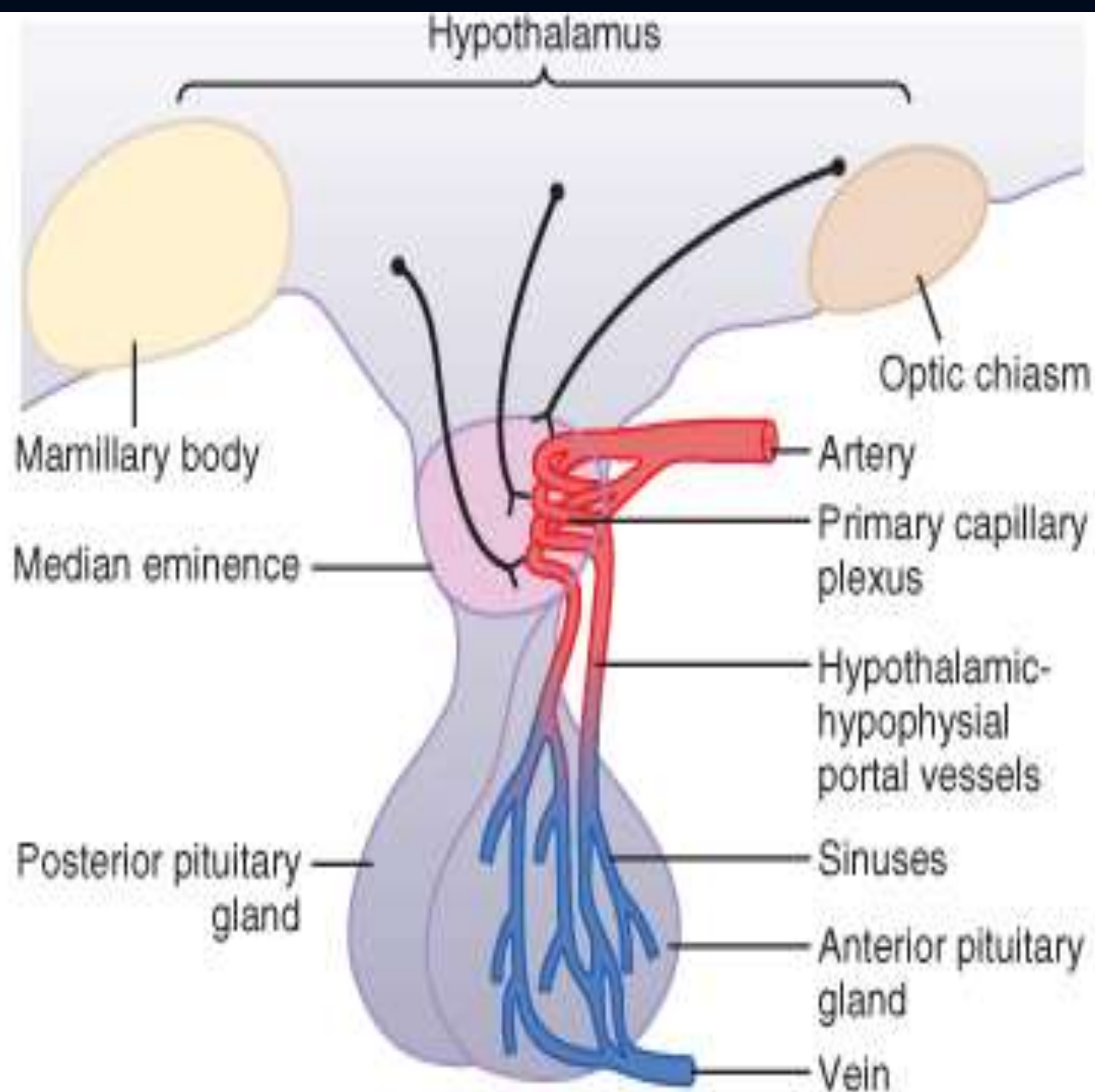


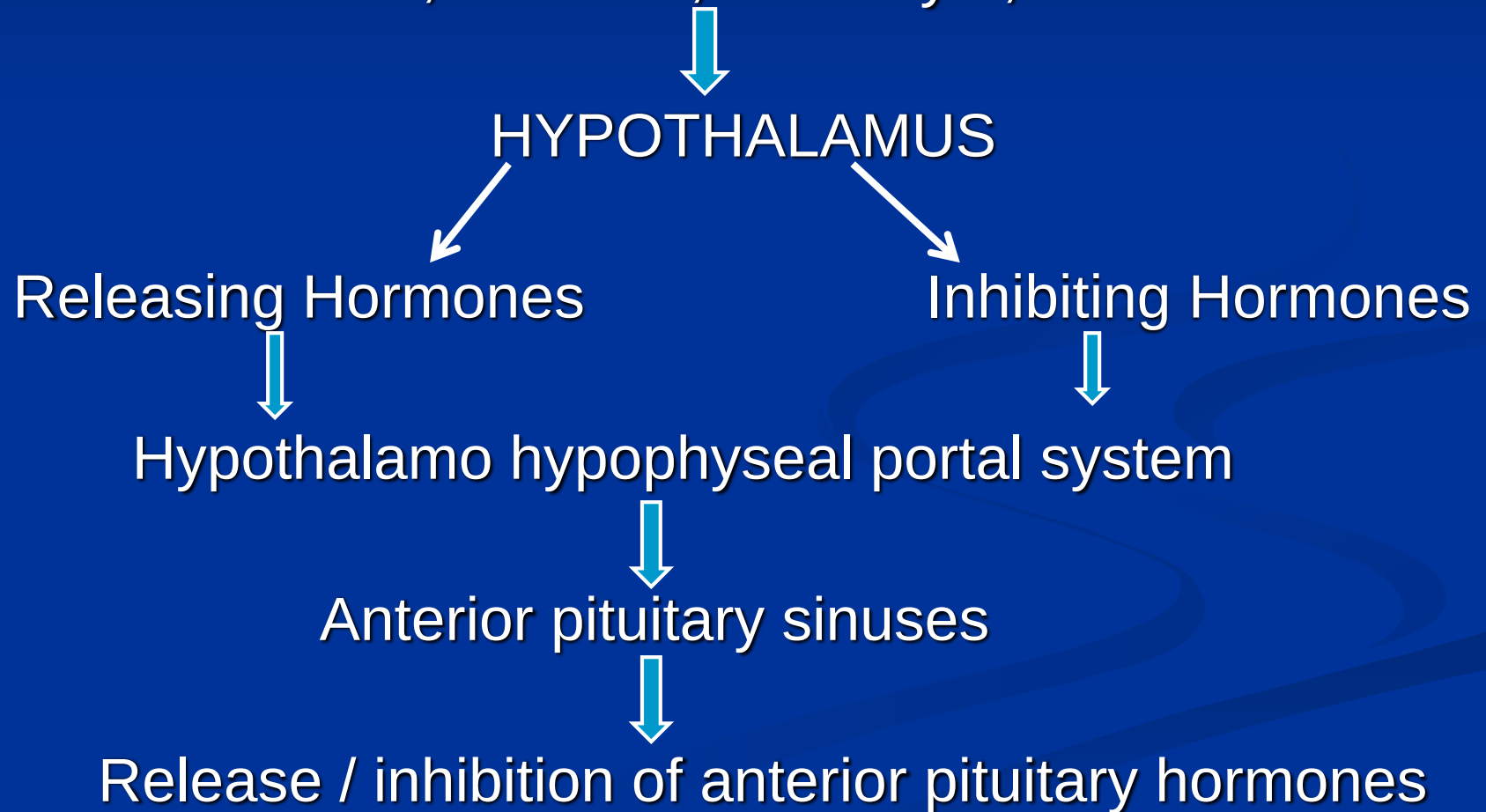


Hypothalamic releasing & inhibitory hormones

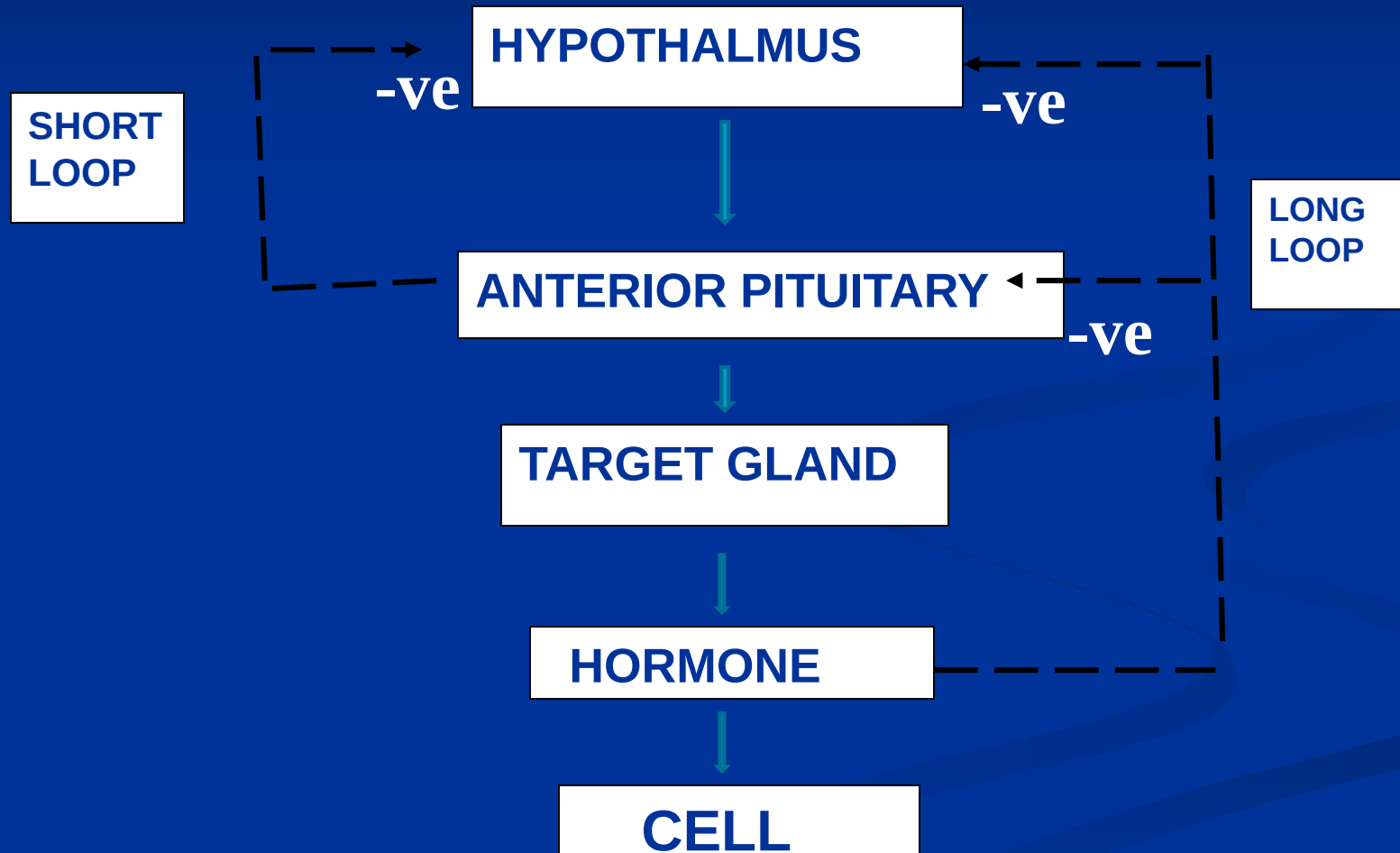
- TRH-Thyrotropin Releasing Hormone: Release of TSH.
 - CRH-corticotropin Releasing Hormone: Release of ACTH.
 - GHRH-Release of growth hormone.
 - GHIH-Inhibition of release of GH.
 - GnRH-Gonadotropin releasing hormone: Release of FSH & LH.
