Thyroid Function Tests (TFT)

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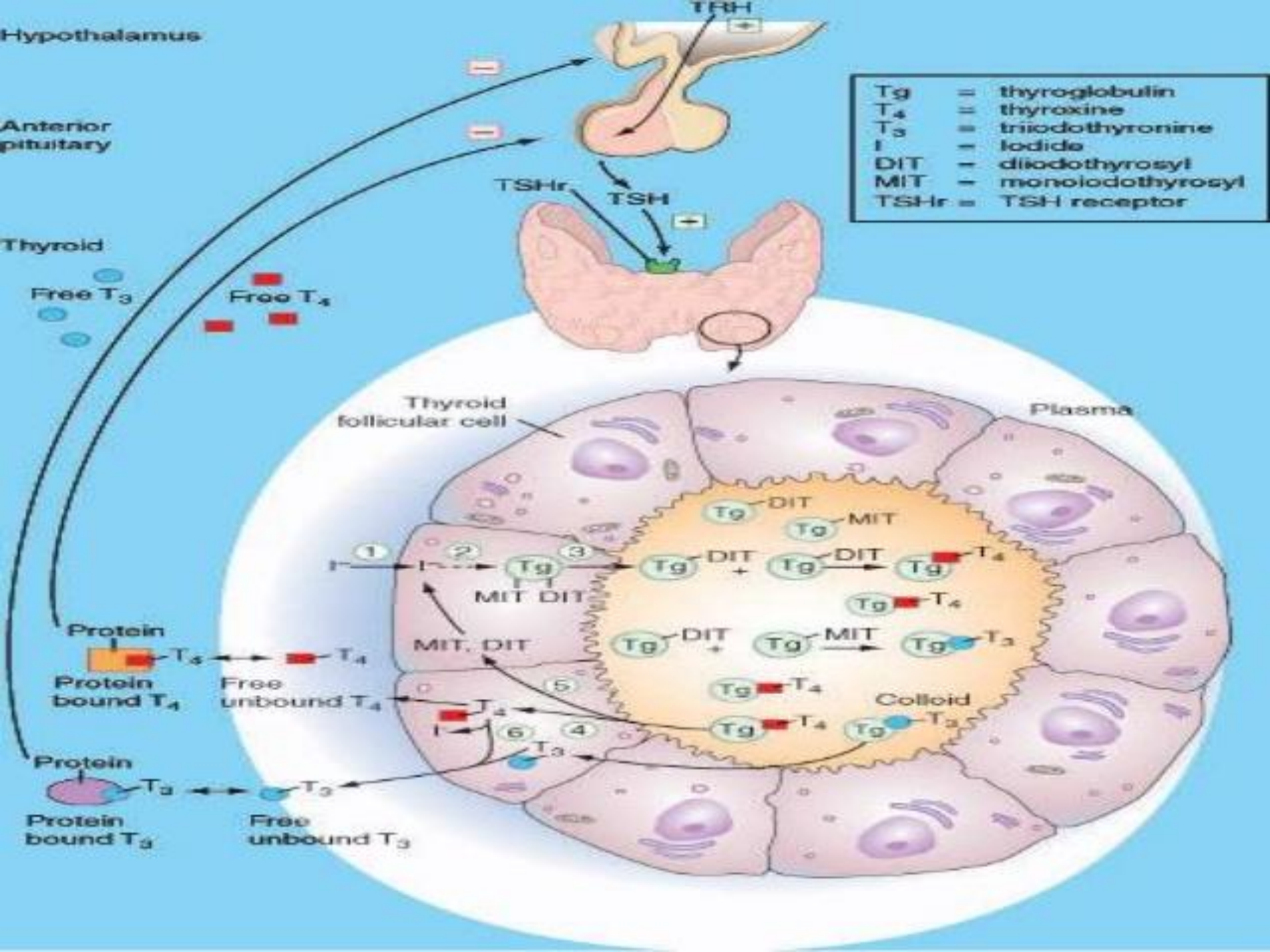
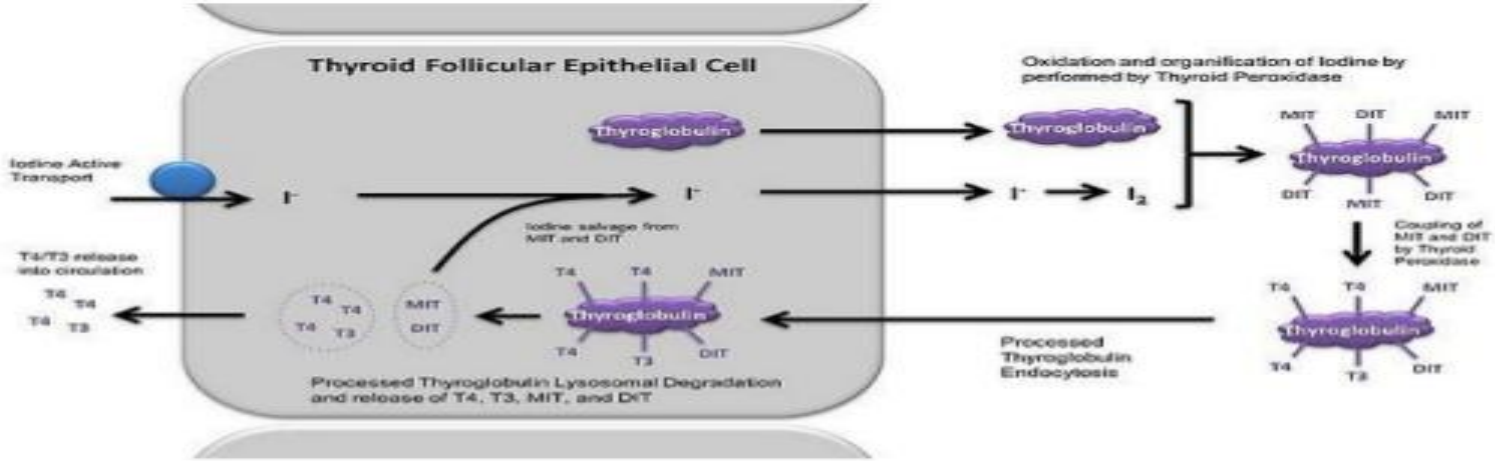

