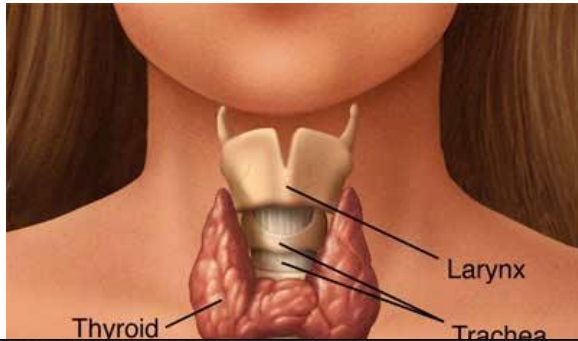


Thyroid Function Test

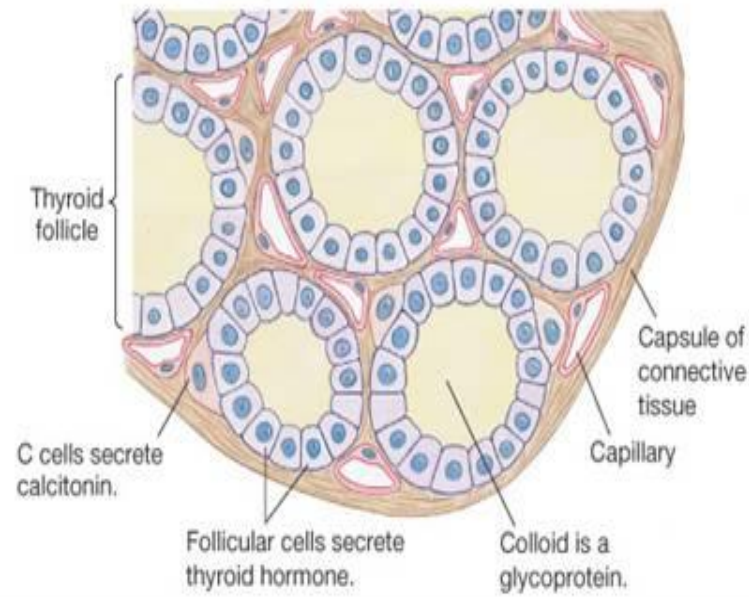
Learning objectives

- ✓ Normal functioning of thyroid gland including production and regulation of thyroid hormones.
- ✓ Various parameters used to assess thyroid function.
- ✓ Thyroid function tests in various thyroid dysfunctions.
- ✓ Analytical and radiological methodologies to assess thyroid functions.