 - Prolactin inhibitory hormone - Inhibition of Prolactin secretion.
-
- ❖ Most releasing hormones-peptides.
 - ❖ Prolactin inhibitory hormone - dopamine(catecholamine).

Control of Anterior Pituitary by Hypothalamus

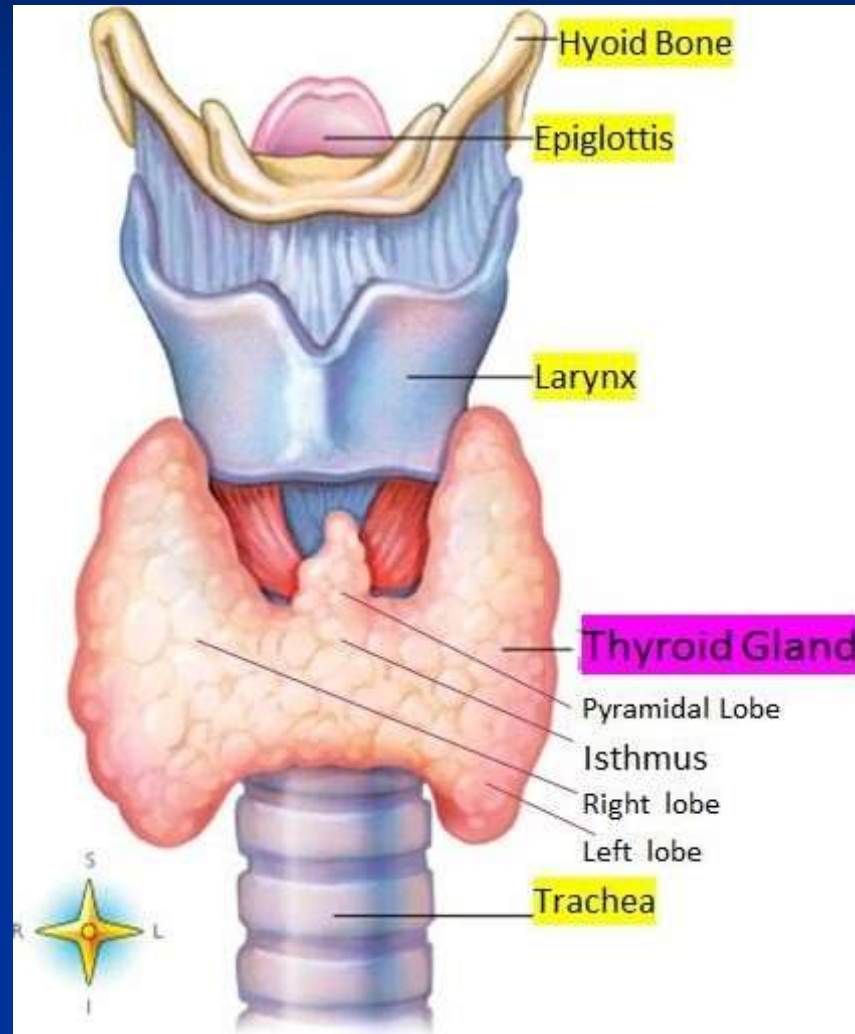
Stimuli - Pain, Exciting /depressing thoughts, Olfactory Hormone levels, nutrients, electrolyte, water balance.



