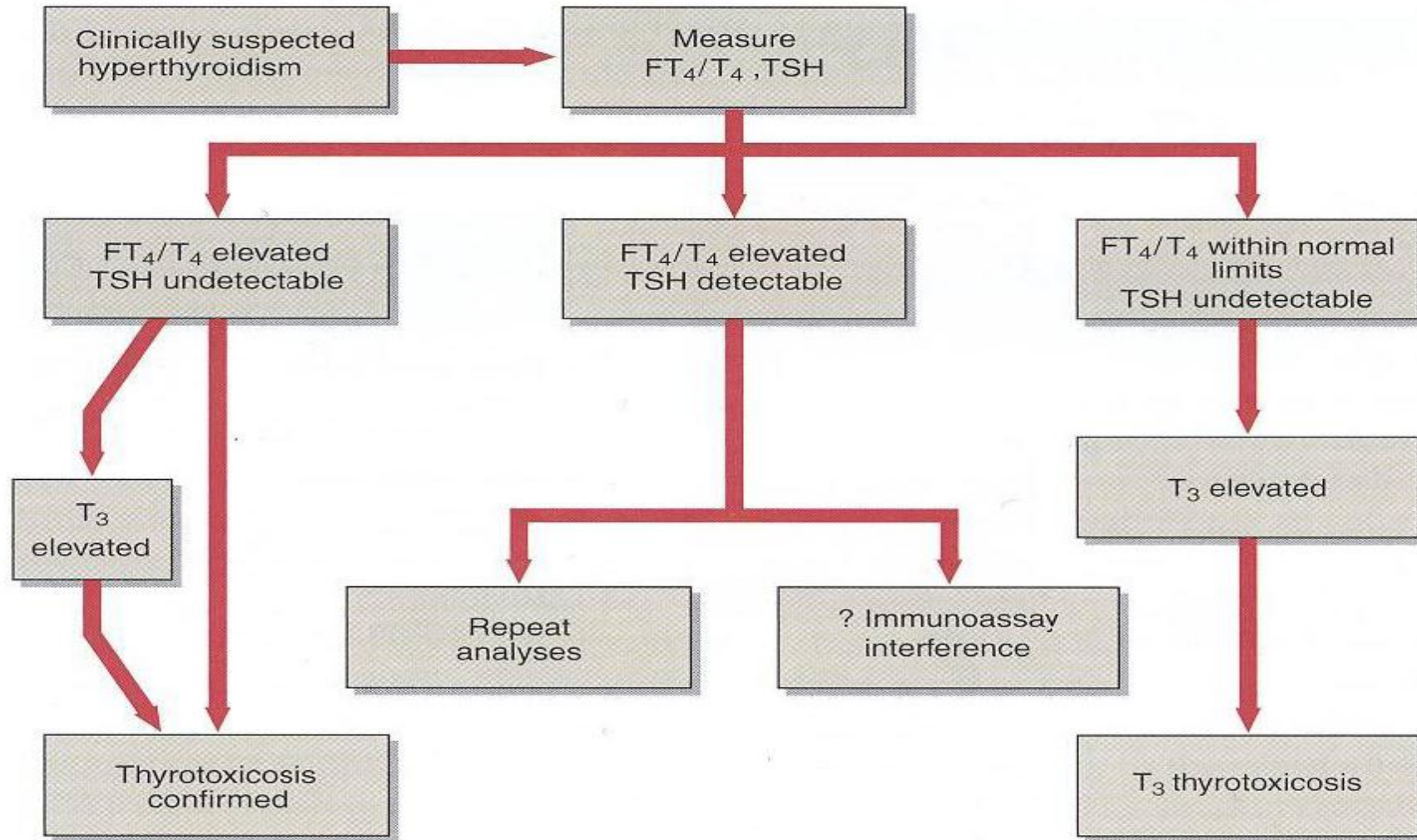


Fig. 2 Strategy for the biochemical investigation of suspected hyperthyroidism.

# Thermogenesis

Thermogenesis is the process of *heat production affected by thyroid hormone*.