Hypothalamus
TRH
+
−
Anterior pituitary
−
TSHr
TSH
+
Thyroid
Free T_3
Free T_4
Tg = thyroglobulin
T_4 = thyroxine
T_3 = triiodothyronine
I = Iodide
DIT = diiodothyrosyl
MIT = monoiodothyrosyl
TSHr = TSH receptor
Thyroid follicular cell
Plasma
Tg
DIT
MIT
T_4
T_3
1
2
3
4
5
6
I^-
I
MIT DIT
MIT, DIT
Colloid
Protein
Protein bound T_4
Free unbound T_4
Protein
Protein bound T_3
Free unbound T_3

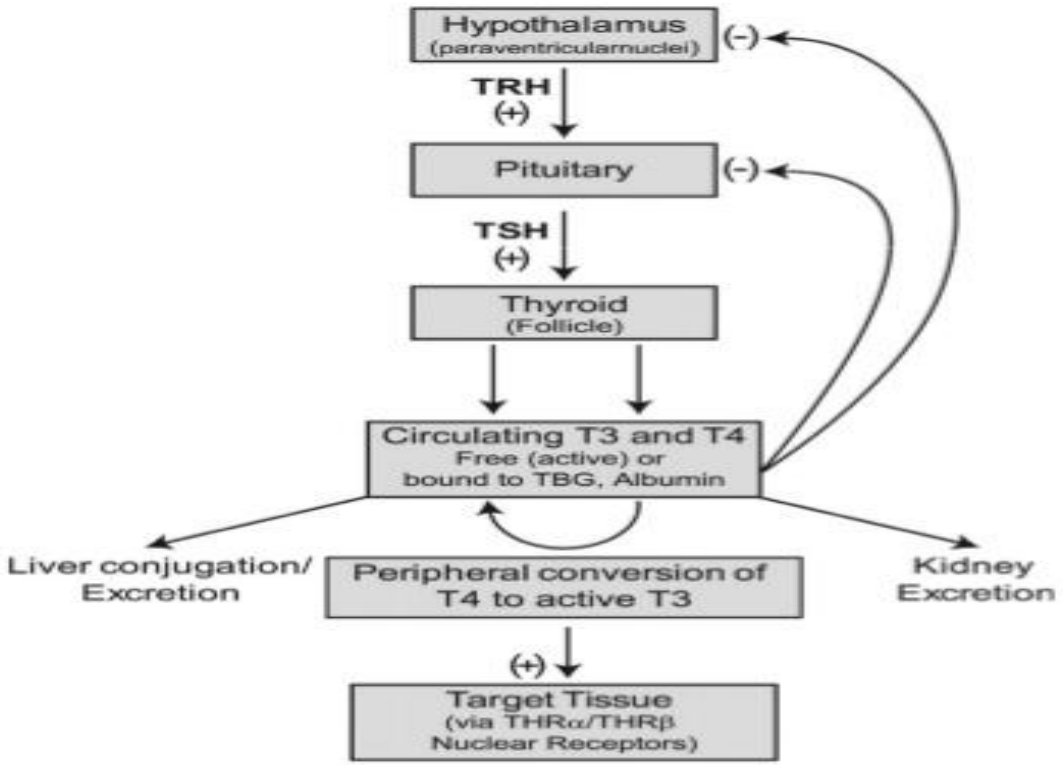
***Biosynthesis of thyroid hormones:-**



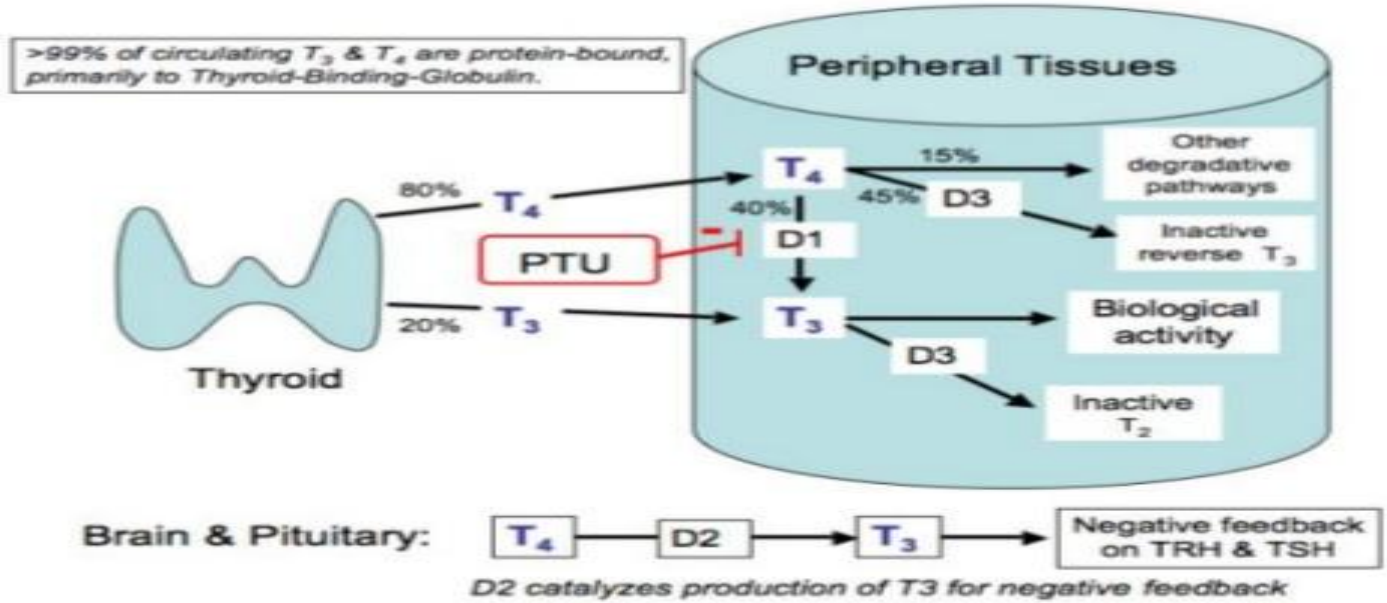
Steps:

1. Iodide (I^-) enters the thryroid cell via sodium iodide sympo rter
2. It enters the colloid through pendrin receptor
3. It is oxidized into Iodine (I^0) by peroxidase enzyme
4. Then it is organified into M IT and DIT (mono and di iodo thyronine)
5. Then after coupling it forms T_3 (Tri iodo thyronine) and T_4 (Thyroxine)
6. T_3 and T_4 conjugate with TBG (thyroid binding globulin)
7. conjugated TBG is stored in colloid till required
8. W hile releasing into blood stream, it is first endocytosed into thyroid cell and then de - coupled to form, T_3 and T_4 with M IT and DIT
9. M IT and DIT can be reutilized for coupling
10. T_3 and T_4 are released into the blood stream

