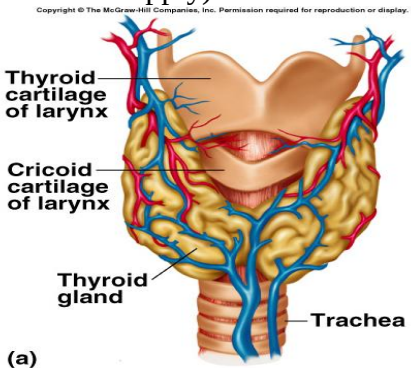
Endocrine Physiology Outlines
Thyroid Gland

- One of the largest pure endocrine glands in the body (≈ 20gms).
- Involved in production, storage & release of thyroid hormones.
- Embryologically, it originates from an invagination of the floor of the pharynx.

- Its size depends on:
  1. age …↑ age α ↑ size.
  2. sex … female > male.
  3. physiological condition … (pregnancy, lactation)

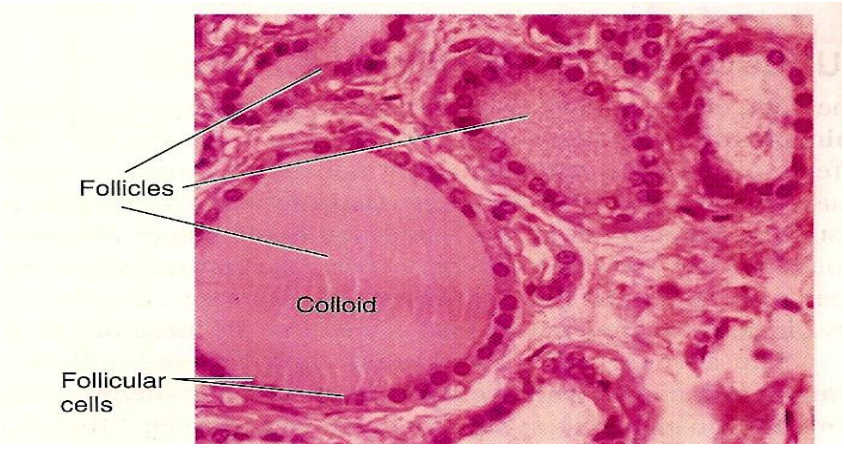
- Shape and Site:
  - Butterfly-shaped organ, located in front of the neck just below the larynx, on either side of & anterior to the trachea.
  - Formed of 2 lobes (Rt & Lt), & connected by a band called 'isthmus'.
  - Not visible under normal conditions, but can be felt during swallowing.
  - Highly vascularized (rich in blood supply).



- **Thyroid gland structure and histology - Euthyroid (normal thyroid)**

1. Multiple Follicles (Acini): (active & inactive)

- Are the functional unit.
  - Thousands in no.
  - ≈ 100 to 300 µmeters in diameter.
  - Each follicle is spherical in structure.
  - Follicular wall is lined with a single layer of cuboidal epithelioid cells that secrete into the interior of the follicles.



- Each follicle is filled with pink-staining proteinaceous material called **colloid**.
  - When the gland is **INACTIVE**, colloid is abundant, follicles are large, & lining cells are flat.
  - When the gland is **ACTIVE**, follicles are small, lining cells are cuboid or columnar, & the edge of colloid is scalloped, forming many small "reabsorption lacunae".
- Each follicle is surrounded by a good & rich blood supply.
- Individual thyroid cells rest on a basal lamina that separates them from the adjacent capillaries.
- Endothelial cells are attenuated at places, forming gaps (fenestrations) in the walls of the capillaries.
- There are microvilli projections into the colloid from apex of thyroid cells, & canaliculi extend into them.
- Prominent endoplasmic reticulum (a common feature in most glandular cells), & secretory droplets of thyroglobulins.

2. Colloid:

Jell-like substance that contains large glycoproteins (proteins linked by carbohydrates) called thyroglobulin, which stores thyroid hormones within its molecules.