A brief review of Thyroid gland

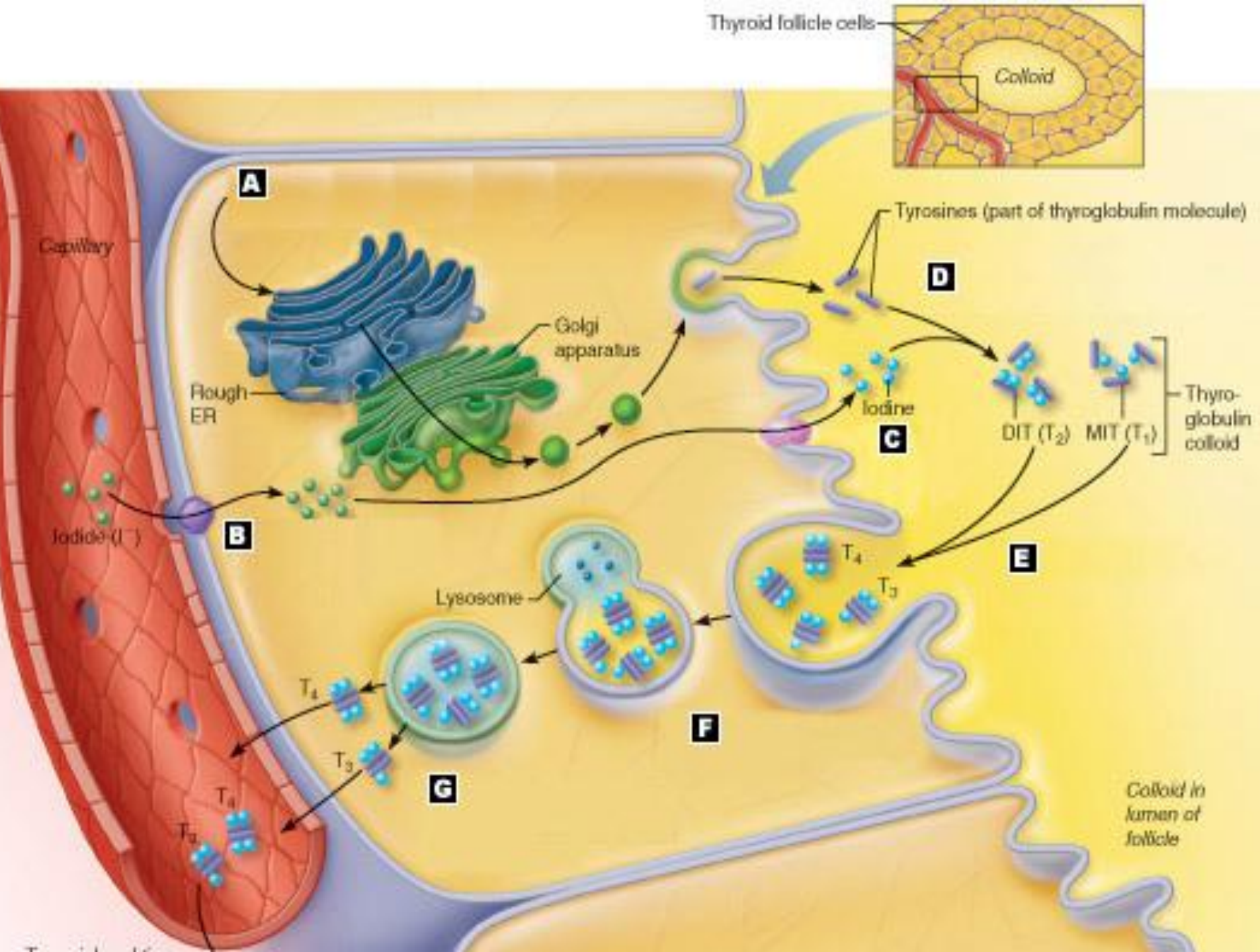


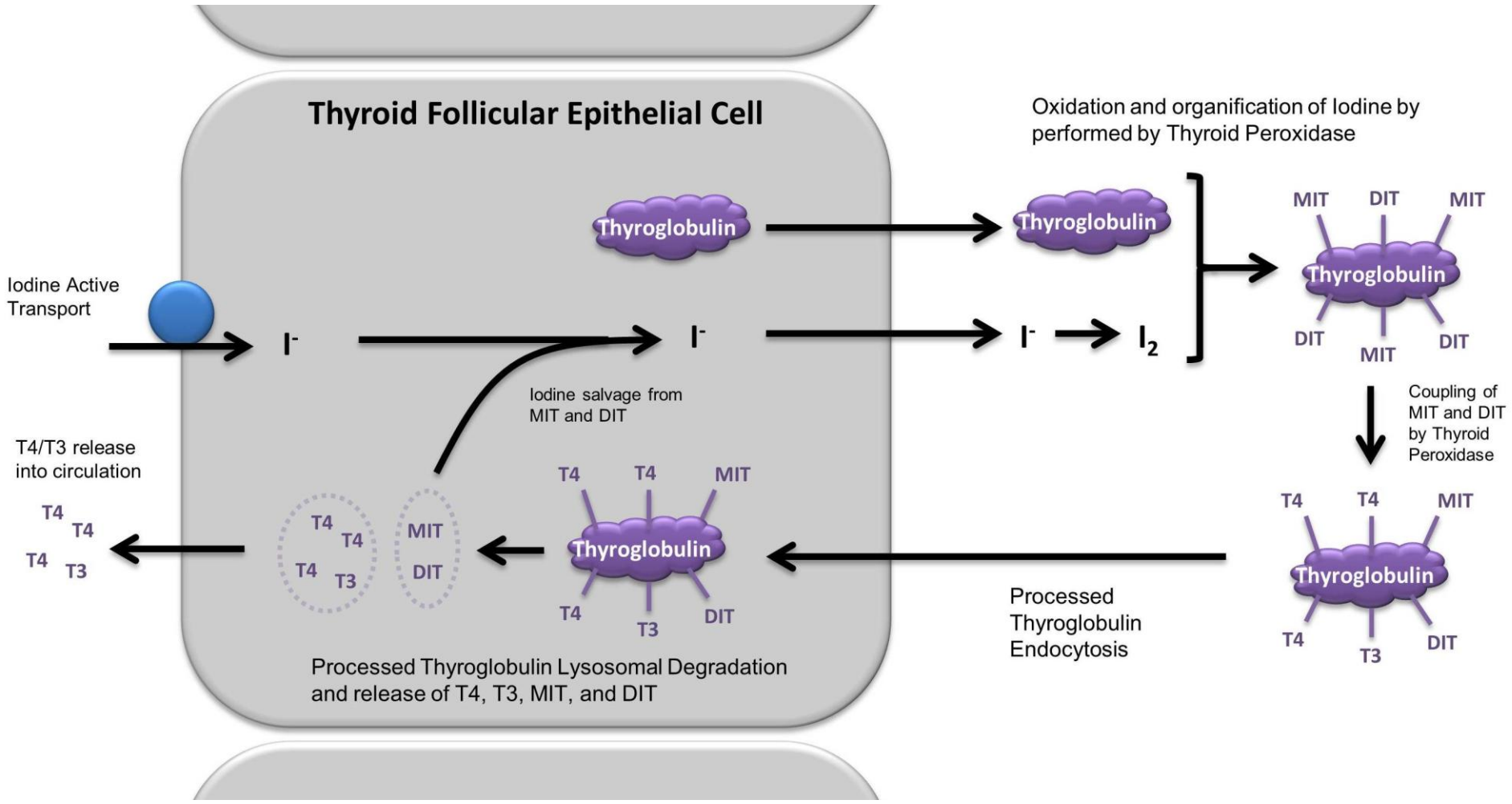
(b) Section of thyroid gland



- **Butterfly shaped gland located in front of neck.**
- **Weight : 15 – 20 gm**
- **Thyroid follicle is the secretory unit**
- **two-in-one gland :**
 - **Thyroid follicular cells secrete thyroid hormone**
 - **Parafollicular (C) cells secrete calcitonin**

THYROID SYNTHESIS AND TRANSPORT





Products of Thyroid gland

- **Mono-iodotyrosine (MIT) and Di-iodotyrosine (DIT)**
- **Thyroid hormones**
 - **Thyroxine (T4)** (3,5,3',5'-L-tetraiodothyronine)
 - **Tri-iodothyronine (T3)** (3,5,3'-L-triiodothyronine)
- **Reverse T₃ (rT₃)** (3,3',5'-L-triiodotyrosine)