REGULATION OF HORMONES BY HYPOTHALAMIC-PITUITARY AXIS



Thyroid Hormone

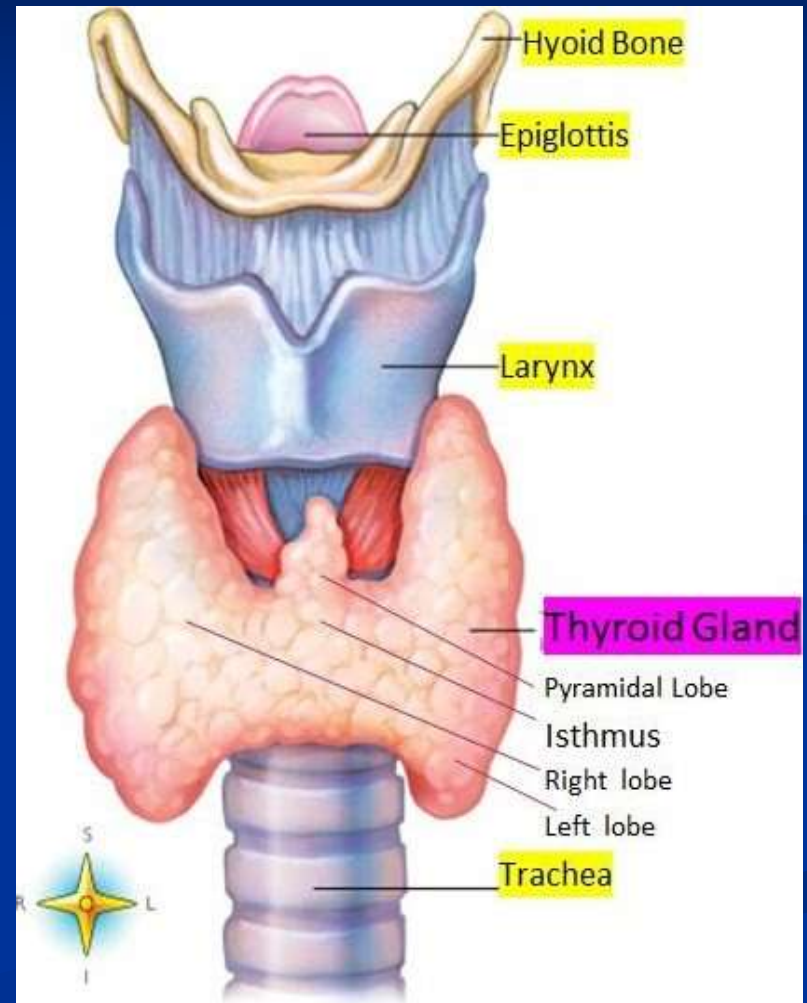


Thyroid Gland

- Described first by Thomas Wharton: 1909-noble prize in physiology.
- Increased incidence of disorders.
- Largest endocrine gland.
- Regulates the rate at which body utilizes oxygen & speed of activity of cells.
- Widespread & important influence on body processes.

Functional Anatomy of Thyroid Gland

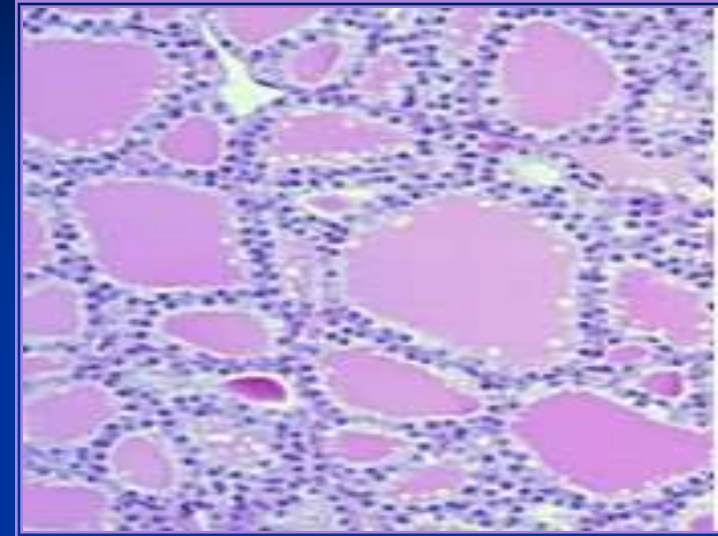
- H shaped
- Thyroid- shield, wraps around trachea, below cricoid cartilage
- Two lobes joined by isthmus
- Weight-15-20 gms
- High blood flow



Thyroid Gland

Histology

- ❖ Follicles- 3 millions in each gland. Filled with secretory substance- colloid.
- ❖ Lined by cuboidal epithelium.
- ❖ Follicles contain large glycoprotein- thyroglobulin containing thyroid hormones.
- ❖ Parafollicular cells- secrete calcitonin.

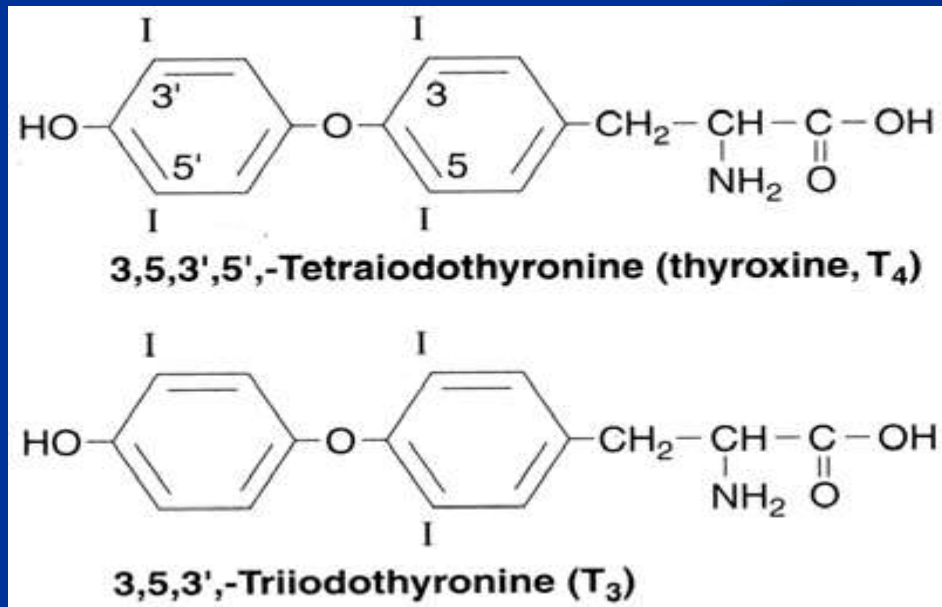


Fetal Thyroid

- From 12th week of gestation fetal thyroid begins to secrete hormones.
- Thyroid hormones are essential for normal growth & development of fetal CNS, skeletal systems.
- Maternal TSH & thyroxine cannot cross placental barrier, however iodine can cross the barrier.

Chemistry of Thyroid Hormone

- Iodine containing amino acid derivative (tyrosine)
- 93 % hormone secreted by T. gland is Thyroxine (T_4).
- 7 % is triiodothyronine (T_3).
- In tissues- $T_4 \longrightarrow T_3$ by de-iodination
- Two benzene rings bridged by ether linkage