3. Parafollicular cells or "C-cells:

- Spherical cell, which has no relation to colloid or cuboidal cells.
- Secrete **Calcitonin**, which is involved in calcium homeostasis.

Thyroid gland secretions (Hormones)

- **Thyroid follicular cells secrete '2' important thyroid hormones:**
  - Thyroxine or tetraiodothyronine (T_4)
  - Triiodothyronine (T_3)
    - Can be stored in thyroid gland for couple of months.
    - Having significant effect on ↑ metabolic rate of the body.
- **Thyroid parafollicular cells secrete:**
  - Calcitonin
    - Important hormone for Ca^{2+} metabolism & homeostasis.

Amount secreted:

- Thyroxine or tetraiodothyronine (T_4) …93%
- Triiodothyronine (T_3) …7%

- Almost all T_4 is converted to T_3 in tissues, & some reverse T_3.
- **T_3** is the active form of **T_4**.
- **T_3** ≈ 4 times > potent (active/important) than **T_4** in tissue, but it present in much smaller quantities in blood, & persists for a much shorter time than does **T_4**.
- **T_3** has great affinity to nuclear receptors than **T_4**.
- Reverse T_3 (RT_3) is inactive.

Transfer of thyroid hormones in blood

- Almost all **THs** are carried in the blood, mostly in an **inactive form**, bound to 3 different types of proteins:
    a. Thyroxine binding globulin … 80%
    b. Thyroxine binding pre-albumin … ≈ 10%
    c. Plasma albumin (serum albumin) … ≈ 10%

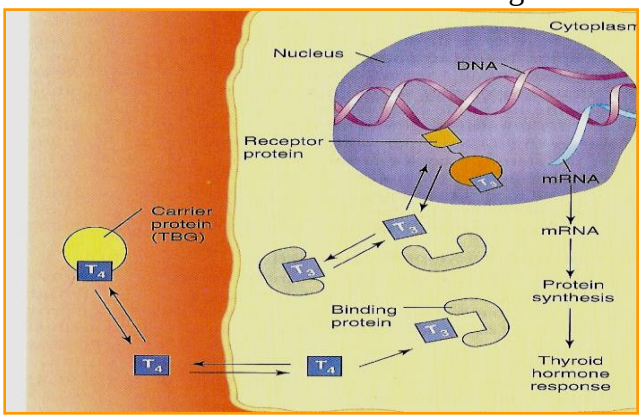
N.B.

- **T_4** has greater affinity to bind proteins than **T_3**.
- Only very little **T_3** (0.25-0.3%) & **T_4** (0.03%) are carried in the blood in the **free active form**.

	T_3	**T_4**
Normal Plasma level	1.2 – 3.1 n mol/L	60-160 n mol/L
Free	0.3 ng	0.15 ug
Bound	99.8%	99.98%
Binding Proteins	Thyroxin Binding Globulin	Thyroxin Binding Globulin
Duration of action	1-2 days	4-6 days
Site of formation/ Source	Thyroid Cells + T4	Thyroid Cells
Potency	4-5 times More potent	Less potent

