# PATHOPHYSIOLOGY AND LABORATORY MEASUREMENT OF HORMONES OF THE THYROID GLAND.

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## STUDY OUTLINE

- FUNCTIONAL ANATOMY OF THE THYROID GLAND
- SYNTHESIS, SECRETION, AND METABOLISM OF THE THYROID HORMONES.
- THE MECHANISM OF THYROID HORMONE ACTION.
- ROLE OF THE THYROID HORMONES IN DEVELOPMENT, GROWTH, AND METABOLISM.
- THYROID HORMONE DEFICIENCY AND EXCESS.
- LABORATORY MEASUREMENT OF THYROID HORMONES.

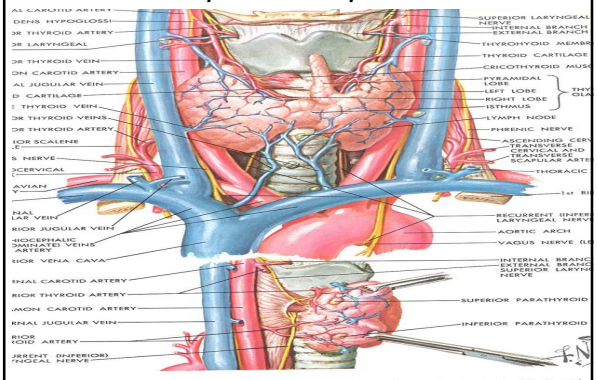


## FUNCTIONAL ANATOMY OF THE THYROID GLAND.

- **ANATOMY**. The human thyroid gland consists of two lobes attached to either side of the trachea by connective tissue. The two lobes are connected by a band of thyroid tissue or isthmus, which lies just below the cricoid cartilage. A normal thyroid gland in a healthy adult weighs about 20 g.
- **BLOOD SUPPLY**. Each lobe of the thyroid receives its arterial blood supply from a superior and an inferior thyroid artery, which arise from the external carotid and subclavian artery, respectively. Blood leaves the lobes of the thyroid by a series of thyroid veins that drain into the external jugular and innominate veins. This circulation provides a rich blood supply to the thyroid gland, giving it a higher rate of bloodflow per gram than even that of the kidneys.
- **INNERVATION**.It receives adrenergic innervation from the cervical ganglia and cholinergic innervation from the vagus nerves. Which regulates vasomotor function to increase the delivery of TSH, iodide, and metabolic substrates to the thyroid gland.

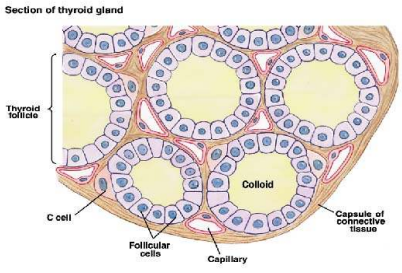


## Anatomy of the Thyroid Gland






## THE FUNCTIONAL UNIT OF THE THYROID.






## THYROID FOLLICLES.

- The lobes of the thyroid gland consist of aggregates of many spherical follicles, lined by a single layer of epithelial cells.
- The apical membranes of the follicular cells are covered with microvilli Which extend into the lumen.
- The lateral membranes of the follicular cells are connected by tight junctions, which provide a seal for the contents of the lumen.
- The lumen of the follicle contains a thick, gel-like substance called colloid. The colloid is a solution composed primarily of thyroglobulin, a large protein that is a storage form of the thyroid hormones. The high viscosity of the colloid is due to the high concentration (10 to 25%) of thyroglobulin.
- The thyroid follicle produces and secretes two thyroid hormones, thyroxine (T4) and triiodothyronine (T3).
- The parafollicular cell usually embedded in the wall of the follicle, inside the basal lamina surrounding the follicle secretes calcitonin

## SYNTHESIS AND SECRETION OF THYROID HORMONES(T4 and T3).

- This process involves the synthesis of a thyroglobulin precursor, the uptake of iodide, and the formation of iodothyronine residues.

Synthesis and Secretion of the Thyroglobulin Precursor.

- It is the first step in the formation of T4 and T3.

This 660-kDa glycoprotein composed of two similar 330-kDa subunits held together by disulfide bridges.