***Regulation of thyroid hormone production**

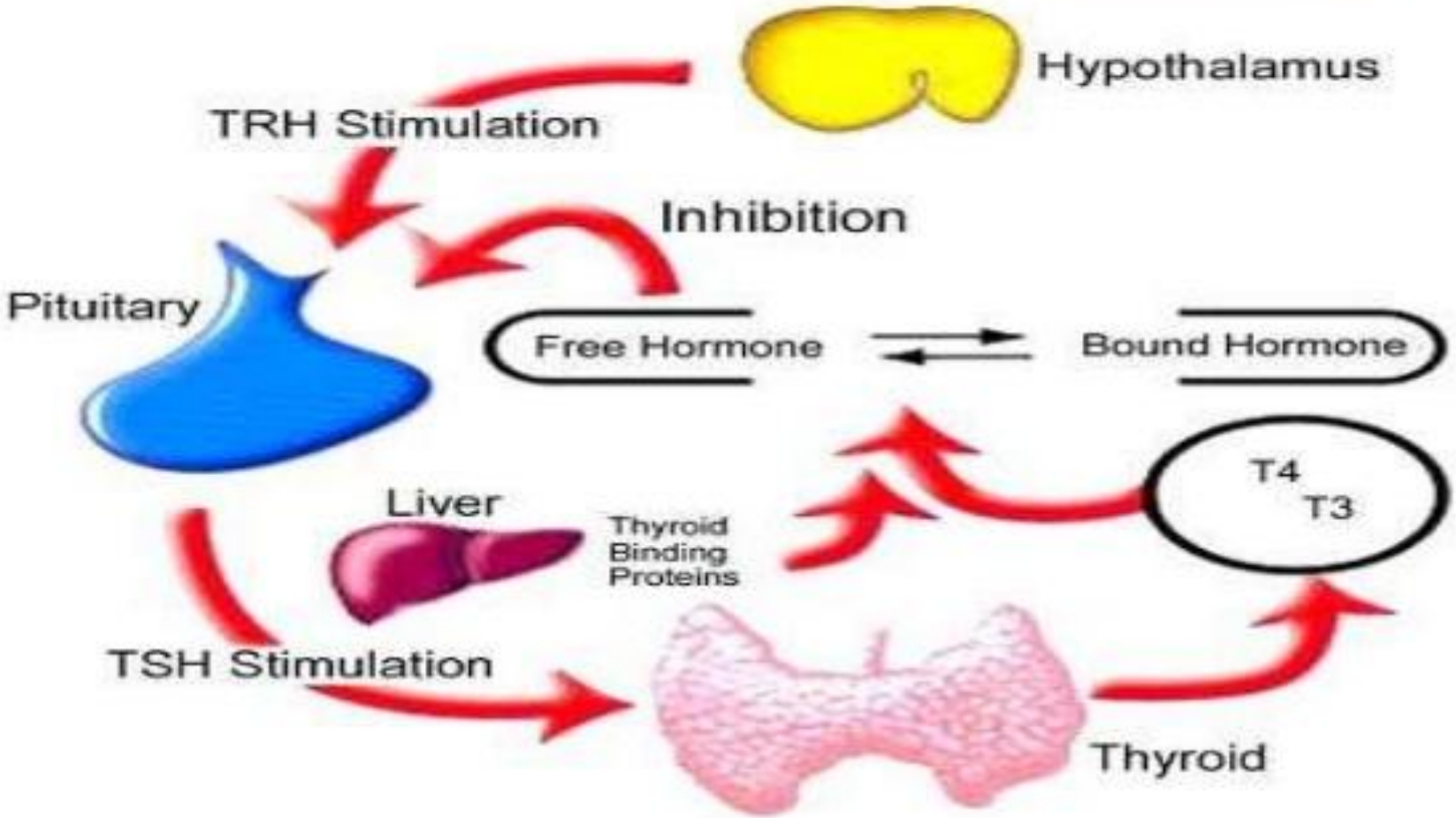


What happens to thyroid hormones after release



Action of thyroid hormone on the body:

HPT axis


Hypothalamus
TRH Stimulation
Inhibition
Pituitary
Free Hormone
Bound Hormone
T4
T3
Liver
Thyroid
Binding
Proteins
TSH Stimulation
Thyroid

COMMON TESTS TO EVALUATE THE THYROID

- Blood:
  - TSH
  - Free T4, T3 (rarely T4, T3U, FTI)
- Radiology:
  - Radionuclear - thyroid function vs. imaging
  - Other imaging: ultrasound, CT, MRI
- Pathology:
  - FNA biopsy

CLASSIFICATION OF TESTS BASED ON FUNCTIONS OF THYROID

❑Tests measuring blood levels of thyroid hormones:

- Sr PBI
- Circulating T3 and T4 level
- Circulating TSH level
- Plasma tyrosine level

❑Tests based on primary function if thyroid viz substrate input & hormone synthesis:

- RIU(Radioiodine uptake studies)
- PBI^{131}
- T3 suppression test
- TSH stimulation test
- TRH stimulation test

❑Tests based on metabolic effects of thyroid hormones

- BMR
- Sr cholestrol
- Sr creatine level
- Sr uric acid level
- Sr CK enzyme

❑Scanning of thyroid gland

❑Immunological tests to detect autoimmune diseases of thyroid gland:

- Agar gel diffusion test(PPT test)
- TRCH test: tanned red cell haemagglutination test
- Complement fixation test

Indications of TFT

- Diagnosing thyroid disorder in symptomatic person
- Screening newborns for hypothyroidism
- Monitoring thyroid replacement therapy in hypothyroidism patients
- Diagnosis & monitoring female infertility patients
- Screening adults for thyroid disorders

Hypothyroidism

Causes:

PRIMARY: (high TSH)

- **Autoimmune :** Hashimoto`s, Atrophic
- **Iatrogenic:** I^{131} t/t, subtotal/total thyroidectomy, external irradiation of neck for Ca
- **Drugs**: I excess, lithium, antithyroid drugs, p- aminosalicylic acid,Interferon
- **Congenital hypothyroidism:** absent/ectopic thyroid gland, dyshormonogenesis, TSHR mutation
- **Iodine deficiency**
- **Infiltrative disorders**

SECONDARY: (Low TSH)

- **Hypopitutarism:** tumors, surgery, irradiation ,infiltrative disorders, sheehan`s syndrome,trauma
- **Isolated TSH deficiency or inactivity**

TERTIARY : (LOW TSH ,Low TRH)

Diseases of hypothalamus

TRANSIENT: silent / postpartum thyroiditis, subacute thyroiditis

Clinical Features of Hypothyroidism

Tiredness

Forgetfulness/Slower Thinking

Moodiness/ Irritability

Depression

Inability to Concentrate

Thinning Hair/Hair Loss

Loss of Body Hair

Dry, Patchy Skin

Weight Gain

Cold Intolerance

Elevated Cholesterol

Family History of Thyroid Disease or Diabetes

Puffy Eyes

Enlarged Thyroid (Goiter)