Mechanism of action of thyroid hormones

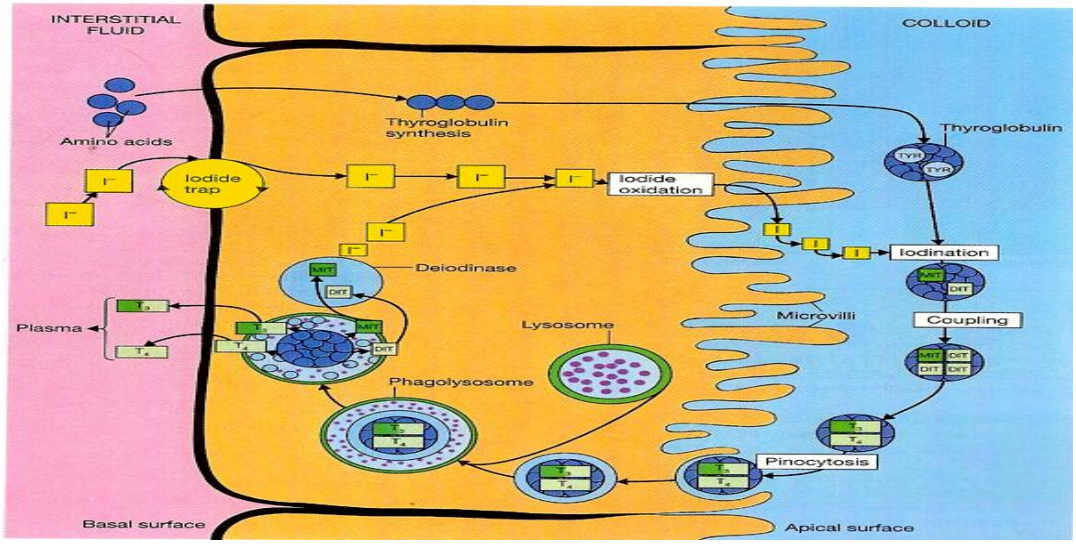
- TRH act on anterior pituitary by activating phospholipase-C system.
- TSH act on thyroid gland by activating cAMP system.
- THs act on target cells.
    - THs are lipophilic amino acid derivative hormones.
    - Their receptors are located within the nucleus of target cells.



Synthesis of thyroid hormones

- **T_3** & **T_4** are synthesized in the colloid by:
    1. Iodine formation.
    2. Thyroglobulin formatiom.
    3. Iodination.

4. Condensation (coupling).
5. Thyroid hormones secretion.
6. Deiodination.



1. Iodine formation:

- Iodine (I^o) is a raw material essential for THs synthesis.
- Found in food, e.g. salt, & sea food, in the form of "iodide (I^-)".
- 120-150 µg of I^- is needed daily to maintain normal thyroid fx in adults (or ≈1mg/wk).
- Iodide (I^-) actively transported (trap) into the follicle (90 – 95%).
- (I^-) will be 30X in thyroid cells > blood concentration.
- (I^-) secreted into colloid along concentration gradient.
- **Peroxidase** enzyme found near apex of follicular cells, where it oxidizes iodide (I^-) to iodine (I^o).

2. Thyroglobulin formatiom:

- Thyroglobulin is a glycoprotein, made up of 2 subunits, & has a MW of 660,000.
- Synthesized in the thyroid cells following entry aa from ECF.
- Secreted into colloid by <u>exocytosis</u> of granules that also contain thyroid Peroxidase.

3. Iodination:

- Iodine attach to tyrosine within thyroglobulin chain.
- Iodinase enzyme is found in the apical membrane → Colloid → start iodination process.

1 Iodine + 1 tyrosine → (iodinase) Mono-iodo-tyrosine (MIT)

2 Iodine + 1 tyrosine → Di-iodo-tyrosine (DIT)

4. Condensation (coupling):

- MIT & DIT or 2 DIT molecules coupled together.

  MIT + DIT = **T_3**

  DIT + DIT = **T_4**

<u>N.B.</u>

- <u>Not all</u> DIT & MIT → thyroid hormones.
- Only 25% of DIT & MIT give rise to thyroid hormones.

- T_3 can also be formed by <u>de-iodination</u> (removing 1 iodine atom) of T_4 by deiodinase enzyme.

5. Thyroid hormones secretion:

- After formation of THs, they remain bound to thyroglobulin in the colloid until secreted.
- Hormones are surrounded in colloid by acid pool, then converted into 'colloid droplet'.
- **TSH** stimulates pinocytosis of thyroglobulin into the follicular cell.
  - Lysozome enzymes hydrolyze peptide bonds & release T_3 & T_4 from thyroglobulin.
  - T_3 & T_4 will be discharged freely & secreted into capillaries, attaching to TBG.