- Ⓢ **Thyroid hormone has an active role in thermogenesis**
- Ⓢ About 30% thermogenesis depends on thyroid
- Ⓢ Thyroid regulates metabolism and ATP turnover
- Ⓢ It increases ATP synthesis and consumption by many possible mechanisms
- Ⓢ  $\text{Na}^+/\text{K}^+$  gradient requires ATP to maintain it
- Ⓢ The gradient is used to transport nutrients inside the cell
- Ⓢ Thyroid reduces  $\text{Na}^+/\text{K}^+$  gradient across the cell membrane by increasing metabolism (more nutrient transport in the cell)
- Ⓢ This increases the demand for ATP to maintain the gradient
- Ⓢ ATP synthesis and consumption is increased that produce heat

## From Male Slides

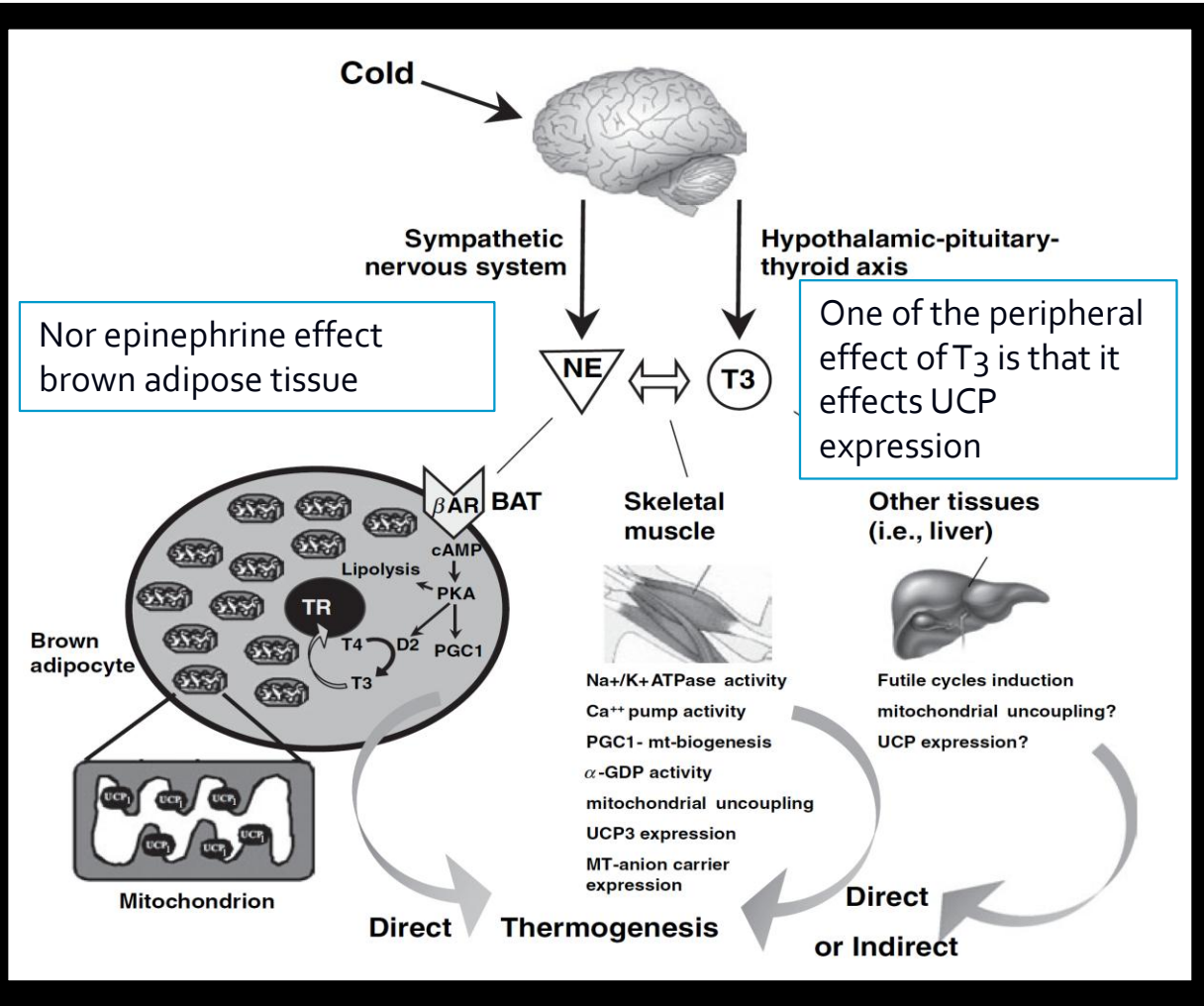
- Thyroid hormones cause increased proton leak into the matrix across the inner mitochondrial membrane.
- Protons are pumped back into the matrix by uncoupling proteins (UCPs) without ATP synthesis.
- This process produces heat.
- The mitochondria of brown adipose tissue contain UCP-1 (thermogenin).
- Produces heat via uncoupling of electron transport chain and oxidative phosphorylation.