Peripheral metabolism of thyroid hormones

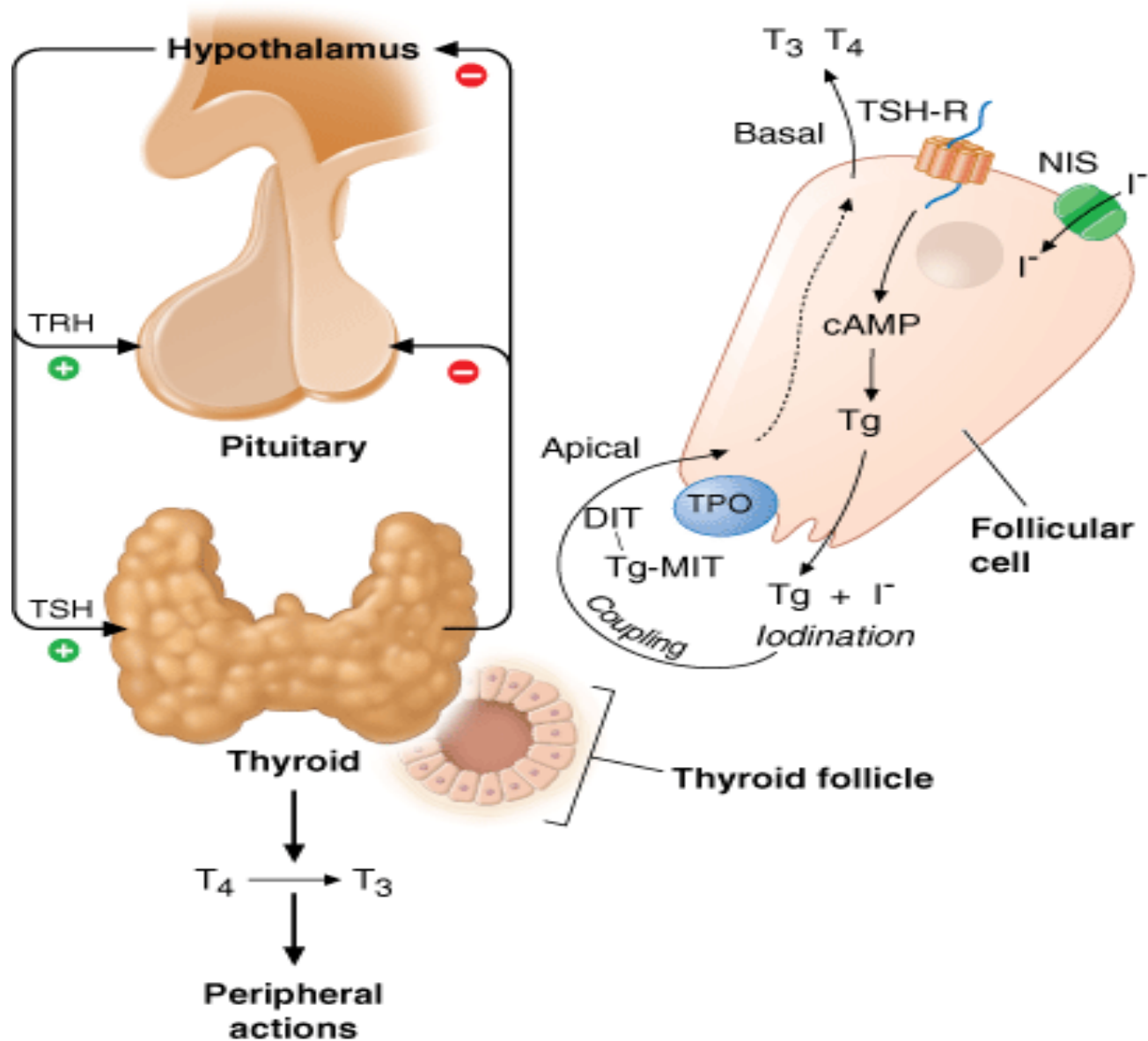
- Only T_3 binds intranuclear thyroid hormone receptors (TRs)
- De-iodinases remove iodine moiety from T_4
- 3 types D1, D2 and D3
- 40 % $T_4 \rightarrow T_3$ by D1 and D2
- 45 % $T_4 \rightarrow rT_3$ by D1 and D3

Biological functions of thyroid hormone

1. Growth and development of fetus and child
2. Calorigenic effect or **thermogenesis** is the major effect of thyroid hormone.
 - It is mediated by uncoupling of oxidative phosphorylation.
 - Increases O_2 consumption within tissue
 - Enhances mitochondrial metabolism
 - Increases sensitivity to catecholamines

- 3. Earliest effect of T4 is stimulation of RNA synthesis and consequent increase in protein synthesis. Higher concentration of T3 causes protein catabolism and negative nitrogen balance.**
4. Basal Metabolic Rate(BMR) is increased(Thyroxine increases cellular metabolism)
- 5. Gluconeogenesis and carbohydrate oxidation are increased.**
- 6. Fatty acid metabolism is increased. Cholesterol degradation is increased and hence cholesterol level in blood is decreased, which is another hallmark of hyperthyroidism.**

Regulation of thyroid hormone production



Thyroid hormones in circulation

- Both T_3 and T_4 are highly plasma protein bound.
- Unbound form is biologically active.