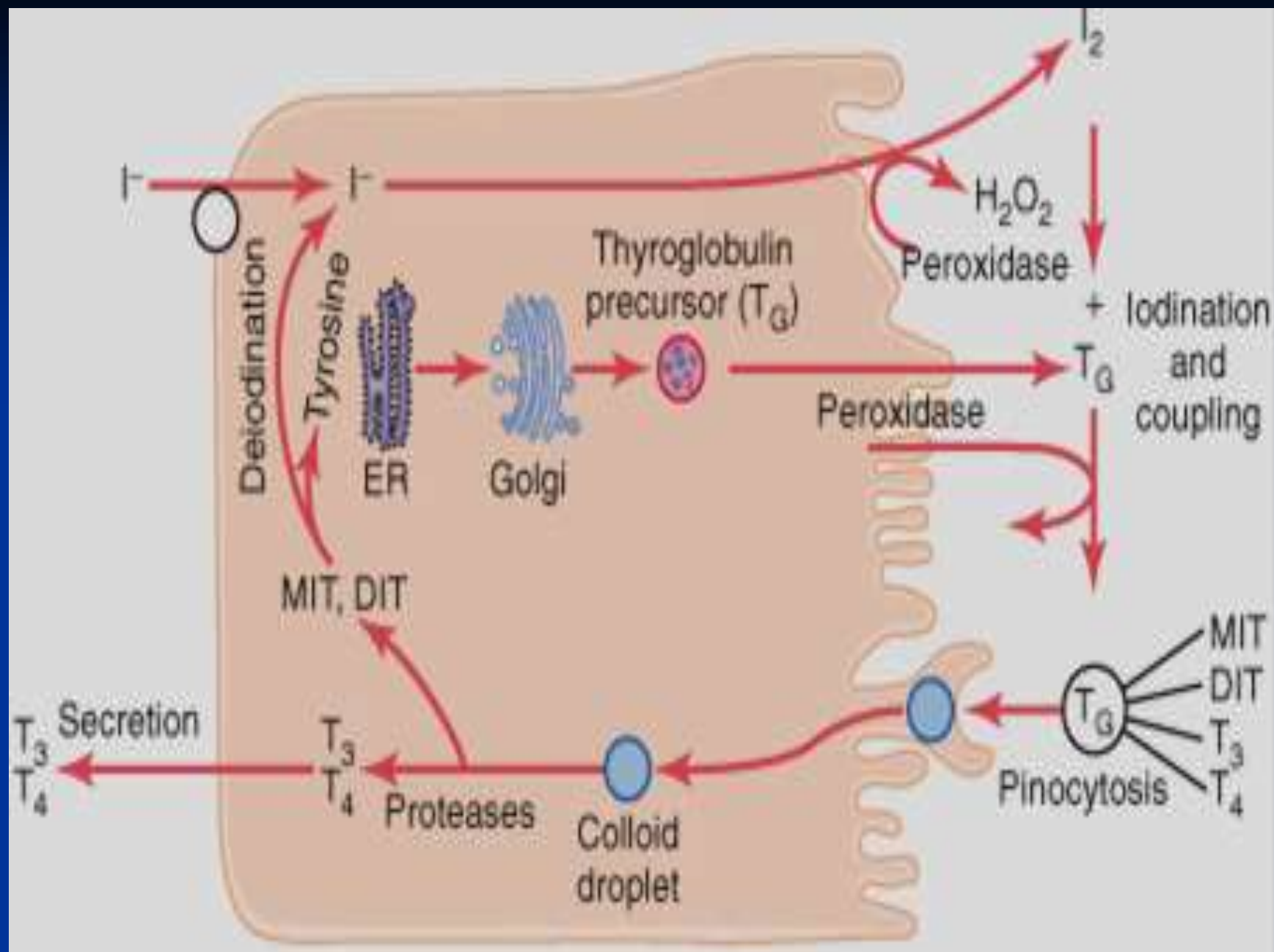
Thyroid Hormone

T_3 is:

- 4 times more potent than T_4 .
- present in smaller quantities.
- Persists for shorter time than T_4 .

Synthesis & secretion of Thyroid Hormone

1. Iodide Trapping.
2. Formation & secretion of Thyroglobulin.
3. Oxidation of iodide ions.
4. Iodination of tyrosine & formation of thyroid hormones -
“Organification” of thyroglobulin.
5. Storage of Thyroglobulin.
6. Release of Thyroid hormone : T_4 & T_3

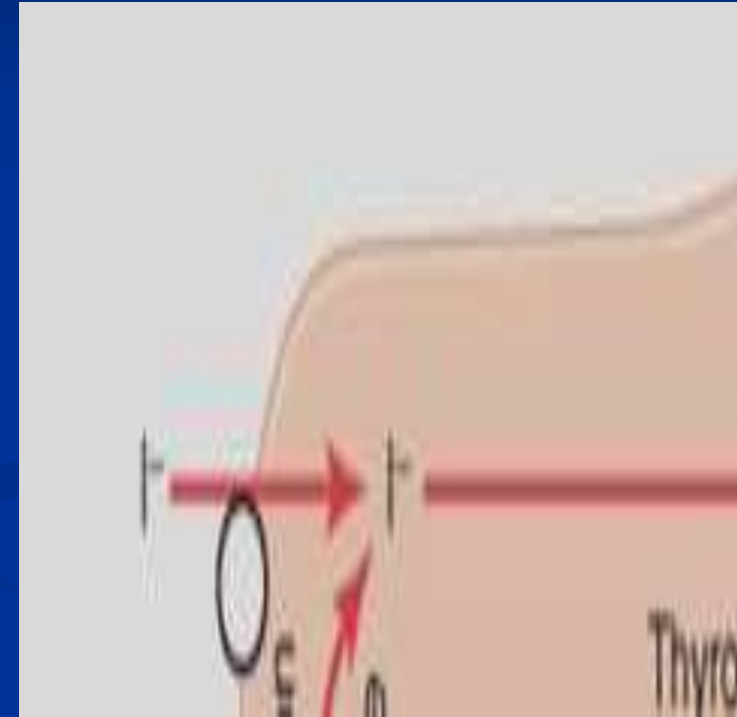


Iodine Metabolism

- Iodine is a raw material for Thyroid Hormone synthesis.
- Sources - soil near sea, sea fish.
- People away from sea- iodine deficiency-Himalaya ,sub Himalaya regions.
- Common table salt is iodized with 1 part Na iodide to every 1,00,000 parts of NaCl.
- Fate of Ingested iodides: absorbed from GIT into blood.
 $\frac{1}{5}^{\text{th}}$ is taken up by Thyroid gland and rest is excreted by kidneys.

1. Iodide Pump (Iodide Trapping)

- Food iodide from blood is taken up by the follicular cells of thyroid – a process called iodide trapping.
- The Thyroid cell membrane facing capillaries contain a symporter or iodide pump : Na^+ / I^- symporter (NIS)
- Traps iodide by active transport mechanism & concentrates the iodide 30 – 250 times than in the blood.

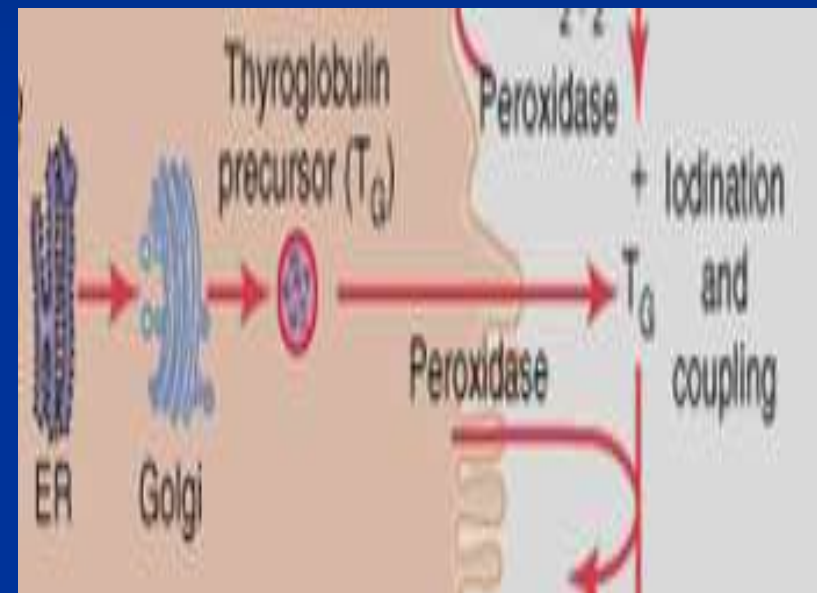


2. Formation & secretion of thyroglobulin

- Thyroid cells are typical protein secreting glandular cells.
- Endoplasmic Reticulum & Golgi Apparatus synthesize & secrete into the follicles, a large glycoprotein molecule : thyroglobulin.

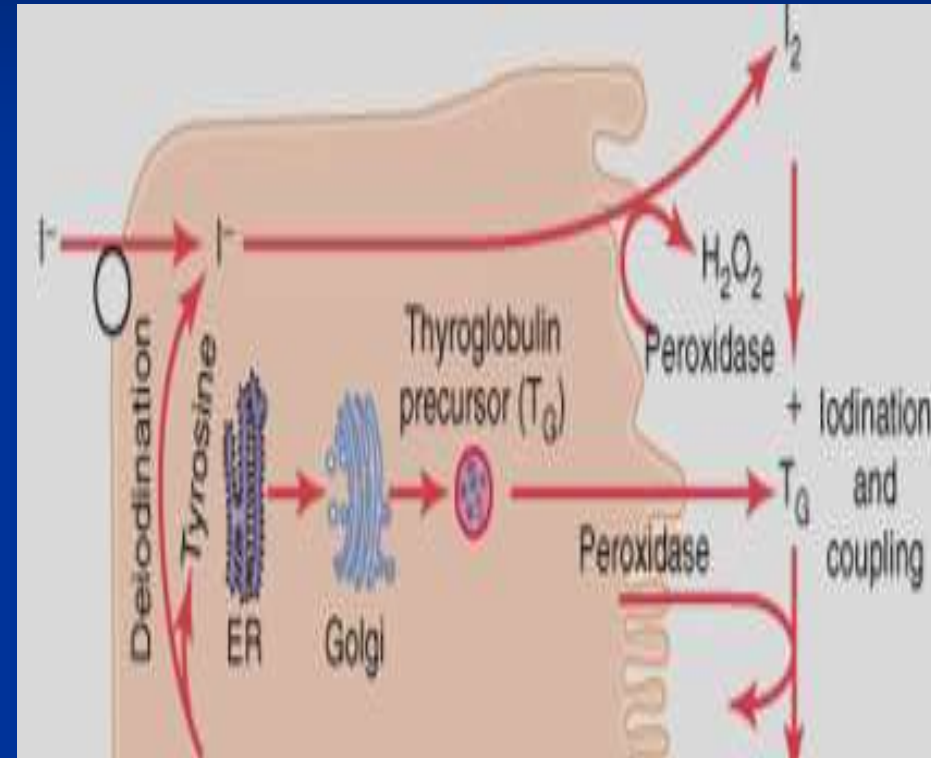
(TG - with MW 3,35,000)

- TG contains about 70 tyrosine amino acids.