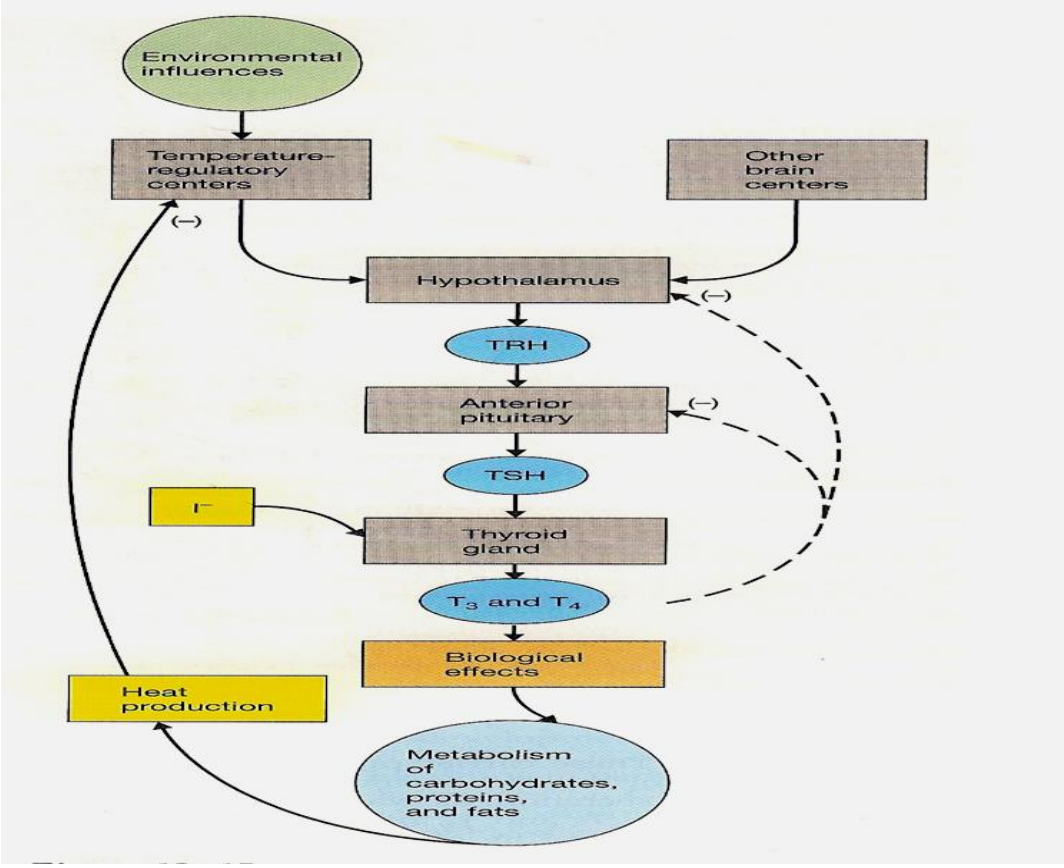
6. Deiodination:

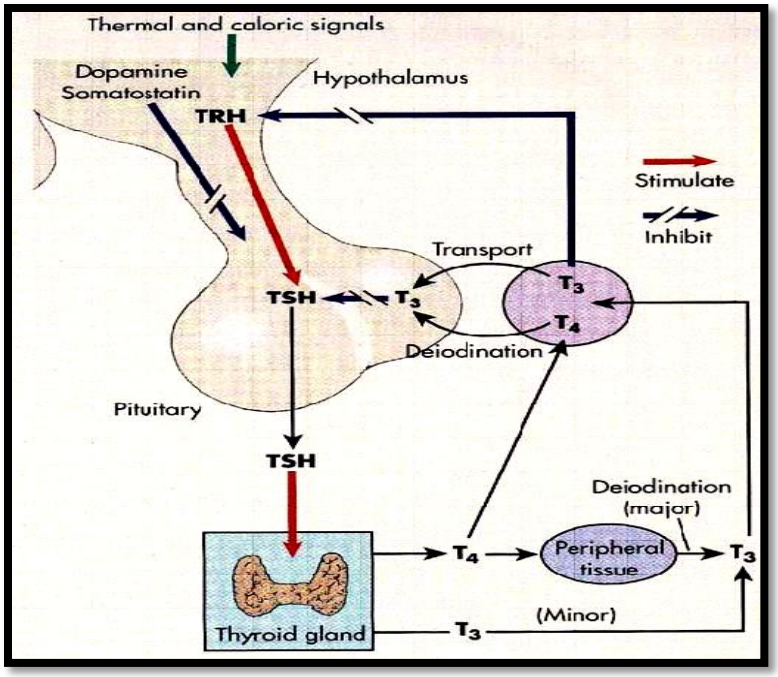
- Inside follicular cells, DIT & MIT forms are <u>NOT</u> secreted into the blood.
- DIT & MIT will be <u>deiodinized</u> to (I^o) & tyrosine.
- Deiodized tyrosine will recycled back to synthesize <u>New</u> MIT & DIT.

<u>Control of thyroid hormones secreations</u>

- Function of thyroid gland is influenced by:
  - Central axis (TRH)
  - Pituitary function (TSH)
  - Diseases of the gland (Graves, etc.)
  - Environmental factors (iodine intake)

- Negative feedback control mechanism of thyroid secretion:
  - THs → -ve feed back mechanism to hypothalamus to inhibit (TRH) release, and to anterior pituitary gland in order to inhibit responsiveness to Hypothalamus (TRH).





Functions of thyroid hormones

- Thyroid hormones affect every cell, many organs & general health of the body: (Heart, lungs, gastrointestinal tract, liver, kidneys, brain, uterus, eyes, skin, …)
- **Generally, THs:**
  - Regulates basal metabolic rate
  - Growth
  - Brain function, memory, concentration
  - Required for proper fetal neural growth
  - Increases the gain of catecholamines
  - Muscle movement (↑ contraction speed)
  - Normal heart beat (Improves cardiac contractility)
  - Increases bowel motility
  - Cholesterol melting, & ↓ LDL

Regulate basal metabolic rate:

1. Increases metabolic rate & heat:
   - Stimulates increased consumption of glucose, fatty acids & other molecules.
2. Increases metabolic heat, by ↑ mitochondrial no, key enzymes & activity → ↑ ATP,
3. Stimulates rate of cellular respiration by:
   - Production of uncoupling proteins.
   - Increase active transport by plasma membrane Na^+/K^+ pumps.
   - Stimulates O_2 consumption of most of cells in the body.

Growth:

1. Necessary for normal growth & maturation.
   - Normal secretion of GH.
   - Potentiate Somatomedin.
   - Skeletal maturation:

- Increase growth & maturation of bone
- Ossification of cartilage, teeth development & eruption.
- Increase growth & maturation of skin epidermis, hair follicles & nails.

2. Nervous system:
   - Promotes maturation of nervous system.
   - Increase NS activity, as it increases the gain of catecholamines
   - Increases speed & amplitude of peripheral nerve reflexes
   - Mental development
   - Enhance wakefulness & alertness
   - Enhance memory & learning capacity
   - Required for normal emotional tone
   - Required for proper fetal & neonatal brain growth & development

