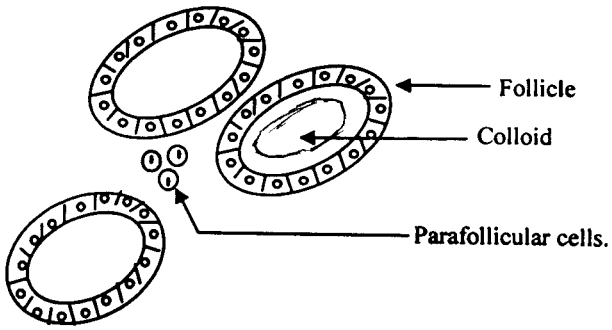
Thyroid gland

Structure: - Composed of:-

a. **Thyroid follicles:** - a hollow spherical structure lined with single layer of cuboidal cells called A cells or follicular cells and secrete T3 and T4. The follicle is filled with thyroid colloid that contains protein called thyroglobulin which is the storage form of T3 and T4.

b. **Parafollicular cells (c cells):-** Masses of cells between the follicles and secrete calcitonin.



The thyroid hormones:

1) **Iodinated derivative of the amino acid tyrosin:**
   - Tetra-iodo thyronine (thyroxine) (T_4).
   - Tri-iodo thyronine (T_3).
2) **Calcitonin:** tonin = lower
   A polypeptide secreted from C cells or parafollicular cells.

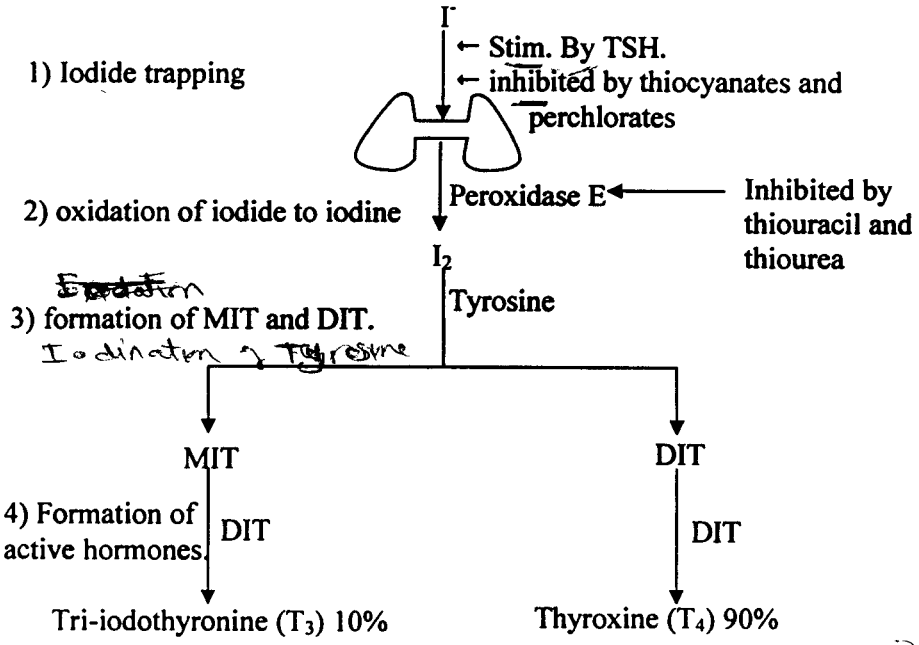
Synthesis of hormones: 4 steps

1. **Iodide pump:-** (Iodide trapping mechanism):
   - The thyroid gland takes and concentrates inorganic iodide against electrochemical gradient. Iodide concentration in thyroid tissue is 25 times its concentration in plasma.
   - It is stimulated by thyroid stimulating hormone.
   - It is inhibited by monovalent ions. e.g. thiocyanates and perchlorates. This inhibition is competitive.
2. **Oxidation of ionised iodide to elemental iodine:**

$$2I^- \xrightarrow{\text{peroxidase enzyme}} I_2$$

   It is inhibited by antithyroid drugs containing SH group e.g. thiouracil and thiourea. -
3. **Formation of mono and di-iodotyrosin (M.I.T. & D.I.T.):** By the union of I_2 and tyrosin (a.a.) while tyrosin is still a part of the globulin molecule.