Hoarseness/ Deepening of Voice

Persistent Dry or Sore Throat

Difficulty Swallowing

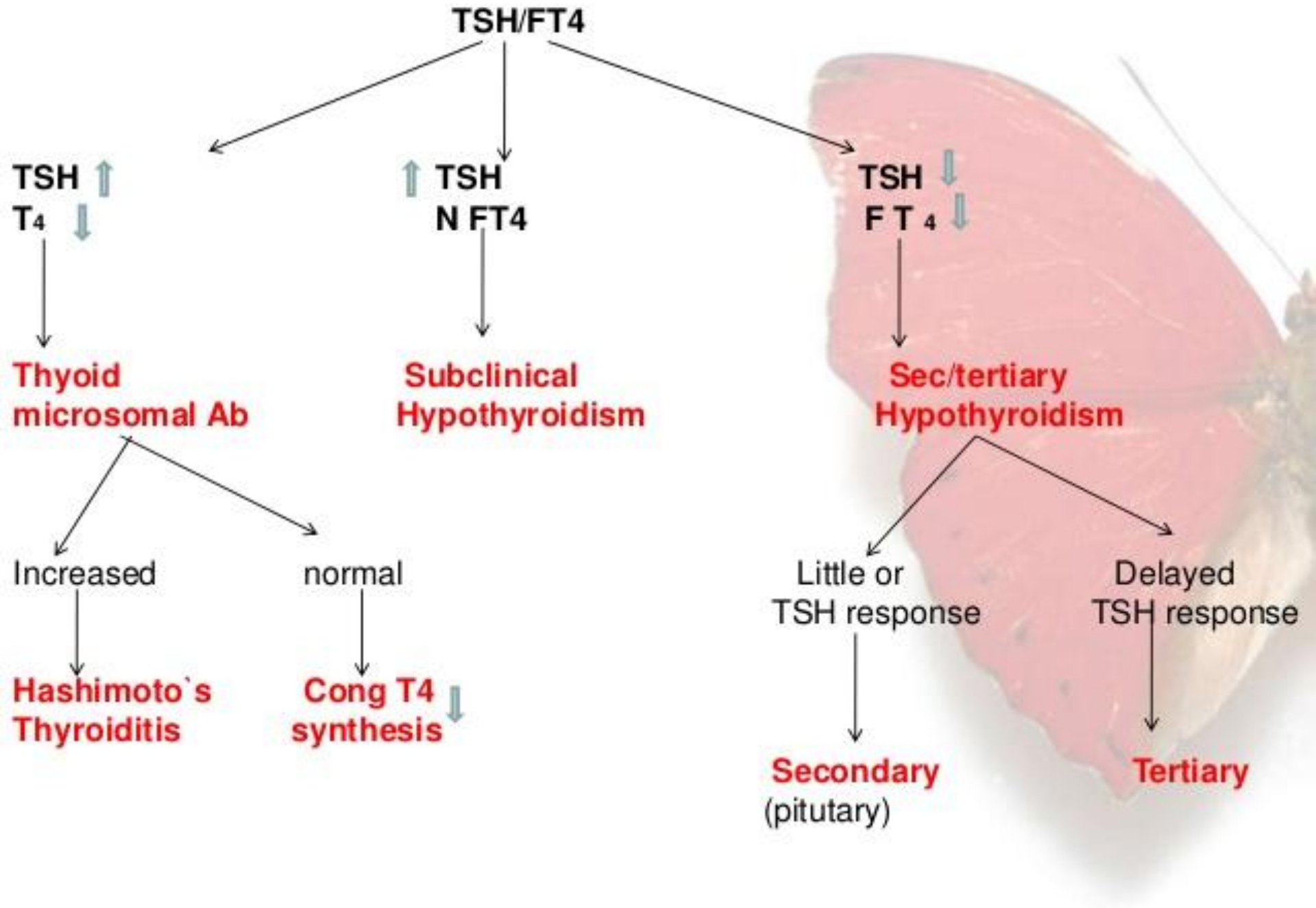
Slower Heartbeat

Menstrual Irregularities/ Heavy Period

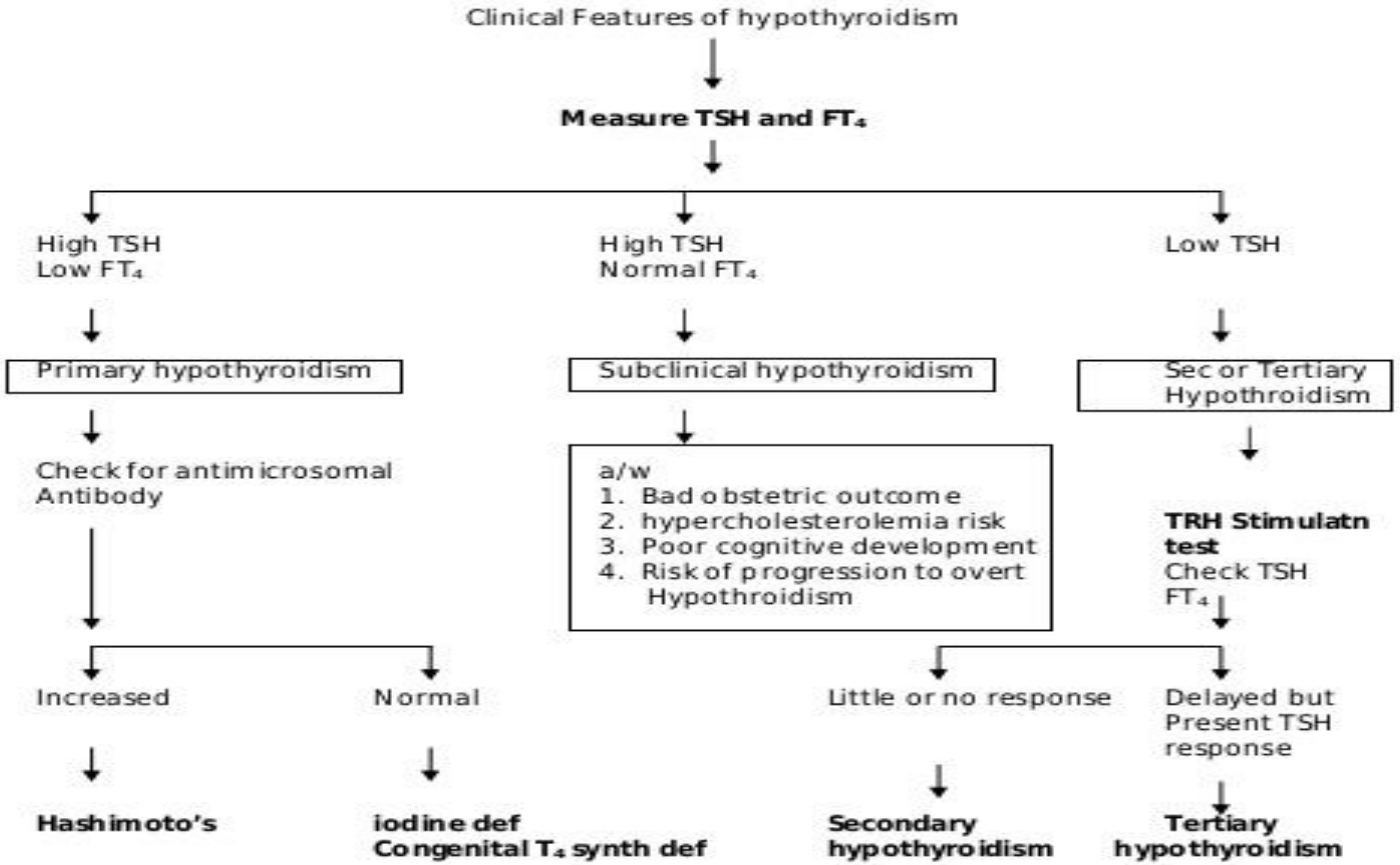
Infertility

Constipation

Muscle Weakness/ Cramps


TSH/FT4
TSH ⇧
T4 ⇩
⇧ TSH
N FT4
TSH ⇩
F T 4 ⇩
Thyoid microsomal Ab
Subclinical Hypothyroidism
Sec/tertiary Hypothyroidism
Increased
normal
Little or TSH response
Delayed TSH response
Hashimoto`s Thyroiditis
Cong T4 synthesis ⇩
Secondary (pitutary)
Tertiary

Laboratory features:



Hyperthyroidism

Causes:

PRIMARY HYPERTHYROIDISM

Grave`s disease
Toxic MNG
Toxic Adenoma
Functioning thyroid carcinoma mets
Activating mutation of TSH receptor
Struma ovarii
Drugs: iodine excess(Jod basedow phenomenon)