- The subunits are synthesized by ribosomes on the rough ER and then undergo dimerization and glycosylation in the smooth ER.
- The completed glycoprotein is packaged into vesicles by the Golgi apparatus.
- These vesicles migrate to the apical membrane of the follicular cell and fuse with it.
- The thyroglobulin precursor protein is then extruded onto the apical surface of the cell, where iodination takes place.



## Iodide uptake

- The iodide used for iodination of the thyroglobulin precursor protein comes from the blood perfusing the thyroid gland.
- The basal plasma membranes of follicular cells, which are near the capillaries that supply the follicle, contain iodide transporters (Na/I symporter).
- These transporters move iodide across the basal membrane and into the cytosol of the follicular cell, by an active transport mechanism that requires ATP, is saturable, and can also transport certain other anions, such as bromide, thiocyanate, and perchlorate.
- It enables the follicular cell to concentrate iodide many times over the concentrationof iodide present in the blood.
- Once inside follicular cells, the iodide ions diffuse rapidly to the apical membrane, where they are used for iodination of the thyroglobulin precursor.

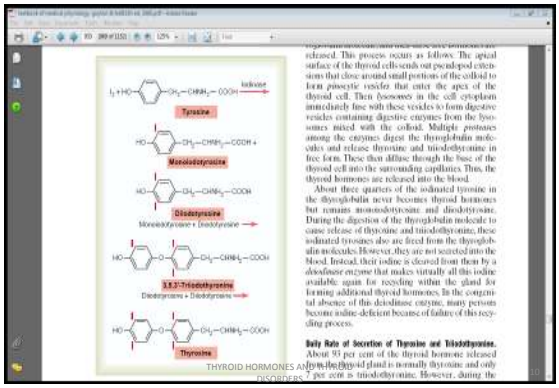


## Formation of the Iodothyronine Residues.

- The next step in the formation of thyroglobulin is the addition of one or two iodine atoms to certain tyrosine residues in the precursor protein.
- The precursor of thyroglobulin contains 134 tyrosine residues, but only a small fraction of these become iodinated.
- A typical thyroglobulin molecule contains only20 to 30 atoms of iodine.
- The iodination of thyroglobulin is catalyzed by the enzyme **thyroid peroxidase**, which is bound to the apical membranes of follicular cells.
- Thyroid peroxidase binds an iodide ion and a tyrosine residue in the thyroglobulin precursor, bringing them in close proximity.
- The enzyme oxidizes the iodide ion and the tyrosine residue to shortlived free radicals, using hydrogen peroxide that has been generated within the mitochondria of follicular cells.
- The free radicals then undergo addition. The product formed is a monoiodotyrosine (MIT) residue, which remains in peptide linkage in the thyroglobulin structure.
- Second iodine atom may be added to a MIT residue by this same enzymatic process, forming a diiodotyrosine (DIT) residue.



## IODINATION



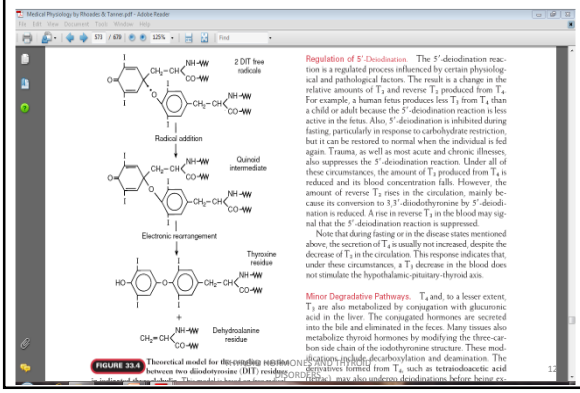



## COUPLING OF IODINATED TYROSINE RESIDUES

- Iodinated tyrosine residues that are close together in the thyroglobulin precursor molecule undergo a **coupling reaction**, which forms the iodothyronine structure.
- Thyroid peroxidase, the same enzyme that initially oxidizes iodine, is believed to catalyze the coupling reaction through the oxidation of neighboring iodinated tyrosine residues to short-lived free radicals. These free radicals undergo addition.
- The addition reaction produces an iodothyronine residue and a **dehydroalanine residue**, both of which remain in peptide linkage in the thyroglobulin structure.
- For example, when two neighboring DIT residues couple by this mechanism, T4 is formed.
- After being iodinated, the thyroglobulin molecule is stored as part of the colloid in the lumen of the follicle.
- Only about 20 to 25% of the DIT and MIT residues in the thyroglobulin molecule become coupled to form iodothyronines.
- For example, a typical thyroglobulin molecule contains five to six uncoupled residues of DIT and two to three residues of T4.
- However, T3 is formed in only about one of three thyroglobulin molecules. As a result, the thyroid secretes substantially more T4 than T3.