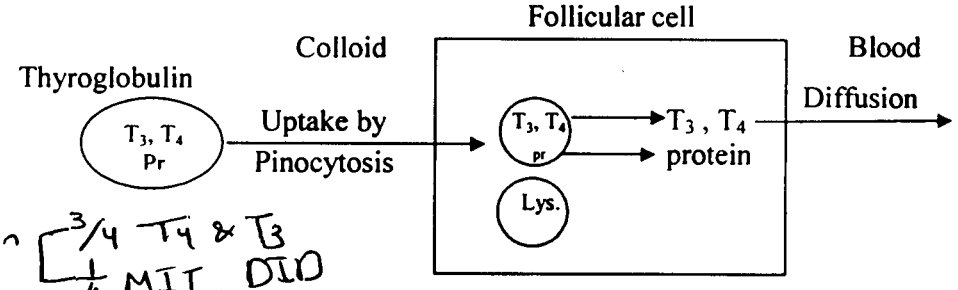
4. **Formation of active hormones by oxidative coupling:**
   D.I.T. + D.I.T. → T4 90%.
   M.I.T. + D.I.T. → T3 10%
   Much of T3 is formed by deiodination of T4 in plasma.



Storage of the hormones:
Hormones are stored as thyroglobulin in the colloid. Thyroglobulin has a MW 700,000 and can not reach the circulation unless thyroid cells are destroyed as in thyroiditis and thyroidectomy.

Release of the hormone:

- Follicular (A) cells uptake small globules of colloid actively by pinocytosis forming a pinocytic vesicle.
- The pinocytic vesicle then combines with lysosomes which contain protease (proteinase) enzyme that leads to hydrolysis of thyroglobulin and release of T_3 and T_4.
- T_3 and T_4 then diffuse from follicular cells to blood while protein molecule is retained in the gland.



Transport of hormones in the blood:-

On entering the blood T_3 and T_4 are transported in 2 forms:-

1) Bound form (main form about 99%):-
   a. 80% bound with globulin called thyroxine binding globulin (TBG).
   b. 20% bound to [redacted] → bind to only T_4 → ↓ low affinity
2) Free form (minute amount 1%):- It is the physiologically active hormone

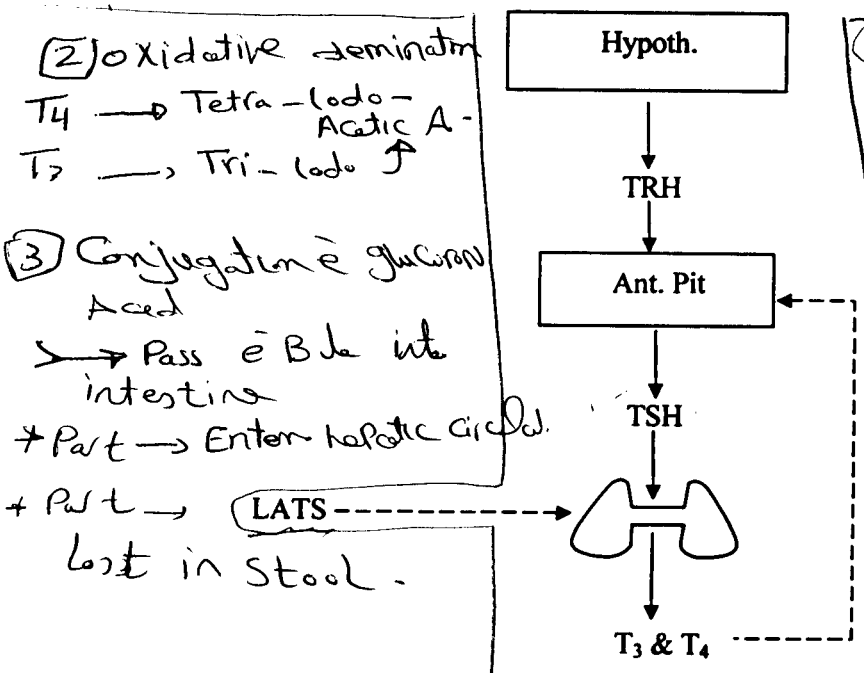
Functions of TBG: (function of bound form of the hormone):-

a. It prevents the loss of the hormone in urine.
b. It acts as a reservoir for the hormone in plasma and protects the body against acute increase or decrease in thyroid function

Control of secretion of thyroid hormones:

1. **Pituitary control:-** (thyroid stimulating hormone) (TSH):
   - TSH is secreted from the basophilic cells of the pituitary gland.
   - The effects of TSH are mediated [redacted].
   - Action of TSH
     a- stimulates nearly all steps of formation and release of T_3 and T_4.
     1. Active uptake of iodine by the thyroid.
     2. Iodination of tyrosine.
     3. Condensation of iodinated tyrosine to form T_3 and T_4.
     4. Activation of the protease enzyme which release T_3 and T_4.

     b- Increases size and vascularity of the thyroid gland
   - Somatostatin has a tonic inhibitory effect on TSH.