- Stimulates protein synthesis.
- Help regulating lipid by ↑ fat catabolism → ↑ FFAs in plasma.
- Help regulating CHO metabolism by:
  - Increase glucose absorption from intestines
  - Normoglycemia, by ↑ glucose uptake by cells, ↑ gluconeogensis, ↑ glycolysis, ↑ insulin.
- Decrease synthesis & increase degradation of mucopolysaccharides in subcutaneous tissue.
- Musculature:
  - Help growth as it increases protein anabolism.
  - Increases rate & force of skeletal muscle contraction.
- Cardiovascular system:
  - Improves cardiac contractility.
    - Potentiate catecholamines "sympathetic system" effect on CVS → ↑CO, ↑SV, ↑HR; by affecting β receptors in heart.
- Respiratory system:
  - Increase resting respiratory rate & depth of respiration "tidal volume", by increasing ventilatory response to hypercapnia & hypoxia.
    - ↑ metabolism will ↑ CO_2, & accordingly chemoreceptors will be stimulated.
  - THs ↑ O_2 consumption by:
    - ↑ RBC mass & ↑ O_2 dissociation (release) from hemoglobin.
    - ↑ 2,3, DPG → shifting curve to Rt.
- Gastrointestinal system:
  - ↑ GIT motility, ↑ absorption, & ↑ secretion of enzymes.
  - Body weight is expected to ↓, because of greater metabolism; however, this will ↑ appetite → accordingly BW ? stay the same.
- Renal system:
  - Increase blood flow & Glomerular filtration rate.
- Reproductive system:
  - Required for normal menstrual cycle.
  - Required for normal follicular development & ovulation.
  - Required for normal maintenance of pregnancy.
  - Required for normal spermatogenesis in male.

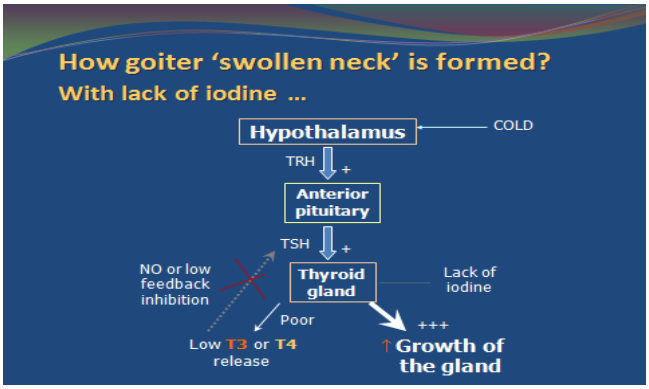
- **Calcitonin** → involved in calcium metabolism and homeostasis.

Abnormal thyroid hormones secretions

I: Hypothyroidism

a. In Adults (Myxedema)

- ↓ Output of THs, resulting in a hypo-metabolic state.
- Onset is gradual & so insidious that it may take years for clinical manifestations to appear.
- **Incidence:**
  - Congenital 1 : 5000 births
  - Under age 20 1 : 1500
  - Over age 20 1 : 150
  - Over age 60 1 : 50
  - Male / female 1 : 5
- Follicular cells become less active.
- **Etiology:**
  - **1ry hypothyroidism:** (90%)… (diseases is in the gland)
    a. autoimmune disease such as "Hashimoto's throiditis".
    b. lack of iodine.
    If No Iodine → ↓ **T_3** & **T_4** → ↑ **TRH** → ↑ **TSH**→ ↑ growth (size) of the gland → simple goiter.



    c. absence of deiodination enzyme.
    → NO recycle synthesis of DIT & MIT → accumulate, & will not be used for new THs formation → ↓ THs.
  - **2ry hypothyroidism: (<10%)** … (disease is in pituitary gland):

→ ↓ TSH production → ↓ THs production.

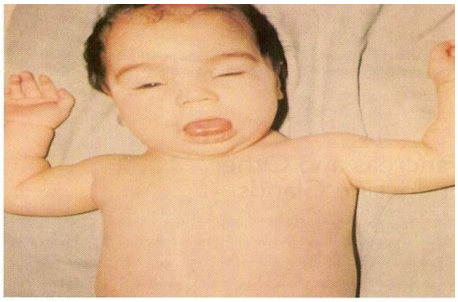
- **Tertiary hypothyroidism: (Rare)** … (disease in hypothalamus)
  → ↓ TRH production → ↓ TSH production → ↓ THs production.