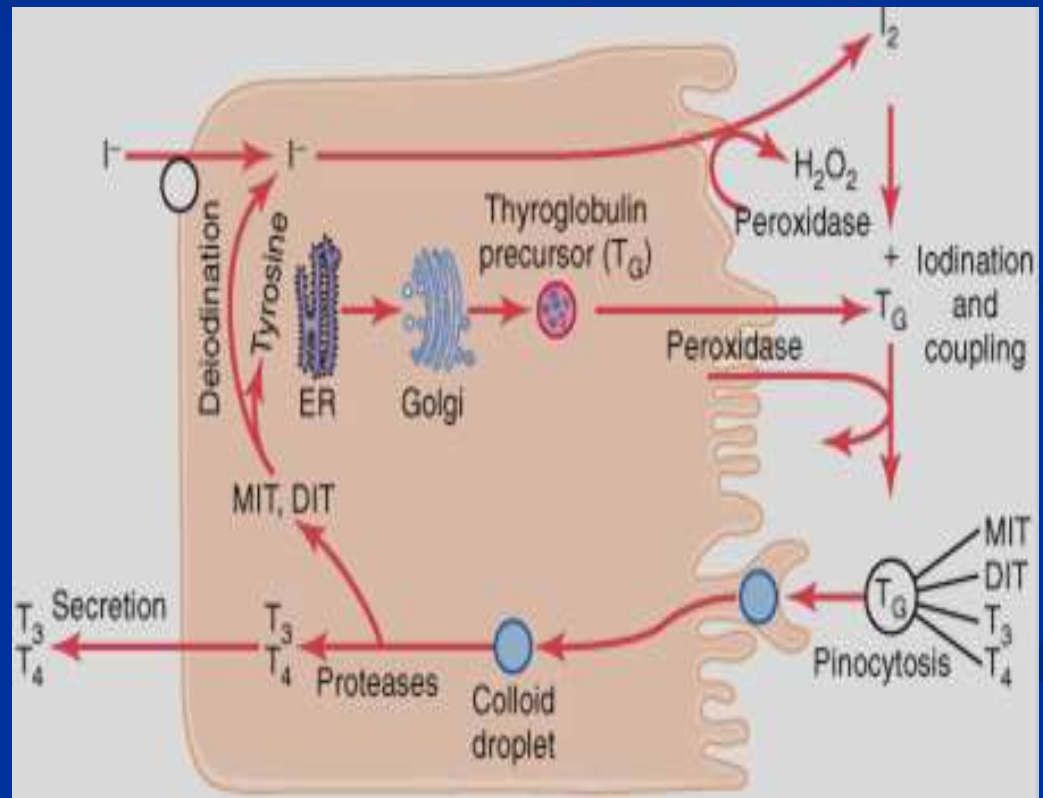
3. Oxidation of iodide ions

- Conversion of the iodide ions to an oxidized form of iodine (I^0 or I_3^-) by the enzyme peroxidase which is attached to apical membrane of the cell in presence of H_2O_2 .

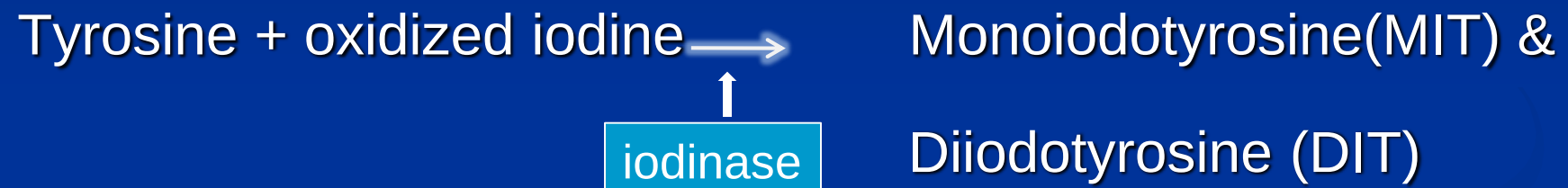


4. Iodination of tyrosine & formation of thyroid hormones- “Organification” of thyroglobulin

Iodination of tyrosine -
The binding of
oxidised iodine with
tyrosine in
Thyroglobulin
molecule in presence
of enzyme iodine.