2. **Hypothalamic control:-** The hypothalamus secretes thyrotropin releasing hormone (TRH) which in turn stimulates release of TSH.
   - TRH is a tripeptide.
   - TRH is rapidly inactivated by plasma enzyme.

   The hypothalamic control is important in certain conditions, mainly stress.
3. **Feed back control:-** (Negative feedback mechanism by thyroid hormones):- Increased thyroid hormones in blood inhibits TSH secretion from the ant. Pituitary and vice versa.

   Feed back is important for day to day regulation.
4. **Iodine supply:-** Iodine is essential for formation of T3 and T4. Deficiency of iodine in diet leads to morphological changes in the thyroid gland ending with hypothyroidism.

Effects of thyroid hormones:

The thyroid hormones have three major effect:

1. Metabolic effect.
2. Stimulation of growth and development in children.
3. Effect on various body functions.

I- Effect on metabolism:

1. **Increase oxygen consumption:-** (calorigenic action) (↑BMR).
   - The thyroid hormones stimulate the oxygen consumption of almost all metabolically active tissues with the exception of brain, retina, gonads, lung and lymphoid tissues.
   - The thyroid hormones decrease the O_2 consumption of adenohypophysis due to decreased TSH secretion.
   - Most of the effects of thyroid hormones are secondary to its stimulation of the oxygen consumption.
   - This calorigenic action is done through:-
     a. Stimulation of respiratory and metabolic enzymes →↑ utilization of various food stuffs and O_2 →↑ liberation of energy and ↑ ATP formation.
     b. Increased number and size of mitochondria →↑utilization of food stuffs and O_2 →↑ liberation of energy and ↑ ATP formation.
     c. Stimulation of ATPase activity e.g. Na^+- K^+ ATPase →↑ heat production.

Note:- High levels of thyroid H (as in thyrotoxicosis) → uncoupling of oxidative phosphorylation → production of large amount of heat but little ATP.

2. **Effect on carbohydrate metabolism:** Stimulates all aspects of CHO metabolism.

- Increases intestinal glucose absorption.
- Increases liver glycogenolysis due to increased response to catecholamines.
- ↑ gluconeogenesis.
- ↑glucose utilization by tissues.
- ↑ insulin secretion.

3. **Effect on lipid metabolism:** Stimulate all aspects of lipid metabolism.
   - ↑Fat mobilization from its stores (Lipolysis) and ↑ oxidation of free fatty acids by cells.
   - ↑ T_3 and T_4 →↓ cholesterol, phospholipids and triglycerides in the plasma.
   - ↓T_3 and T_4 →↑ cholesterol, phospholipids and triglycerides in the plasma and ↑ deposition of fat in the liver.
   - Thyroid hormones ↓ plasma cholesterol level by ↑its rate of secretion with bile.
4. **Effect on protein metabolism:-**
   - Normally, thyroid hormones ↑ protein synthesis in almost all tissues (anabolic).
   - Excess thyroid hormones causes more protein catabolism than protein synthesis (catabolic).
   - Skin normally contains a variety of proteins combined with polysaccharides, hyaluronic acid and chondriotin sulfuric acid. In hypothyroidism, these complexes accumulate promoting water retention and characteristic puffiness of the skin (myxedema).
5. **Effect on vitamin metabolism:-**
   - When metabolic rate is ↑, the need for vitamin is ↑ and vitamin deficiency may appear.
   - Thyroid hormones are necessary for hepatic conversion of carotenes to vit A, and ↑ carotenes in blood (carotenemia) in hypothyroidism is responsible for the yellowish tint of the skin. In carotenemia, the sclera is not yellow a fact that distinguish it from jaundice.

II- Effects on growth and development:-

Thyroid hormones are essential for physical, mental and sexual growth.