- **UCP<sub>1</sub>** is the best known and best characterized of the UCPs, is present in the inner mitochondrial membrane of brown adipose tissue.
- Other UCP are found in the inner mitochondrial membrane of organs and tissues other than the brown adipose tissue (**Ubiquitous distribution**)



# UCP

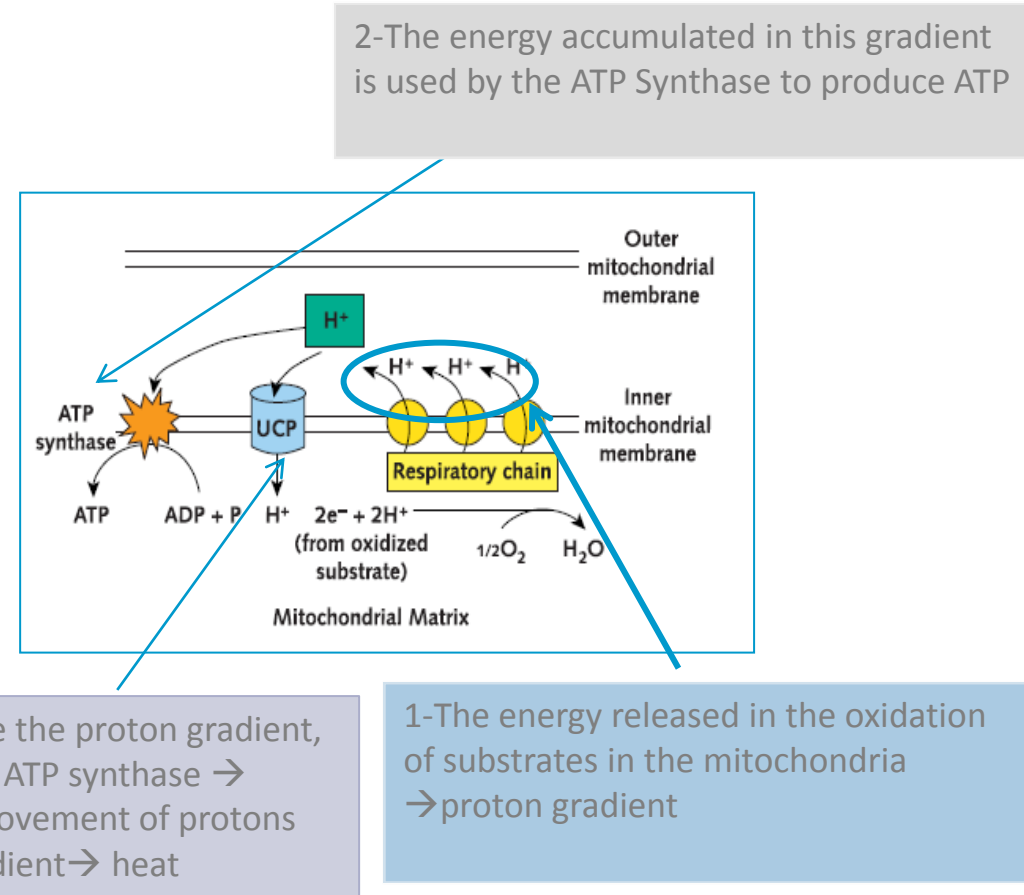
## Mechanism of action of uncoupling proteins (UCP):