4. Iodination of tyrosine & formation of thyroid hormones- “Organification” of thyroglobulin

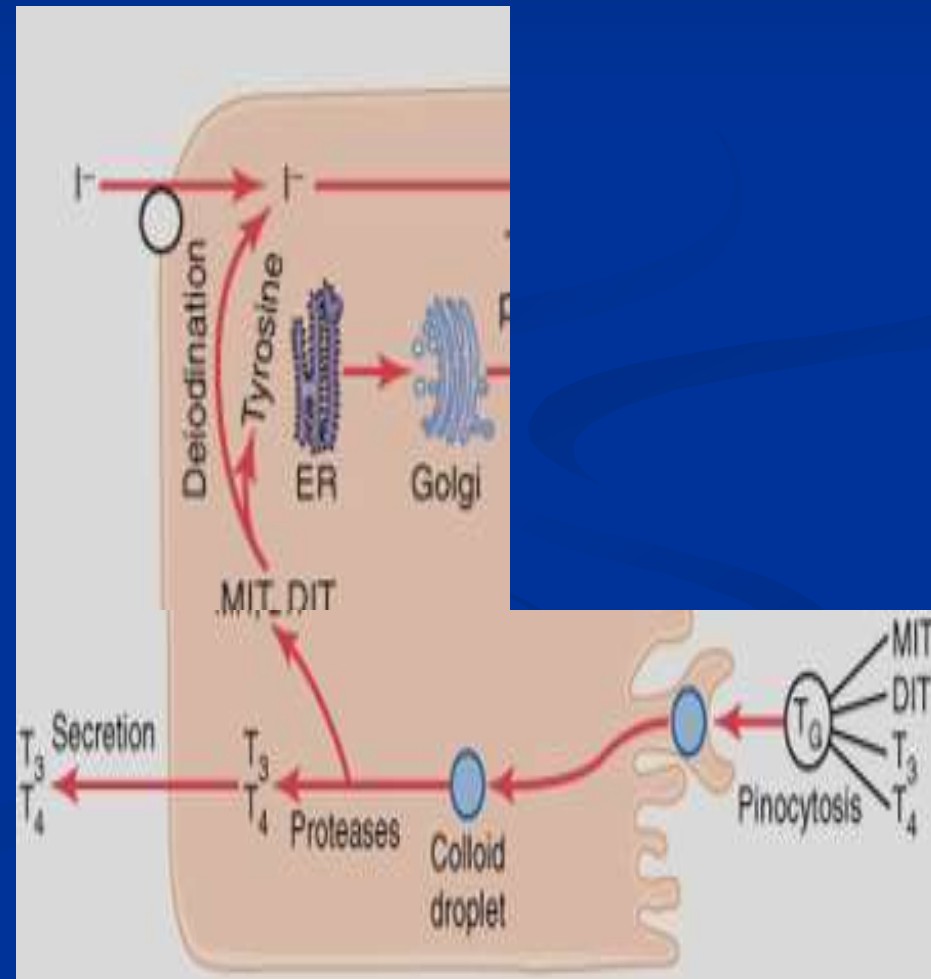


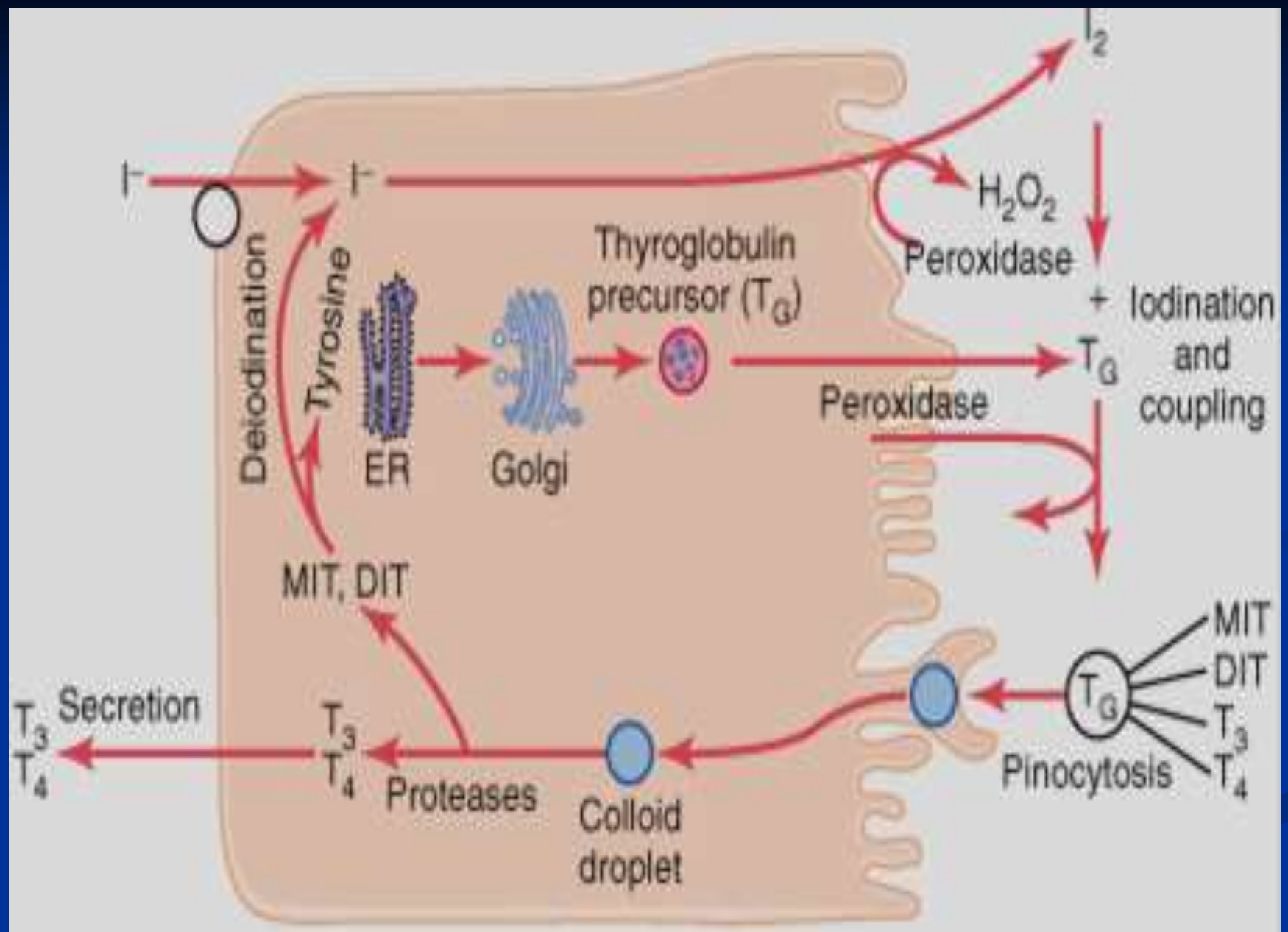
Coupling :-



- ❖ $\frac{3}{4}$ th of iodinated tyrosine in the TG never becomes Thyroid hormone, but remains MIT, DIT.

- ❖ The follicle cells engulf a little TG (containing T_4 & T_3) by endocytosis.
- ❖ Lysosomes within these cells release T_4 & T_3 from TG.
- ❖ During this digestion, iodinated tyrosines are also freed from TG, but not released into blood.
- ❖ Instead Iodine is cleaved by *deiodinase* enzyme thus recycling Iodine.



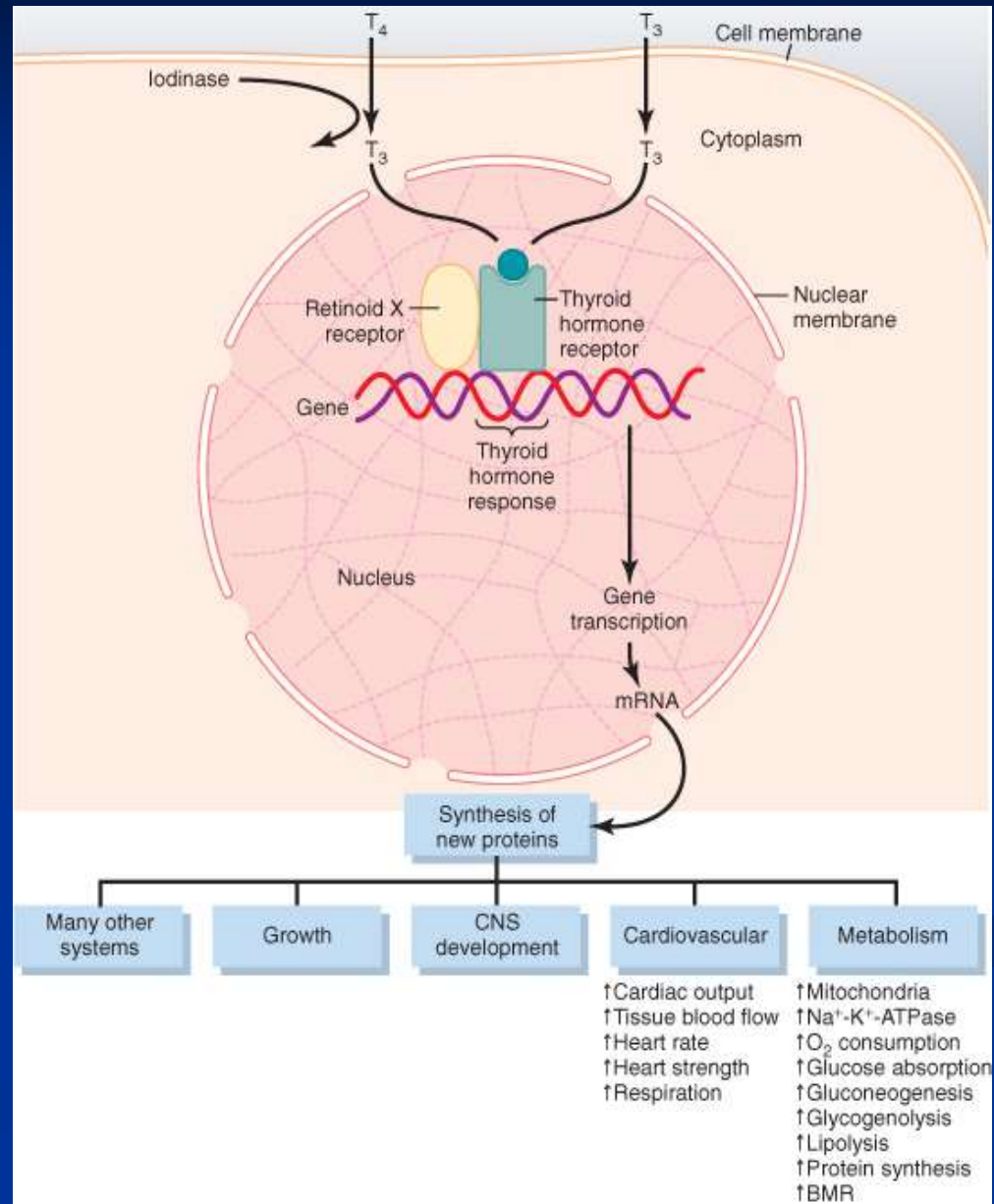


Transport of Thyroid Hormone in blood

- Approximately 99 % of Thyroid hormone is bound to 3 plasma proteins:
 - 1) Thyroxine binding globulin (TBG) ~75%;
 - 2) Thyroid binding prealbumin (TBPA) 15-20 %;
 - 3) Albumin ~5-10 %.
- Released from plasma proteins into blood slowly-reservoir.
- After entering tissues again it binds with intracellular proteins & used slowly.

Mechanism of Thyroid hormone action

- Virtually all cells are target cells.
- Receptor- Intranuclear, attached to specific chromosome.
- Hormone receptor complex binds to DNA.
- Increases or decreases expression of various genes which code for different enzymes, structural proteins, transport proteins etc.