Binding Proteins

- Main function → maintenance of a large pool of hormone that can be mobilised when needed .
- Plasma proteins that bind thyroid hormones are
 - Albumin – more CAPACITY
 - Prealbumin – Transthyretin (thyroxine binding prealbumin)
 - Globulin – thyroxine binding globulin (TBG) – more AFFINITY

- T3 & T4 are LIPOPHILLIC ; their free forms in plasma are in equilibrium with a larger pool of protein bound thyroid hormones
- Free thyroid hormones are added to the circulating pool by the thyroid
- These free hormones are the physiologically active forms that send feedback to inhibit pituitary secretion of TSH

Alteration in Thyroid hormone binding proteins



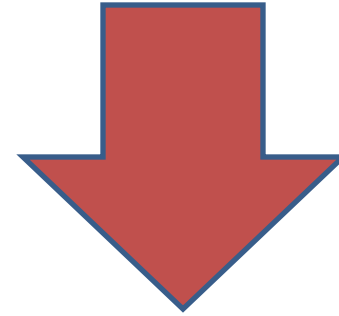
Increase in TBG concentration or affinity

Genetic causes

Non thyroidal illness such as HIV infections , hepatitis an estrogen producing tumors

Pregnancy , new born

Drugs such as OCPs, Estrogens, Tamoxifen



Decrease in TBG concentration or affinity

Genetic causes

Non thyroidal illness such as surgical stress, chronic liver disease, nephrotic syndrome

Drugs such as anabolic steroids, large doses of glucocorticoids

Clinical disorders of Thyroid gland

- Based on history, clinical examination and laboratory results; patients can be classified into :

» **Euthyroid**

» **Hypothyroid**

Hypothyroidism	Hyperthyroidism
Mental dullness	Nervousness
Increased sleep, lethargy	Sleeplessness
Hoarseness of voice	Excessive sweating
Cold intolerance	Heat intolerance
Weight gain	Weight loss
Constipation	Diarrhoea
Signs : Bradycardia, dry skin	Signs : tachycardia , systolic murmurs

Etiology of Primary and Secondary Hypo & Hyperthyroidism

Hypothyroidism	Hyperthyroidism
ENDOGENOUS	ENDOGENOUS
Autoimmune thyroid diseases : <ul style="list-style-type: none"> <input type="checkbox"/> Hashimoto thyroiditis <input type="checkbox"/> Atrophic thyroiditis <input type="checkbox"/> Post partum thyroiditis 	Autoimmune thyroid diseases : <ul style="list-style-type: none"> <input type="checkbox"/> Graves <input type="checkbox"/> Hashitoxicosis <input type="checkbox"/> Post partum thyroiditis
Na ⁺ / Iodide pump dysfunction	Toxic multinodular goiter : Toxic adenoma, familial
Thyroperoxidase enzyme deficiency, Developmental disorders etc.	HCG secreting tumors.
EXOGENOUS	EXOGENOUS
Iodine excess or deficiency , dietary goiterogens	Thyroid destruction by viral or bacterial thyroiditis
Drugs such as lithium , thionamides	Iodine induced hyperthyroidism

Thyroid auto antibodies

- Main auto antibodies are :
 - Thyroid peroxidase autoantibodies (TPOAs)
 - Thyroglobulin autoantibodies (TGAs)
 - Thyroid microsomal autoantibodies (TMAs)
 - Thyroid receptor autoantibodies (TRAs)