## COUPLING REACTION



## SECRETION OF THYROID HORMONES(T4 and T3).

- When the thyroid gland is stimulated to secrete thyroid hormones, vigorous pinocytosis occurs at the apical membranes of follicular cells.
- Pseudopods from the apical membrane reach into the lumen of the follicle, engulfing bits of the colloid.
- Endocytotic vesicles or colloid droplets formed by this pinocytotic activity migrate toward the basal region of the follicular cell.
- Lysosomes, which are mainly located in the basal region of resting follicular cells, migrate toward the apical region of the stimulated cells. The lysosomes fuse with the colloid droplets and hydrolyze the thyroglobulin to its constituent amino acids.
- As a result, T4 and T3 and the other iodinated amino acids are released into the cytosol.
- The DIT and MIT generated by the hydrolysis of thyroglobulin are deiodinated in the follicular cell. The released iodide is then reutilized by the follicular cell for the iodination of thyroglobulin.



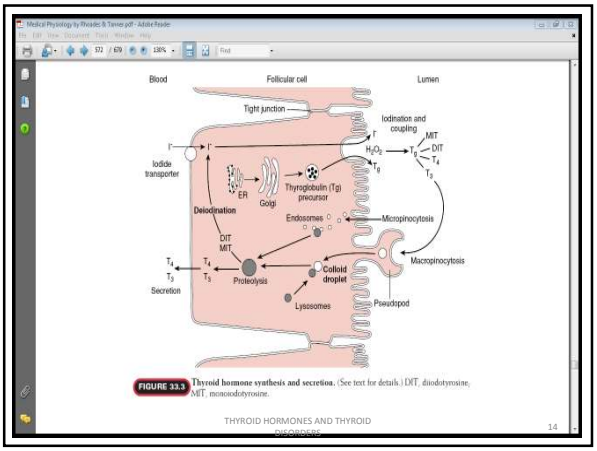



FIGURE 33.3 **Thyroid hormone synthesis and secretion.** (See text for details.) DIT, diiodotyrosine; MIT, monoiodotyrosine.



## TRANSPORT OF T4 and T3

- Most of the T4 and T3 molecules that enter the bloodstream become bound to plasma proteins.
- About 70% of the T4 and 80% of the T3 are noncovalently bound to thyroxine-binding globulin (TBG), a 54-kDa glycoprotein that is synthesized and secreted by the liver. Each molecule of TBG has a single binding site for a thyroid hormone molecule.
- The remaining T4 and T3 in the blood are bound to transthyretin or to thyroxine binding prealbumin. Albumin and some lipoprotein play a minor role.
- Less than 1% of the T4 and T3 in blood is in the free form, and it is in equilibrium with the large proteinbound fraction. It is this small amount of free thyroid hormone that interacts with target cells.
- The protein-bound form of T4 and T3 represents a large reservoir of preformed hormone that can replenish the small amount of circulating free hormone as it is cleared from the blood.
- The half-life of T4 is about 7 days; the half-life of T3 is about 1 day.



## METABOLISM THYROID HORMONES

- Thyroid hormones are both activated and inactivated by deiodination reactions in the peripheral tissues.
- The enzymes that catalyze the various deiodination reactions are regulated, resulting in different thyroid hormone concentrations in various tissues in different physiological and pathophysiological conditions.
- Conversion of T4 to T3. As noted earlier, T4 is the major secretory product of the thyroid gland and is the predominant thyroid hormone in the blood.
- However, about 40% of the T4 secreted by the thyroid gland is converted to T3 by enzymatic removal of the iodine atom at position 5' of the thyronine ring structure.
- This reaction is catalyzed by a 5'-deiodinase (type 1) located in the liver, kidneys, and thyroid gland. The T3 formed by this deiodination and that secreted by the thyroid react with thyroid hormone receptors in target cells; therefore, T3 is the physiologically active form of the thyroid hormones.
- Type 2 deiodinase is believed to function primarily to maintain intracellular T3 in target tissues, but it may also contribute to the generation of circulating T3.