Functions of Thyroid hormone

A) Generalised actions-

- Increased cellular metabolic activities
- Calorigenic action (Thermogenesis)

B). Effect on growth- Physical, mental, sexual.

C) Effect on specific metabolisms

- i) Carbohydrate metabolism, ii) Protein metabolism,
- iii) Fat metabolism iv) Vitamin metabolism

D) Actions on various systems.

E) Body weight.

Generalized actions of Thyroid hormone

- Calorigenic Action/Thyroid Hormone Thermogenesis.
It Stimulates heat production.
- Rate of utilization of foods for energy is greatly accelerated.
- This increases Basal metabolic rate by 60 to 100 %.
- It increases the number and activity of mitochondria.
- It increases active transport of ions through cell membranes.
eg it stimulates Na-K ATPase & thus increases transport of Na^{++} , K^{+} through the cell membrane.

Thyroid hormone: Effect on growth (Physical, mental, sexual)

- ❖ Increased rate of skeletal growth.
- ❖ Stimulate endochondral ossification, linear growth of bones, maturation of epiphysial bone centres.
- ❖ Thyroid hormone promotes growth & development of the brain during fetal life & for 1st few years of postnatal life.

Thyroid hormone: Effect on Specific body mechanisms

1. Stimulation of Carbohydrate Metabolism:-

Thyroid hormone stimulates almost all aspects of carbohydrate metabolism.

- A. Rapid uptake of glucose by cells.
- B. Enhanced glycolysis.
- C. Enhanced gluconeogenesis.
- D. Increased rate of absorption from GIT.
- E. Increased insulin secretion.

Thyroid hormone: Effect on Specific body mechanisms

2. Effect on Protein Metabolism:

- T_4 in physiological dose is anabolic: increased protein synthesis, +ve N_2 balance.
- T_4 in pharmacological dose is catabolic & -ve N_2 balance.
- Mobilization of bone protein.

Thyroid hormone: Effect on Specific body mechanisms

3. Stimulation of Fat Metabolism:

- Mobilization of fat from fat tissue – decreased fat stores.
- Increased free fatty acid concentration in plasma & increased oxidation of FFA.
- Increased hepatic removal of cholesterol.

Thyroid hormone: Effect on Specific body mechanisms

4. Vitamins:

- It increases the quantities of many bodily enzymes.
- Vitamins are part of some enzymes or coenzymes.
- 4. Thus it causes increased need for vitamins.
- Thyroid helps in hepatic conversion of carotene to vitamin A.

Thyroid hormone: Effect on Specific body mechanisms

5. Effect on Body weight:

- Decreased body weight in hyperthyroidism due to more catabolism of protein & fat.
- Increased body weight in hypothyroidism.

Actions of Thyroid hormone on different systems

1) Cardiovascular system :

A. Blood flow (B.F.)

Enhances metabolism. Hence more use of O_2 and more metabolic end products.

All these cause vasodilatation increasing blood flow to tissues.

B. Increases Cardiac Output (C.O.)

C. Increases Heart Rate by directly affecting excitability of the heart (important clinical sign for hyperthyroidism).

D. Increase systolic BP.

Actions of Thyroid hormone on different systems

2) Respiratory System:

Increases rate & depth of respiration due to more utilization of O_2 & more formation of CO_2 .

3) Gastrointestinal system:

- ❖ Increases appetite and food intake.
- ❖ Increases rate of secretion of digestive juices.
- ❖ Increases motility of the GIT.

Actions of Thyroid hormone on different systems

4) Central Nervous System:

- ❖ Normal activity of synapses in spinal cord & brain.
- ❖ Increased levels-increased mentation, irritability, restlessness, fine tremors.
- ❖ Decreased levels-decrease mentation.

Sleep:

- Because of exhaustive effects of TH on the musculature & CNS, a hyperthyroid subject has feeling of constant tiredness but due to excitable synapses, difficult to sleep.
- Hypothyroidism-extreme somnolence-12 to 14 hours a day.

Actions of Thyroid hormone on different systems

6) Muscles:

- Even if slight increase in thyroid hormone levels, muscles react vigorously. (brisk reflexes)
- But when hormone quantity becomes excessive, it results in muscle weakness and loss of muscle mass (because of excess protein catabolism).

Actions of Thyroid hormone on different systems

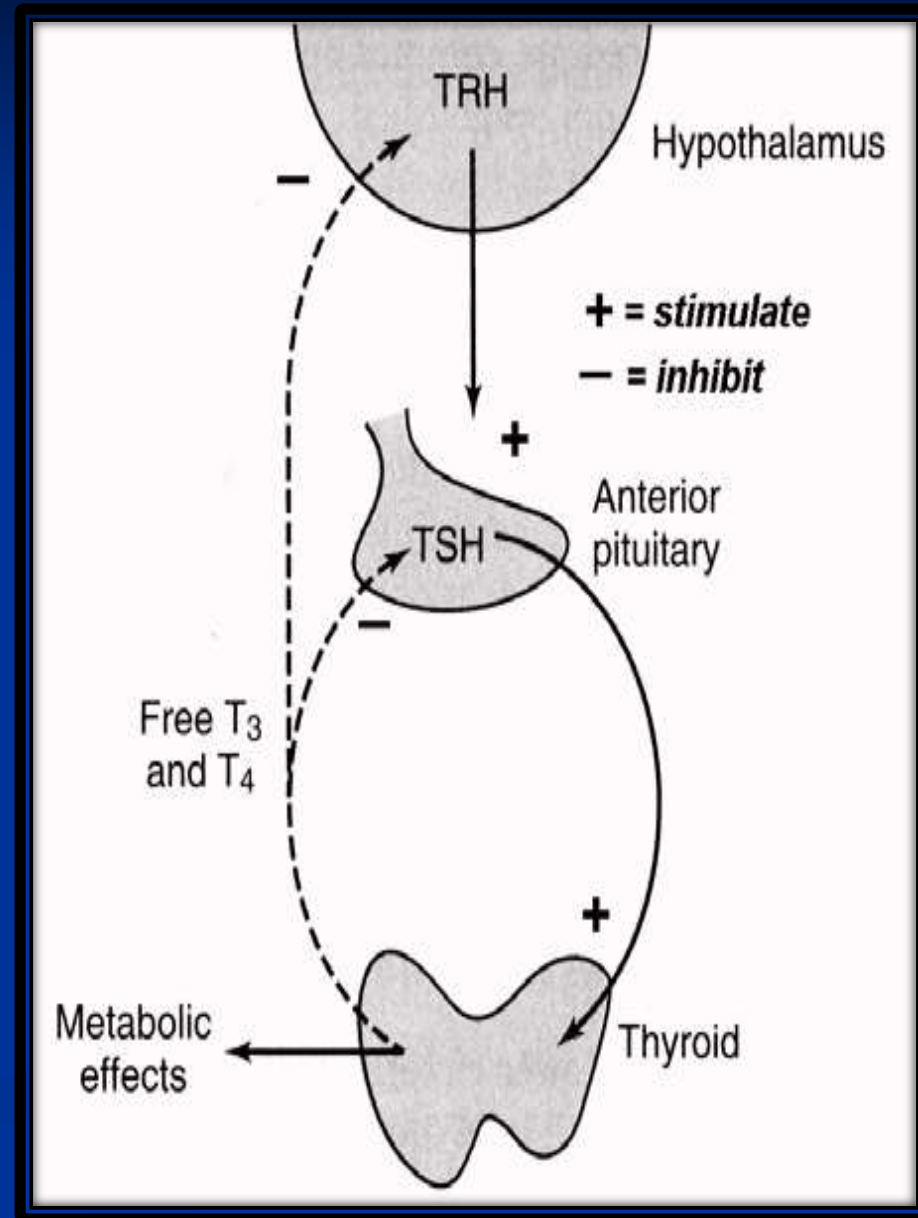
7) Reproductive system:

- For normal menstrual cycle & fertility in females.
- Children-normal sexual development.
- Deficiency – absence of secondary sexual characters.

Regulation of Thyroid Hormone Secretion

Specific feedback mechanism through hypothalamus & Anterior pituitary gland.