Signs and Symptoms of Hypothyroidism:

- Goiter.
- Decreased metabolic rate.
- Slow heart rate & pulse. ? heart failure. Pericardial effusion.
- ↓ appetite, ↑ weight gain, & constipation.
- Prolonged sleep, & dizziness.
- Impaired concentration, loss of memory, depression.
- Slow thinking & mask face.
- Lethargy.
- Fatigue.
- Muscle weakness & slow contractions (? Stiffness)
- Irregular menstruation, heavy periods, ? infertility.
- Coarse skin.
- Hair loss.
- Intolerence to cold (↓ ability to adapt cold).
- Myxoedema → swollen & puffy appearance of body, due to deposition of protein-carbohydrate complexes 'mucopolysaccharides' & fluid in subcutaneous tissue.

I: Hypothyroidism
b. In Children (Cretinism)

- Hypothyroidism in from end of 1st trimester to 6 months postnatally, or in the 1st few years of life.
- **Additional Signs & Symptoms:**
  - Severe mental retardation.
  - Short stature (due to ↓ growth of bones, muscle, & brain).



Diagnosis of hypothyroidism

- Serum THs.
- Below normal.
- Primary hypothyroidism: ↓ **T_3** & **T_4** → reflex ↑ **TSH**
- Secondary or tertiary hypothyroidism: ↓ **T_3** & **T_4** , ↓ **TRH** & ↓ **TSH**

- **Treatment of hypothyroidism:**
  Daily oral Thyroxine

II: Hyperthyroidism (thyrotoxicosis)

- Excessive secretion of THs, resulting in hyper-metabolic state.
- **Incidence:**
  - 2 - 5% of all females between age of 30-50 yrs
  - Male / female 1 : 7
  - Can be precipitated by a life 'crisis'
- Follicular cells become overactive.
- **Etiology**:
  - **1ry hyperthyroidism: (99%)** … (diseases is in the gland)
    - Autoimmune disease, e.g. Grave's disease (90% of cases).
    - ↑ thyroid stimulating antibodies (IgG), which exerts TSH-like effects on thyroid.
    - Not affected by negative feedback.
      ↑ **T_3** & **T_4** → reflex ↓ **TSH**.
  - **2ry hyperthyroidism: (Rare)** … (disease is higher up)
    ↑ **TRH** → ↑ **TSH** → ↑ **T_3** & **T_4**.
- **Signs and Symptoms of GD:**
  - Goiter.
  - Increase basal metabolic rate & heat production.
  - Increase heart rate (palpitation) & rapid bounding pulse.
  - Sinus tachycardia, atrial fibrillation, ? heart failure due to high output.
  - Shortness of breath.
  - Exophthalmos, due to retro-orbital oedema (irreversible).
  - Lid lag, due to weakness of extraoccular muscles (reversible).
  - Corneal ulcers.
  - Anxiety, restlessness & paranoia.
  - Sleeplessness (insomnia).
  - Agitation & tremor.
  - ↑ appetite, ↓ weight & diarrhea.
  - Warm moist skin.
  - Intolerence to heat.

- **Diagnosis of hyperthyroidism**
  - Serum THs.
  - Above normal.
  - Primary hyperthyroidism: ↑ **T_3** & **T_4** → reflex ↓ **TSH**
  - Secondary or tertiary hyperthyroidism: ↑ **T_3** & **T_4** , ↑ **TRH** & ↑ **TSH**

- **Treatment of hypothyroidism:**
  - Radioiodine Therapy
  - Stop Thyroid Hormone Production
    - Anti-thyroid Drugs often Helpful
    - Anti-iodination process, such as PTU ‘Propylthiouracil’; MMI ‘methylmercaptoimidazole’
    - Replacement Therapy Often Needed
  - Surgery Maybe Necessary
  - Monitoring Tailored to Individual Patient Status & Needs