## Deiodinations That Inactivate T4 and T3.

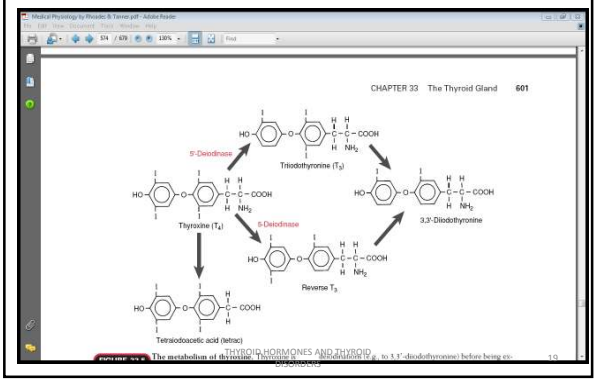
- Both T4 and T3 undergo enzymatic deiodinations, particularly in the liver and kidneys, which inactivate them.
- About 40% of the T4 secreted by the human thyroid gland is deiodinated at the 5 position on the thyronine ring structure by a 5-deiodinase.
- This produces reverse T3. Since reverse T3 has little or no thyroid hormone activity, this deiodination reaction is a major pathway for the metabolic inactivation or disposal of T4.
- Triiodothyronine and reverse T3 also undergo deiodination to yield 3,3-diiodothyronine. This inactivate metabolite may be further deiodinated before being excreted.



## *Minor Degradative Pathways OF Thyroid Hormone*

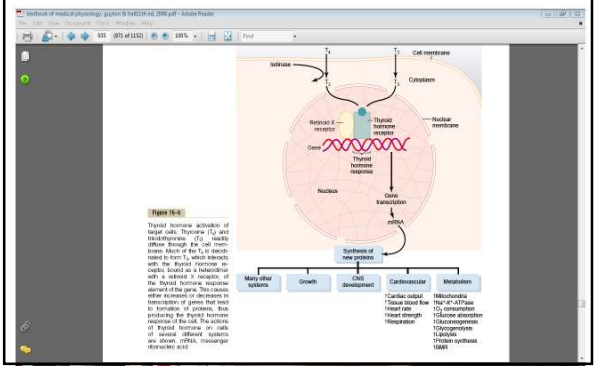
- T4 and, to a lesser extent, T3 are also metabolized by conjugation with glucuronic acid in the liver.
- The conjugated hormones are secreted into the bile and eliminated in the feces.
- Many tissues also metabolize thyroid hormones by modifying the three-carbon side chain of the iodothyronine structure. These modifications include decarboxylation and deamination.
- The derivatives formed from T4, such as tetraiodoacetic acid (tetrac), may also undergo deiodinations before being excreted.