1. **Physical growth:** Thyroid hormones stimulates:
   - Ossification, linear and epiphyseal growth of bones.
   - Normal eruption and development of teeth.
   - Normal skeletal muscle function.
   - Normal growth of skin and hair follicles.
2. **Mental growth:** Thyroid hormones are important for:
   - Growth of cerebral and cerebellar cortex.

- Branching of axon and dendrites.
- Myelination of normal fibers.
- Wakefulness, alertness memory and learning.
- Deficiency of T3 and T4 leads to irreversible damage.

3. **Sexual growth:** Thyroid hormones are essential for gonadal hormones to exert their actions

III- Other effects: (Effects on various body functions):-

1) Effect on nervous system:-

a. **CNS**:- In general thyroid hormones have stimulatory effect on CNS.
- In hyperthyroidism there is rapid mentation, extreme nervousness and insomnia.
- In hypothyroidism there is slow mentation, calmness and hypersomnia.
- Some of the effects of thyroid H. on the brain are probably secondary to ↑ responses to catecholamines with consequent ↑ activation of RAS.

b. **Peripheral N.S.:-** Thyroid H↑ reactivity of neural synapses → hyper reflexia and ms. tremors.

2) Effect on CVS:-

a. **Blood flow:-** ↑ metabolism → V.D. in most tissues →↑bl. Flow especially in skin leading to ↑ heat loss.

b. **Heart:-** ↑ Sensitivity of the heart to catecholamines (due to ↑ number and affinity of B- adrenergic receptors) →↑ H.R. and contractility →↑ stroke volume.

c. **Blood pressure:-** In hyperthyroidism mean ABP is usually unchanged, but pulse pressure ↑ because systolic B.P. ↑ by 10 – 15 mm Hg due to ↑ S.v and diastolic ↓ also by 10 – 15 mm Hg due to V.D.

3) GIT:- Thyroid hormones ↑ appetite, food intake, digestive secretion and motility.

4) Respiration:- ↑ O_2 consumption and CO_2 formation → activation of all mechanisms that ↑ rate and depth of respiration.

5) Relation to other hormones:-
- Thyroid hormones potentiate action of GH and catecholamines.
- Helps inactivation of glucocorticoids.
- ↓release of TSH.

Disturbance of thyroid functions:

I- Hypothyroidism results in:
1. Cretinism : in infants.
2. Myxoedema:- in adults.

II- Hyperthyroidism:- (thyrotoxicosis).

Items	Myxoedema (Adults hypothyroidism)	Hyperthyroidism
Cause	1. **Primary:-** Atrophy or surgical removal of thyroid. 2. **Secondary:-** Failure of TSH secretion. Failure of TRF secretion.	a. Primary (Grave's disease). It is an autoimmune disease caused by formation of long acting thyroid stimulator (LATS) antibodies. LATS is IgG formed by B lymphocytes and. • Produce the same effect of TSH. • Not inhibited by feed back control of T_3 and T_4. b. Secondary:- Due to ↑TSH or TRH.
Metabolism:-		
1. BMR.	Decrease down to - 40%: a. Patient cannot tolerate cold. b. Skin: Dry, coarse, yellow (carotenemia) and puffy. Nails : Brittle. c. Increased body weight inspite of decreased appetite	Increased up to + 100% 1) Patient cannot tolerate heat. 2) Skin: Moist due to increased sweating, flushed due to V.D. 3) Decreased body weight inspite of increased appetite.
2. CHO	1. Decreased intestinal glucose absorption. 2. Increased muscle and liver glycogen.	1. Increased intestinal glucose absorption. 2. Decreased muscle and liver glycogen.
c. FAT	Hypercholestrolaemia and atherosclerosis.	Hypocholestrolaemia
d. Ptn.	Retention of fluids rich in ptn. bound to polysaccharides under the skin (Myxoedematous tissue), unlike oedema; it is non pitting.	Protein catabolism (-ve nitrogen balance) creatine loss is increased and muscles are weak (thyrotoxic myopathy)
e. vitamins	1. Increased carotenes → yellowish skin 2. Decreased vitamin A →Night blindness.	Relative lack of all vitamins due to increased metabolism.
Systems:		
1. Nervous	1. Poor memory, slow thinking 2. Hypersomnia. 3. Hyporeflexia.	1- Increased excitability & irritability. 2- Insomnia (inability to sleep). 3- Hyperreflexia. 4- Fine tremors in outstretched fingers 10-15 / sec.
2. C.V.S.	1. Decreased H.R. and C.O.P 2. Decreased blood flow. 3. Heart enlarged. ECG low	1. Increased H.R. and C.O.P 2. Increased blood flow. 3. Increased systolic p.

