

❖ **Synthesis and Release of Thyroid Hormones:**

- **Iodine** is taken up from the plasma by the epithelial cells of the thyroid gland (*follicular cells*) actively by a carrier that carries iodine and sodium into the cells, or iodine is used from the cells themselves.

→ Then iodine passes from the cells it into the colloid, during the passage the iodine is **oxidized** to be utilized.

-Follicular cells of the thyroid also synthesize a protein: **Thyroglobulin** (that also passes to the colloid) which is made up of 70-140 amino acids (Tyrosines), only 4-8 of those are normally incorporated into thyroid hormones and bind to Iodine.

→ **Iodination** occurs: Iodine binds to Tyrosine → *Monoiodotyrosine* and *Diiodotyrosine* are formed.

→ After iodination, **Coupling** occurs:

- Diiodotyrosine + Diiodotyrosine → **Thyroxine T4**

- Monoiodotyrosine + Diiodotyrosine → **Triiodothyronine T3** and **Reverse T3**

Note: Iodination and coupling ONLY occur if Tyrosine is bound to Thyroglobulin, they don't occur on free tyrosines.

→ **Pinocytosis:** Thyroglobulin carries all these into the follicular cells → inside the cells; they are lysed under the effect of certain enzymes → T3 and T4 become free → released into the blood. Little reverse T3 is released as well.

Q: Are MIT and DIT released also into the blood?

No. Normally they are lysed and even the tyrosine it become detached from the iodine to be utilized again. But abnormally we can uptrace of some DIT and MIT in blood when there is hypersecretion or a tumor.

Note: Thyroid gland produces hormones and the storage of these hormones in the gland is sufficient for about 1 month, while the body storage of iodine is sufficient for about 3 months.

❖ **The metabolism of Thyroxine T4:**

- Remember: T4 is a pro-hormone.
- Under the effect of some enzymes It produces: **T3** (the most active one), **reverse T3** (the inactive one), **DIT** (Diiodothyronine comes only from the metabolism of T4), and **Tetrac** (tetraiodoacetic acid).

❖ **Thyroid hormone turnover:**

- Check table #1 and notice that:
 - Thyroid gland mainly produces T4.
 - T3 and rT3 mainly come from T4.

*The doctor read the percentages in the marked rows.

	T ₄	T ₃	rT ₃
Daily production (µg)	90	35	35 ✓
From thyroid (%)	100	25	5 ✓
From T ₄ (%)	—	75	95 ✓
Extracellular pool (µg)	850	40	40
Plasma concentration			
Total (µg/dl)	8.0	0.12	0.04 ✓
Free (ng/dl)	2.0	0.28	0.20 ✓
Half-life (days)	7	1	0.8 ✓

❖ **Thyroid hormone binding protein:**

- *Remember:* thyroid hormones are very small (composed of 2 amino acids) and therefore they have to be bound to proteins.
- 99.5% of T3 is bound to proteins and very little percentage of it is free and even less in case of T4 where 99.98% of it is bound to protein.
- There are three types of proteins that bind to thyroid hormones :
TBG (thyroid-binding globulin), **Albumin** and **TBPA** (thyroxine-binding prealbumin).
- Check the percentage table #2 and notice that T3 doesn't bind to TBPA.
- The advantages for Thyroid hormones to be bound to proteins:
 - 1) To prevent them from loss during filtration since they are too small.
 - 2) To keep the normal conc. of thyroid hormones constant in the blood.
 - 3) To prolong their half-lives.

	Actual binding T4 %	Actual binding T3 %
TBG	75	75
Albumin	10	25
TBPA	15	0

❖ **Thyroid hormone intracellular actions and whole body effects:**

- *Remember:* We've studied Thyroid hormones along with steroids; they diffuse inside the cell and even inside the nuclei → then bind to their receptors → affecting DNA → then produce mRNA → produce physiological responses:
 1. Increasing Na⁺, K⁺ ATPase.
 2. Increasing respiratory enzymes.
 3. Increasing other enzymes and proteins.
 4. Proteins for growth and maturation.

→ all these results increases Oxygen consumption; so we need to:

 - a. increase the oxygen supply by: 1- increasing cardiac output 2- increasing ventilation
 - b. increase substrates by: 1-increasing food intake 2- increasing mobilization of endogenous carbohydrates, proteins and fats.