## METABOLISM OF THYROXINE






## MECHANISM OF ACTION OF THYROID HORMONE

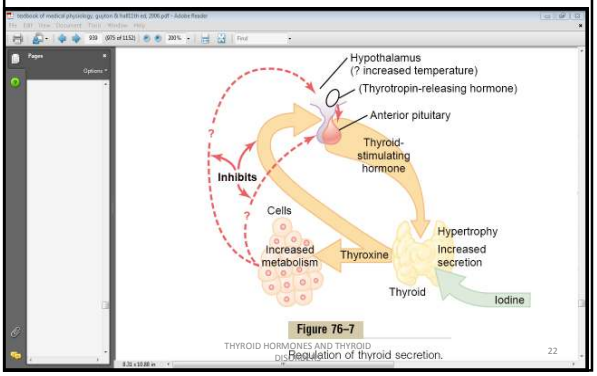



## CONT'

- Most cells of the body are targets for the action of thyroid hormones ( CNS show little response in adults). The sensitivity or responsiveness of a particular cell to thyroid hormones correlates to some degree with the number of receptors for these hormones.
- Thyroid hormone receptors (TR) are located in the nuclei of target cells bound to thyroid hormone response elements (TRE) in the DNA.
- TRs are protein molecules of about 50 kDa that are structurally similar to the nuclear receptors for steroid hormones and vitamin D.
- Thyroid receptors bound to the TRE in the absence of T3 generally act to repress gene expression.
- The free forms of T3 and T4 are taken up by target cells from the blood through a carrier-mediated process that requires ATP.
- Once inside the cell, T4 is deiodinated to T3, which enters the nucleus of the cell and binds to its receptor in the chromatin.
- The TR with bound T3 forms a complex with other nuclear receptors (called a heterodimer) or with another TR (homodimer) to activate transcription.
- Other transcription factors may also complex with the TR heterodimer or homodimer. As a result, the production of mRNA for certain proteins is either increased or decreased, changing the cell's capacity to make these proteins.



## Hypothalamic-Pituitary-Thyroid Axis Negative Feedback Mechanism






## REGULATION OF THYROID HORMONES SECRETION.

- Increased thyroid hormone(TH) in the body fluids decreases secretion of TSH by the anterior pituitary.
- This is because increase TH reduces anterior pituitary receptor sensitvity to FSH.
- Regardless of the mechanism of the feedback, its effect is to maintain an almost constant concentration of free thyroid hormones in the circulating body fluids.
- Cold stimulates thermoreceptor center in the hypothalamus Which then secretes TRH. Increase body temperature thus reduces TRH secretion.

### Antithyroid Substances

- Substances that suppress thyroid secretion are called antithyroid substances. The best known of these substances are thiocyanate, propylthiouracil, and high concentrations of inorganic iodides.
- Thiocyanate is a competitive inhibitor of iodide uptake.
- Propylthiouracil, methimazole and carbimazole all block peroxidase enzyme needed for iodination.
- iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and especially decrease its blood supply.



## THE EFFECTS OF THYROID HORMONES ON BODY MECHANISMS

### GROWTH AND DEVELOPMENT

- Thyroid hormone initiates or sustains differentiation and growth.

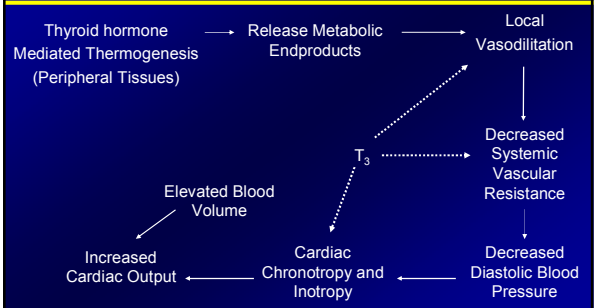
I. Stimulates formation of proteins, which exert trophic effects on tissues

II. Is essential for normal brain development for childhood growth, Untreated congenital hypothyroidism or chronic hypothyroidism during childhood can result in incomplete development and mental retardation.

### CNS

- ✓Thyroid hormones are essential for neural development and maturation and function of the CNS.
- ✓Decreased thyroid hormone concentrations may lead to alterations in cognitive function.
- ✓Patients with hypothyroidism may develop impairment of attention, slowed motor function, and poor memory.
- ✓Thyroid-replacement therapy may improve cognitive function when hypothyroidism is present.

## Thyroid Hormone Influences Cardiovascular Hemodynamics




Laragh JH, et al. *Endocrine Mechanisms in Hypertension.* Vol. 2. New York, NY: Raven Press;1989.



### Thyroid Hormone Influences the Female Reproductive System

- Normal thyroid hormone function is important for reproductive function.
- Hypothyroidism may be associated with menstrual disorders, infertility, risk of miscarriage, and other complications of pregnancy.

### Bone Growth and Development

✓ T3 is an important regulator of skeletal maturation at the growth plate

✓ T3 regulates the expression of factors and other contributors to linear growth directly in the growth plate

✓ T3 also may participate in osteoblast differentiation and proliferation, and chondrocyte maturation leading to bone ossification.



### Metabolic Activities in Most Tissues

- Thyroid Hormones Increase Active Transport of Ions Through Cell Membranes. One of the enzymes that increases its activity in response to thyroid hormone is Na+/K+- ATPase.
- $T_3$ increases basal metabolic rate.