	voltage and flat T due to infiltration with myxoedematous tissue.	Increased pulse pressure may lead to high COP failure
3 GIT	Decreased appetite Constipation.	Increased appetite Diarrhea
4. Resp.	Pulmonary hypoventilation	Pulmonary hyperventilation
5. Gonads.	1. Complete loss of libido in male and female. 2. Menstrual disturbances	1. Impotence (in male). 2. Menstrual disturbances.
6. Eye.	1. Swollen lids. 2. Night blindness. 3. Loss of outer 1/ 3 of eye brow.	Exophthalmos (forward protrusion of eyeball) occurs in 50% of patients. It is due to:- 1- Swelling of retro– orbital tissue 2- Degenerative changes in extraocular ms.→↑ its mass.

Cretinism:- Crete = crete island. ism = disease.

Causes:

1. Congenital absence of thyroid gland (congenital cretinism).
2. failure of the thyroid gland of produce the hormones (genetic deficiency).
3. iodine lack in diet. (endemic cretinism).

Manifestations:

They start to appear a few months after birth because the maternal hormones secreted in milk are sufficient for the early needs of the infant.

I. There is delay in all milestones of normal growth.

1. Delayed (retarded) physical growth → **dwarf.**
   Skeletal growth is more inhibited than soft tissue growth → obesity.
   Eruption of teeth, closure of fontanels, sitting and walking are delayed.
2. Delayed (retarded) mental growth → **idiot.**
   Speech is defective. Cretin is incontinent to urine and stool.
3. Delayed (retarded) sexual growth → **sterile** and impotent.

II. A cretin has special characters:- Due to accumulation of myxematous tissues under the skin and mucous membranes:-

1. Eye: swollen lid with narrow palpebral fissure.
2. Nose: Depressed nose with wide nostrils.
3. Mouth: enlarged tongue protruded because of the small mandible.
4. supraclavicular region: Thick pad of fat.
5. skin: Coarse and dry with scanty hair.

6. Abdominal wall: Weak, protuberant and may show umbilical hernia.

Treatment: By thyroid hormones at any time usually causes normal rerum of physical growth, but, unless the cretin is treated within few months after birth his mental growth will be permanently retarded.

	Cretinism	**Pituitary dwarfism**
Cause	Lack of thyroid hormones.	Lack of growth hormone.
Manifestation:		
1. Physical Growth.	Bones are more affected than soft tissues.	Symmetrical retardation. Head may be relatively large (like a child).
2. Mentality.	Complete idiot	Normal
3. Sexual.	Sterile & impotent	Normal
4. Special characters	Present i.e. ugly face	Nice facial characters.

Tests for thyroid function:

Test	**Hyper function**	**Hypo-function**
I-Non specific tests:		
1. Basal metabolic rate.	Increased < 15%	Decreased > -15%
2. Serum cholesterol level.	Decreased>150 mg%	Increased < 250 mg%
II- specific tests:		
1. protein bound iodine.	Increased.	Decreased.
2. Radio active iodine uptake.	Increased.	Decreased
3. Total plasma T_4 and T_3	Increased.	Decreased.
4. Plasma TSH.		Increased
5. Total thyroxin free and bound.	Increased	decreased

III- Differentiating tests:-

1) TSH stimulation tests: This test differentiates between primary and secondary hypothyroidism.
2) TRF stimulation test: This test differentiates between hypothalamic and pituitary hypothyroidism.

Goiter:-

Definition: Enlargement of thyroid gland.

Types: - According to level of thyroid hormone.

I- Non toxic:- Associated with normal or low level of thyroid hormones e.g.

a. Physiological goiter: - In cases of increased need for thyroid hormones e.g. puberty and pregnancy.
b. Endemic (colloid) goiter:-
   - Occur in certain areas where iodine is deficient e.g. oasis in Egypt.
   - It is associated with low T3 & T4 level.
   - ↓ iodine →↓ T_3 and T_4 in plasma → ↑TSH →↑ thyroglobulin secretion → enlargement of the follicles that will be filled by the colloid.

II- Toxic: - Associated with increased plasma level of T_3 and T_4.