→ The ultimate results: 1- increase thermogenesis 2-increase CO₂ & urea levels and 3- decreased muscle mass & adipose tissue.
- Summary of the effects of thyroid hormones (Refer to table 13-6) :

1. Stimulate calorogenesis.	2. Effects on lipid turnover.
3. Increase cardiac output.	4. Effects on protein metabolism.
5. Increase oxygenation of blood.	6. Promote normal growth.
7. Effects on carbohydrate metabolism	8. Promote development and maturation of nervous system and skeleton.
- *Remember:* normal concentrations of thyroid hormones are essential for normal processes in the body but NOT essential for life such as adrenal cortex hormones.

❖ **Factors affecting thyroid hormones secretion** (table 9-8 in the slides):

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 I ⁻ pump)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

- ✓ Remember that thyroid hormone along with other hormones (Insulin-like growth factor-I "IGF-I", insulin, thyroid hormones, cortisol, androgens and estrogens) contribute to the growth process in humans.
- ✓ But **GH** and **IGF-I** have been implicated as the major determinants of growth in normal **post-uterine life** (after birth).
- ✓ Thyroid Hormone are essential in normal amounts for growth, excess doesn't produce overgrowth as with GH, but causes increase catabolism of proteins and other nutrients. But if they're deficient (thyroid hormones), many processes in the body will be disturbed.
- ✓ Thyroxine at normal conc. has permissive effect on the action of GH on protein synthesis. So, in its absence, aminoacids uptake and protein synthesis are not much stimulated.
 - Let's revise 3 examples on permissive interaction:
 1. Adrenaline and thyroxine.
 2. Cortisol and glucagon.
 3. GH and thyroxine.

Now, reduced thyroid activity in childhood produces dwarfs who are mentally retarded, whereas reduced GH in childhood produces dwarfs with normal intelligence (cretin).

❖ **Pathophysiology of thyroid hormones:**

○ Hyposecretion (underactivity of thyroid):

1. Cretinism:

- Associated with hyposecretion of thyroid hormone during **childhood**.
- It is characterized by: dwarfs; failure of skeletal, sexual and mental growth and development.

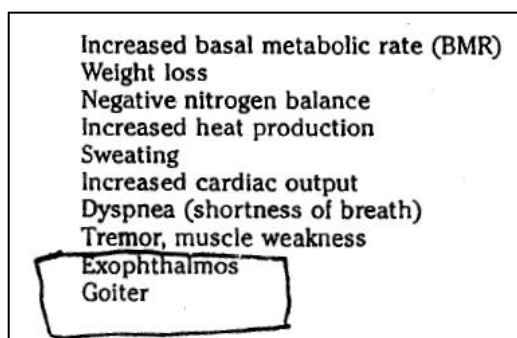
2. Myxedema:

- During **adulthood**.
- It's characterized by slowing down of all bodily processes; this is because of thyroid hormone deficiency.
- The bodily processes that are slowed down:
 1. Tissue oxidation.
 2. Gut movements.
 3. Basal Metabolic Rate (BMR).
 4. Heart and Respiratory Rates.

- 5. Body temperature
- 6. Thought processes.
- 7. Skin.
- 8. Hair
- 9. Blood Cholesterol.
- 10. Slow husky voice
- 11. Appetite.

○ Hypersecretion:

- (referring to table 9-9 in the slides) the symptoms of hypersecretion are :



- The most famous symptoms in over-secretion of thyroid hormones are:

1. **Exophthalmos :**

- The protruding of the eye balls. جحوظ العينين
- Most but not all pts with hyperthyroidism develop some degree of protruding of eye balls.
- It usually occurs due to increased production of antibody called Thyroid Stimulating Immunoglobulin which acts against a protein of the extraocular muscles and the connective tissue behind the eye which causes these tissues to swell.
- It is not due to an excess of the thyroid hormones.

2. **Goiter:**

- The enlargement of the thyroid gland.
- It does occur in both hypothyroidism and hyperthyroidism, because of the continuous stimulation of thyroid cells.
- Sometimes, goiter occurs along with exophthalmos, but not necessarily in all cases it may occur alone.
- The conditions in which goiter presents (referring to table 15-5 in the slides):

1) **Simple (non toxic):** in which T3 and T4 levels are **low**.

2) **Malignant (toxic):** in which T3 and T4 levels are **high**.

Note: We can't differentiate from the appearance either the goiter is toxic or non-toxic!

SORRY FOR ANY MISTAKE.

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