- Calorigenic effects
  - $T_3$ increases oxygen consumption by most peripheral tissues
  - Increases body heat production
- Stimulates lipolysis and release of free fatty acids and glycerol
- Induces expression of lipogenic enzymes
- Stimulates metabolism of cholesterol to bile acids
- Facilitates rapid removal of LDL from plasma
- Generally stimulates all aspects of carbohydrate metabolism and the pathway for protein degradation



### THYROID DISORDERS

- Thyroid disorder usually leads to either thyroid hormone excesses or thyroid hormone deficiency.

**Thyroid hormone deficiency(hypothyroidism)**

Hypothyroidism is a disorder with multiple causes in which the thyroid fails to secrete an adequate amount of thyroid hormone.

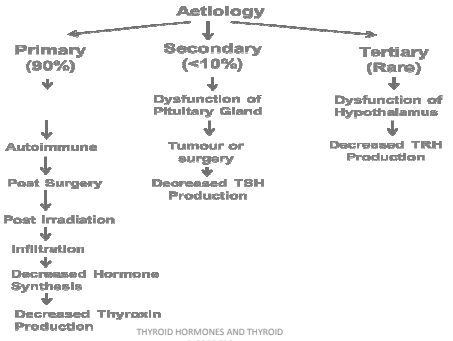
### Signs & Symptoms

malaise, Mental slowness, Headaches, Reduced appetite, Constipation, Sensitivity to drugs, Change in appearance, Anaemia, Heart failure, Hypertension, Bradycardia

Dyspnoea, Cold intolerance / Hypothermia



### HYPOTHYROIDISM






### Primary Hypothyroidism

This usually occur due to an underlying disease that afect the thyroid tissue.
It may be due to insufficient thyroid tissue cause by;

1.Destrution thyroid tissue by autoimmune processes e.g

- Hashimoto thyroiditis;(atrophic and goitrous forms) in this disease antibodies are produce against the thyroid tissue e.g against thyroid peroxidase enzyme, thyroglobulin, and the TSH recerptors. This abs can either cause gland enlargemnt or atrophy. Enlargement and subsequent hypothyroidism in Hashimoto's disease is cause by abs that binds to TSRs and stimultes growth but not TH synthesis.
- End stage Grave's disease.

2. Destruction of tissue by iatrogenic procedures e.g RAI, surgical thyroidectomy, external radiation.
Destruction of tissue by infiltrative processes e.g amyloidosis, lymphoma, and scleroderma.

3 Defects of thyroid hormone biosynthesis e.g congenital enzyme defects, congenital mutation in TSH receptors, iodine deficiency or excesses and drug induce(e.g lithium,)

## SECONDARY HYPOTHYROIDISM

- This is cause by a defect in the pituitary thyrotrophs. It migth be due to:
- Panhypopituitarism( e.g neoplasm, radiation, surgery)
- Isolated TSH deficiency

tertiary hypothyroidism

This is hypothyroidism cause by a disease of the hypothalamus. e.g congenital, infection and infiltration(sarcoidosis, granulomas)

In genera hypothyroidism migth be cause by a generalized resistance to thyroid hormone



## CLINICAL HALLMARK FOR SEVERE HYPOTHYROIDISM

- Severe hypothyroidism usually present as myxedema in adults, and cretinism.
- MyxedemaThis is the present of nonptting mucus type of edema, cause by the accumulation of a hydrophylic mucopolysaccharide substance in the connective tissue through out the body. It is usually the cause of death particularly from myxedematuos coma(characterized by coma, cardiovascular collapse, hypoventillation, hypoglycaemia, hyponatraemia and lactic acidosis)
- Cretinism is caused by extreme hypothyroidism during fetal life, infancy, or childhood.
- This condition is characterized especially by failure of body growth and by mental retardation. It results from congenital lack of a thyroid gland (*congenital cretinism*), from failure of the thyroid gland to produce thyroid hormone because of a genetic defect of the gland, or from iodine lack in the diet (*endemic cretinism*)



## CLINICAL PRESENTATION OF CRETINISM

**Infantile Cretinism**

- Megaglossal tongue
- Druppy eyelids
- Lack of genital development
- Severe mental retardation