Detection of thyroid antibodies

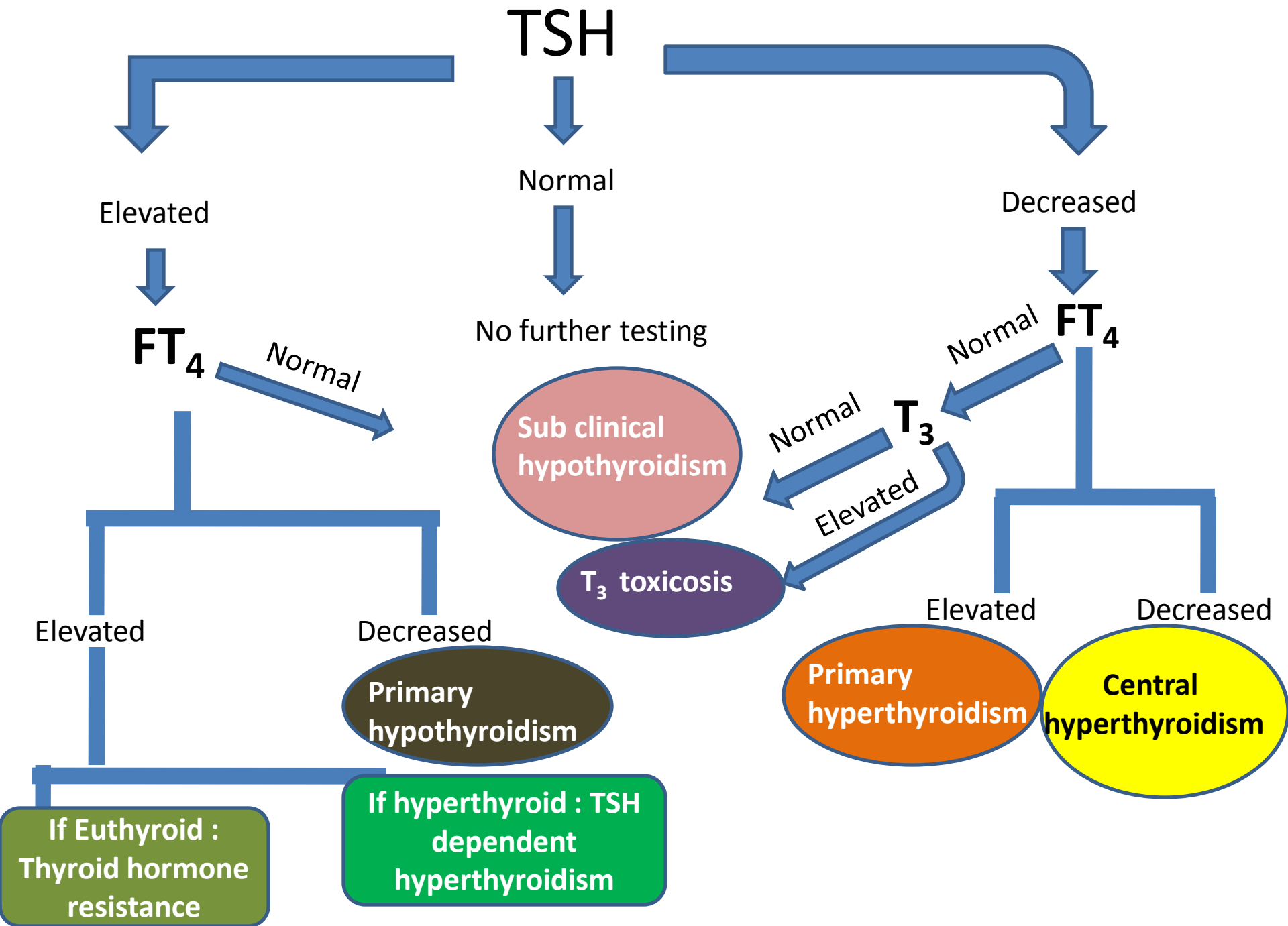
Antibody Name	Disease
Thyroglobulin autoantibodies (TGAs)	Thyroid cancer
Thyroid peroxidase autoantibodies (TPOAs)	Hashimoto s Thyroiditis (auto immune)
Thyroid stimulating immunoglobins	Graves disease

Indications for Thyroid function

tests :-

1. Evaluation of thyroid gland in case of clinical suspicion of thyroid disorder
 - Hyperthyroid
 - Hypothyroid
 - Primary (TSH High)
 - Secondary or tertiary (TSH low)
2. Follow up
3. Screening of congenital hypothyroidism.

??? Screening of asymptomatic individuals





Analytical Methods

Routine TFT Parameters

TSH	Thyroid stimulating hormone	0.5 – 5 mIU/L
T₄	Serum Total thyroxine	65 – 150 nmol/L
T₃	Serum total triiodothyronine	1.8 – 3 nmol / L
fT₄	Free T ₄	10 – 23 pmol / L
fT₃	Free T ₃	4 – 7.4 pmol / L
Thyroid Autoantibodies	TPOAs (Thyroid Peroxidase Antibodies),TGAs (Thyroglobulin Antibodies) , TMAs(Thyroid Microsomal Antigen)	

TSH

- Best initial test for screening
- Hypothyroidism elevated TSH (> 5 mIU/L)
- Hyperthyroidism low TSH (< 0.5 mIU/L)
- All modern TSH methods based on ELISA

TSH

- Specimen collection and storage
 - Serum or plasma is used
 - Stable for 5 days at 2-8 °C and 1 month when frozen
- Secretion is circadian , peak between 2 am and 4 am and nadir between 5 pm to 6 pm
- TSH surges immediately after birth (25 –160 mIU/L) and stabilizes in first few weeks.
- Decrease in first trimester due to HCG stimulation