- Negative feedback effect of free T_4 & T_3 at pituitary level & at hypothalamic level to decrease TSH secretion.
- Day to day maintenance of thyroid secretion depends on interplay of Thyroid hormone with TSH & TRH.
- Almost constant concentration of free Thyroid hormone in circulation is maintained.



Effects of TSH on thyroid gland

- TSH - Increased secretion of T_4 & T_3 by following actions:
 - Increased activity of iodide pump. Hence increased iodide trapping.
 - Increased iodination of tyrosine to form Thyroid hormone.
 - Increased proteolysis of the thyroglobulin in follicles & release of Thyroid hormone.
 - Increased size and secretory activity of the thyroid cells.
 - Increased number of thyroid cells.

Effects of TSH on thyroid gland

- Increase T3,T4 – decrease TSH & vice versa.
- Hyperthyroidism- decrease TSH.
- Hypothyroidism- increase TSH.
- Serum TSH is one of best tests for thyroid function.
Single test is often diagnostic, if accurately done.

Diseases of the Thyroid

- ❖ Hyperthyroidism / thyrotoxicosis / Grave's disease/ toxic goiter
 - Usually-increased size of thyroid gland.
 - Common in females.
 - Causes-
 1. Autoimmune-TSI (thyroid stimulating immunoglobulin) antibody against TSH receptor which activates TSH receptor.
 2. Adenoma of thyroid.
 3. TSH secreting tumour of anterior pituitary.
 4. Iatrogenic.
 - Decrease plasma TSH levels due to high T₃,T₄.

Hyperthyroidism

❖ Symptoms of Hyperthyroidism:

- Swelling in the neck.
- Increased irritability & excitability.
- Intolerance to heat.
- Excessive sweating.
- Weight loss inspite of increased appetite.
- Diarrhoea.

Hyperthyroidism

❖ Symptoms of Hyperthyroidism:

- Muscle weakness, osteoporosis.
- Nervousness & other psychic disorders.
- Extreme fatigue but inability to sleep.
- Oligomenorrhoea, amenorrhoea.
- Protrusion of eyeball.

Hyperthyroidism

❖ Signs:

- Fine tremors.
- Resting tachycardia.
- High volume pulse.
- Exophthalmus.
- Increased body temperature.
- Signs of cardiac failure and vitamin deficiencies.
- Brisk reflexes.

Hyperthyroidism/ Thyrotoxicosis

❖ Exophthalmos:

- Protrusion of the eyeballs.
- Edematous swelling of the retro orbital tissue.
- Degenerative changes in extraocular muscles occur.
- Cause : Immunoglobulins react with eye muscles.



Diagnostic Tests for Hyperthyroidism

1. Measurement of T_4 & T_3 using Radioimmunoassay (↑ levels).
2. TSH concentration is measured using Radioimmunoassay (↓ levels).
3. TSI concentration is measured by Radioimmunoassay (↑ in thyrotoxicosis, ↓ in thyroid adenoma).
4. Basal Metabolic Rate (↑ up to +30 to + 60N) - obsolete.
5. Radioactive Iodine uptake - increased.
6. Serum cholesterol - decreased.

Hyperthyroidism/ Thyrotoxicosis

TREATMENT OF HYPERTHYROIDISM

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graph LR; A[TREATMENT OF HYPERTHYROIDISM] --- B[Medical treatment (Antithyroid substances)]; A --- C[Surgical treatment (Gland removal)]
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Medical treatment
(Antithyroid
substances)

Surgical treatment
(Gland removal)

Antithyroid substances

- Drugs that suppress thyroid secretion are called antithyroid substances.
- ❖ Thiocyanates inhibit iodide trapping by inhibiting iodide pump on basolateral membrane.
- ❖ Propylthiouracil inhibits peroxidase enzyme thereby preventing oxidation of iodine.
- ❖ High concentration of inorganic iodides (Wolff-Chaikoff effect)-
 - Inhibit organification (iodination of thyroglobulin) in the thyroid gland.
 - Diminish thyroid hormone biosynthesis.
 - Inhibit hormonal secretion into the blood stream.

Surgical Treatment

- Surgical removal of most of the thyroid gland.
- PTU (Propylthiouracil) is given before surgery for several weeks to ↓ BMR to the normal level.
- Administration of iodide in high concentration for 1-2 week before surgery to reduce gland size & ↓ blood supply.
- Radioactive iodine which destroys secretory cells of thyroid gland.

Hypothyroidism (Myxoedema)

■ Causes:

1) Autoimmunity against thyroid gland – Hashimoto's thyroiditis

Antibodies against TG peroxidase - destruction & fibrosis of gland occurs → ↓TH.

2) Dietary iodide deficiency → Endemic Goiter → seen in regions with insufficient iodine in soil (Himalayan belts, Swiss Alps, the Andes).

➤ Mechanism: Lack of iodine → prevents formation of T_4 & T_3 → no free hormone to inhibit TSH production → ↑TSH secretion by anterior pituitary → stimulates thyroid cells to secrete TG, thus thyroid grows larger & larger.

Hypothyroidism (Myxoedema)

Causes -

- 3) Deficiency of enzyme system required for iodide trapping, peroxidase, deiodinase etc.
- 4) Food goiter- turnips, cabbages - antithyroid activity.
- 5) Pituitary & hypothalamic cause - rare.
- 6) Iatrogenic- Destruction of gland due to radiation & surgery.

Hypothyroidism (Myxoedema)

Symptoms:

- ↑ sleep (up to 12 – 14 hours/day) - somnolence.
- Mental sluggishness , poor memory.
- Dry, scaly, yellow skin.
- ↑ body weight & reduced appetite.

Hypothyroidism (Myxoedema)

Symptoms:

- Constipation.
- Intolerance to cold.
- Husky voice.
- Edematous appearance throughout body.
- Menorrhagia, polymenorrhoea.

Hypothyroidism (Myxoedema)

Signs-

- Bradycardia.
- Decreased Blood pressure.
- Delayed reflexes.
- Subnormal body temperature.
- Non pitting oedema-esp. under eyes, face due to increased quantity of hyaluronic acid & chondroitin sulphate-tissue gel.



Hypothyroidism (Myxoedema)

- MYXOEDEMA: bagginess around eyes, swelling of face, because of $\uparrow$ quantities of hyaluronic acid & chondroitin sulphate bound with protein $\rightarrow \uparrow$ tissue gel in the interstitial spaces $\rightarrow$ immobile gel. Hence **nonpitting** type of edema seen.



She had puffiness around her nose and eyes.

1a: Before treatment 1b: After treatment

Hypothyroidism (Myxoedema)

➤ Diagnostic tests :

- T₃, T₄ levels are low.
- ↓BMR (-30 to -50).
- TSH – High.
- ↑ serum cholesterol-> 200 mg/dl.
- ↓ radioactive iodine uptake.

➤ Treatment :

- Thyroxine orally - to mimic physiological situation.
- Iodine supplement if Iodine deficiency. Complete cure possible.
- Treat the cause.

Cretinism

- Caused by extreme hypothyroidism during fetal life, infancy or childhood.

Causes:

1. Iodine deficiency in mother during pregnancy.
2. Congenital lack of thyroid gland –rare. (congenital cretinism)
3. Failure of synthesis of Thyroid hormone due to genetic defect.

Cretinism

■ Signs & symptoms:

- Delayed / failure of mental & physical growth.
- Delayed milestones - sluggish child.
- Decreased height - obese, stocky, short child.
- Mental retardation.



Cretinism

Signs & symptoms:

- Skeletal growth more affected than soft tissue growth-large tongue as compared to jaw bones-may obstruct swallowing, breathing.
- Typical cretin face.
- Pot belly abdomen- liver, spleen normal size.
- Treatment: Replacement of thyroid hormones as early as possible to prevent permanent brain damage



Goiter

- Enlargement of thyroid gland.
- Thyroid hormone levels- increased, decreased or normal.
- C/F - swelling, pressure symptoms, thyroid symptoms.



Goiter

Investigations

- Levels of T_4 , T_3 , TSH.
- BMR.
- Radioactive I uptake.
- Thyroid ultrasound.
- Thyroid biopsy.
- Serum cholesterol.
- Plasma PBI (Protein bound iodine), plasma TSI levels.





RECOMMENDED BOOKS FOR READING



GUYTON & HALL, 2ND SOUTH ASIA EDITION.
❖ Chapter 89- Thyroid Metabolic Hormones.