Nor epinephrine effect brown adipose tissue

One of the peripheral effect of T<sub>3</sub> is that it effects UCP expression

T<sub>3</sub> helps in release of heat through hypothalamic-pituitary-thyroid axis by controlling UCP



2-The energy accumulated in this gradient is used by the ATP Synthase to produce ATP

3-UCPs reduce the proton gradient, bypassing the ATP synthase → exothermic movement of protons down the gradient → heat

1-The energy released in the oxidation of substrates in the mitochondria → proton gradient

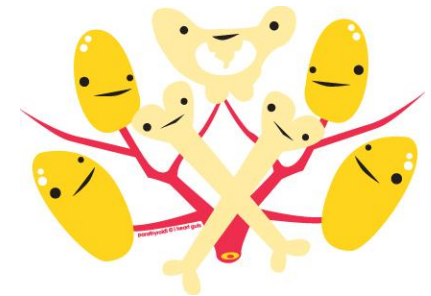
# summary

- Types of thyroid hormones: Thyroxine (T<sub>4</sub>), Tri-iodothyronine (T<sub>3</sub>) & Reverse T<sub>3</sub> (rT<sub>3</sub>)
- T<sub>3</sub>** is the more biologically active form
- Most of **T<sub>4</sub>** is **transported** in plasma bound to **Thyroxin Binding globulin**.
- Thyroid Hormone essential for normal maturation and metabolism of all body tissues
- Regulation of Thyroid Hormone Secretion by thyrotropin releasing hormone (TRH) and Thyroid stimulating hormone(TSH)

## Thyroid Function Tests (TFT):

- **TSH measurement:**  
Indicates thyroid status and first-line test
- **Total T<sub>4</sub> or free T<sub>4</sub>:**  
Indicates thyroid status and Monitors thyroid treatment
- **Total T<sub>3</sub> or free T<sub>3</sub>:**  
T<sub>3</sub> toxicosis and For earlier identification of thyrotoxicosis
- **Antibodies:**  
Diagnosis and monitoring of autoimmune thyroid disease (Hashimoto's thyroiditis)  
Diagnosis of Grave's disease.

- Goitre :Enlarged thyroid gland
- Hypothyroidism Diagnosis **Elevated TSH** level confirms hypothyroidism
- Hyperthyroidism Diagnosis **Suppressed TSH level, Raised thyroid hormone level**, Confirms primary hyperthyroidism
- Thermogenesis: About 30% thermogenesis depends on thyroid gland,.



## Test your knowledge ...!

1-Which one of the following form has the most active biological action:

- A.  $T_3$
- B.  $T_2$
- C.  $rT_3$

2. Hypothyroid children have:

- A. Gigantism
- B. delayed puberty
- C. Wight loss

3. Administration of TSH increases serum  $T_3$  and  $T_4$  in:

- A. Hyperthyroidism of pituitary origin (secondary)
- B. Hypothyroidism of pituitary origin (secondary)
- C. Hyperthyroidism of thyroid origin (primary)
- D. Hypothyroidism of thyroid origin (primary)

3-B

2-B

1-A

## Test your knowledge ...!

4. Which one of the following will be seen in case of primary hyperthyroidism?

- A. T<sub>4</sub> is low
- B. T<sub>3</sub> is low
- C. TSH is low
- D. All are wrong

5. Which one of the following will happen in case of neonatal hypothyroidism?

- A. Acromegaly
- B. Dwarfism
- C. Cretinism
- D. Gigantism

6. High level of T<sub>3</sub> and T<sub>4</sub> and low TSH in serum indicates:

- A. Hyperthyroidism of pituitary origin (secondary)
- B. Hypothyroidism of pituitary origin (secondary)
- C. Hypothyroidism of thyroid origin (primary)
- D. Hyperthyroidism of thyroid origin (primary)

D-9

C-5

C-7





If you find any mistake, please contact us =>

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