Measurement of Total thyroxine (T_4)

- Principal hormone secreted by thyroid gland
- Highly protein bound (> 99.9 %)
- Total T_4 gives very limited clinical information
- If normal serum binding capacity: total T_4 is inversely proportional to TSH and proportional to free T_4

Measurement of Total triiodothyronine

(T₃)

- Principal active thyroid hormone.
- Only 99 % is bound but binding is weak
- Useful in diagnosis and monitoring of T₃ thyrotoxicosis

Other Thyroid parameters

- Thyroglobulin (Tg)
- Thyroid binding globulin (TBG)
- Reverse T₃ (rT₃)
- Tg mRNA in serum
- Thyroid autoantibodies

Cholesterol

- **Hypothyroidism** : cholesterol level ↑ (cholesterol carrying lipoprotein degradation decreased)
- But not diagnostic as raised in other conditions like → DM , HTN , obstructive jaundice
- However this level effective in monitoring the effectiveness of therapy

Radioactive iodine uptake

- Administration of radioactive iodine / technitium pertechnetate allows visualisation of thyroid tissue in neck and throughout body
- It helps to reveal whether uptake is low or high . Esp in following diseases
- Hemithyroid (toxic hyperactive nodule)
- Cold nodule (nodule fails to take tracer)
- Ectopic thyroid tissue

TRH (Thyrotropin Releasing Hormone) Response Test

- Determining basal levels and levels 15 – 30 mins after an IV bolus of TRH
- TRH administration will stimulate the production of TSH
- If the Hypothalamo – Pituitary – Thyroid Axis is normal ; T_3 , T_4 secretions will be increased :

- An abnormal response is seen in:
- **Hyperthyroidism** : the negative feedback effect of high T4 overpowers the stimulant effect of TRH . Here thyroid hormones are elevated
- **Hypopituitarism** : the pituitary could not respond to TRH . Plasma Thyroid levels → subnormal
- **Primary Hypothyroidism** : exaggerated response , negative feedback effect of T4 reduced

Lab findings in Hyperthyroidism

	Plasma total T3 and T4	fT4	Plasma TSH	Response to TRH
Grave's Disease	Increase	High Increase	Decrease	Nil
Toxic Goiter	Increase	High Increase	Decrease	Nil
T3 Toxicosis	T3 Increase T4 Normal	Increase	Decrease	Sluggish
Excess intake of thyroxin	Increase	Mild Increase	Decrease	Sluggish

Lab Findings in Hypothyroidism

	T₃ and T₄ in blood	TSH in blood	Response to TRH
Primary Hypothyroidism	Decreased	Increased	Exaggerated Response
Secondary Hypothyroidism	Decreased	Decreased	No Response

Condition	Conc . Of Binding Protein	Total Plasma T ₃ T ₄	Free Plasma T ₃ T ₄	Plasma TSH	Clinical State
Hyperthyroidism	Normal	High	High	Low	Hyperthyroid
Hypothyroidism	Normal	Low	Low	High	Hypothyroid
Estrogen , Methadone , major tranquilizers	High	High	Normal	Normal	Euthyroid
Glucocorticoids , androgens , danazol	Low	Low	Normal	Normal	Euthyroid

Assignment

- I. Describe synthesis and secretion of thyroxine.
- II. Enumerate the thyroid function tests. Describe any one of them in detail.
- III. Which parameter is seen in congenital hypothyroidism
 - a) Increased TRH
 - b) Decreased TRH
 - c) Increased TSH
 - d) Decreased TSH
- IV. Which condition is associated with increased T_3
 - a) Primary hyperthyroidism
 - b) Primary hypothyroidism
 - c) Primary hypoparathyroidism
 - d) Primary hyperparathyroidism
- V. Thyroxine formation requires which trace element
 - a) Fluoride
 - b) Calcium
 - c) Iodide
 - d) Phosphorus

Viva questions

1. What is the precursor of thyroxin?
2. What is the ratio of T_3 and T_4 in blood?
3. What is the function of TSH?
4. What is the function of thyroid hormones
5. Deficiency of thyroxine results in ?
6. What are the salient feature of hypothyroidism?
7. What is the cause of Graves Disease?