**Cretinism**

- Infancy onset
- Persists throughout life
- Severe mental retardation



## MYXEDEMA



## Diagnosis of hypothyroidism

**Serum T4 OR FT4 measurement**

Serum T4 or fT4

↓

Below Normal

↓

? Primary Hypothyroidism

↓

? Secondary Hypothyroidism

↓

? Tertiary Hypothyroidism

**Serum TSH measurement**

Serum TSH

Above Normal → ? Primary Hypothyroidism

Below Normal → ? Secondary Hypothyroidism → ? Tertiary Hypothyroidism



## Diagnosis of hypothyroidism

**DIAGNOSIS**

TRH Stimulation Test

TSH Response

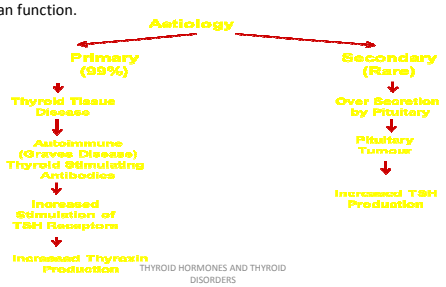
- No Response → Secondary Hypothyroid
- Excessive Response → Primary Hypothyroid
- Delayed Response → Tertiary Hypothyroid

## Hyperthyroidism and Thyrotoxicosis

- Definition of hyperthyroidism;

"Excessive secretion of the thyroid hormone resulting in a hypermetabolic state.

Thyrotoxicosis occurs when tissues are exposed to excess amount of TH, resulting in specific metabolic changes pathophysiologic alterations in organ function.






## CAUSES OF PRIMARY HYPERTHYROIDISM

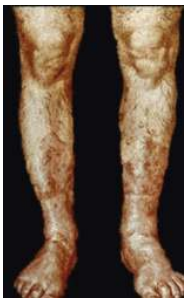
1. **GRAVE'S** DISEASE(DIFFUSE TOXIC GOITRE); This is a state of hyperthyroidism, goitre, and ophthalmopathy which starts between the ages of 20-40 yrs. It is an auto immune disease characterized by abnormal stimulation of the thyroid gland by thyroid stimulating immunoglobulins(TSI) which act through the thyroid stimulating hormone receptor(TSR). TSI binds to TSR and stimulate thyroid growth hyper secretion of TH.

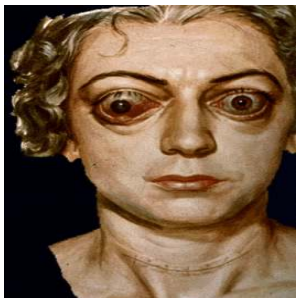
OPTHAMOLPATHY(EXOPHTHALMUS) usually occurs due to production of antibodies against non TSH retro orbital antigen, localised on retro orbital fibroblast and muscle cells

The disease is usually promoted by poorly define factors such as excess iodide and excess Li(in lithium therapy), viral and bacteria infection e.g *Yersinia enterocolitica* infection, parturtion(relative immune tolerance in pregnancy).



## GRAVE'S DISEASE
## MYXEDEMA IN LIMBS AND EXOLPHTHALMIA







## 2. TOXIC ADENOMA AND TOXIC MULTINODULAR GOITER

- Increase TH formation and secretion occur in single nodule > 3cm or multiple thyroid nodules (Plummer's disease). In toxic adenoma several point mutation of TSH receptor gene leads to constitutive activation. Some adenomas have mutatation of the G protein resulting in constitutive activation.
- This adenomas secretes large quantities of T4 & T3 in the present of supress TSH. In contrast to graves disease, TSI and anti thyroperoxidase are absent. It is precipitated by excess iodide intake.

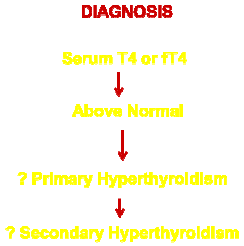
SECONDARY HYPERTHYROIDISM

1. TSH PRODUCING PITUITARY TUMORS
2. Ectopic thyroid hormone production by ovarian teratoma.
3. Thyrotoxicosis factitia. Inadvertent or plan ingestion of large amounts of TH especially by obese patients.

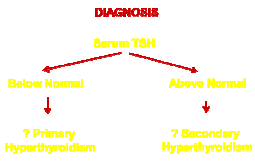


## Diagnosis of hyperthyroidism

**Serum T4 or FT4 measurement**




**Serum TSH measurement**



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