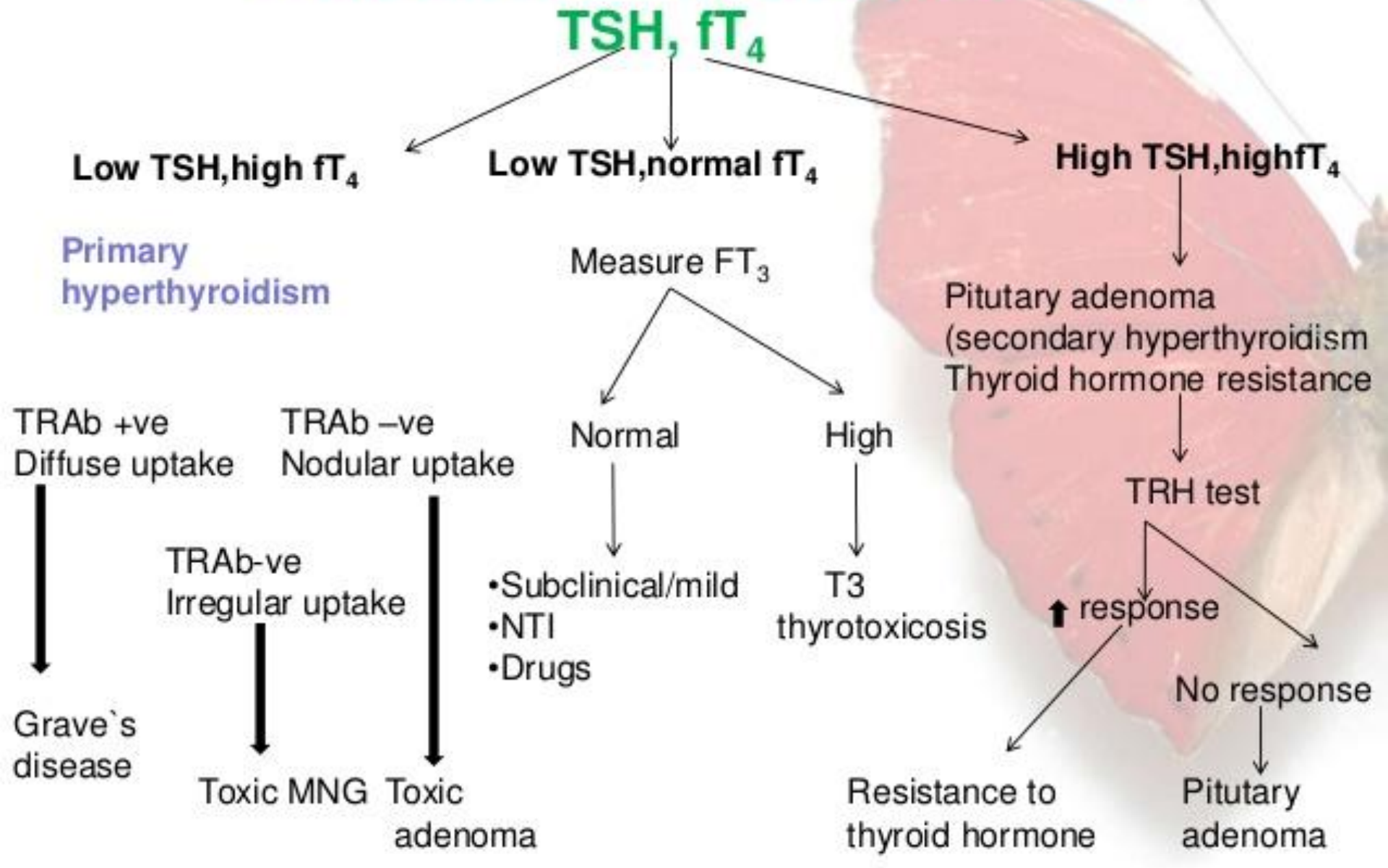
SECONDARY HYPERTHYROISM

TSH secreting pitutary adenoma
TRH syndrome
Chorionic gonadotropin secreting tumors
Gestational thyrotoxicosis

THYROTOXICOSIS WITHOUT HYPERTHYROIDISM

Subacute thyroiditis
Silent thyroiditis
Other causes of thyroid destruction: amiodarone,radiation,infarction of adenoma
Ingestion of excess thyroid hormone

Evaluation of hyperthyroidism



TSH

- First line test in Thyroid function tests
- Normal TSH level excludes thyroid dysfunction

Uses:

- Screening for euthyroidism
- Screening of hypothyroidism in newborns
- Diagnosis of 1 & 2 hypothyroidism
- Diagnosis of clinical & subclinical hyperthyroidism
- Follow up of T3 & T4 replacement therapy in hypothyroidism

TSH

Increase

- Primary hypothyroidism
- Addison`s disease
- Anti TSH antibodies
- PreEclampsia
- Hypothermia,fasting state
- Pitutary adenoma
- Postoperatively
- Acute psychiatric illness
- Thyroiditis
- Drugs:Amiodarone,bensarazide ,clomiphene, iopanoic acid, lithium, methimazole, metoclopramide,morphine,propylthiouracil,radiographic dyes

Decrease

- Primary hyperthyroidism
- Hashimoto`s thyroiditis
- Hypothyroidism(2 or 3) sometimes
- Organic brain syndrome
- Drugs: ASA,heparin,ketoconazole,T3,dopamine, glucocorticoids,octreotide

Methods of TSH estimation

- Radioimmunoassay
- Immunometric assay
- Chemiluminiscent & flourescent techniques(3rd gen)

- **Normal values: TSH 0.4 to 4mU/L**

Concept of FT3 and FT4

- Out of the total T3 and T4 in circulation, most of it remains bound to thyroid binding globulin *, thyroid binding prealbumina nd Thyroid binding albumin. (*note – this is not thyroglobulin)
- Only about 0.05% of each T3 and T4 remains free in circulation. This is FT3 and FT4.
- These are better indicators for thyroid function than total T3 and Total T4. (total=bound+free).
- For example in pregnancy, level of thyroid binding globulin rises; hence though total T3 and total T4 remains same, level of FT3 and FT4 decreases. Notes on Renal function tests.

Differences between T3 and T4

	T3	T4
Secretion	30 microgram /day	80 microgram /day
Source	20 – 25% by gland 75 - 80% by conversion	Solely by gland
Half-life	1 day	7 days
Potency	3-4 times more potent than T4	Potent
Binding	0.2% in unbound	0.02% in unbound

Total thyroxine

•Total thyroxine includes free as well as protein bound thyroxine.

•Normal levels:5 to 12.5ug/dL, largely bound to transport protein espTBG.

• T4 combined with TSH gives the best measurement of thyroid function.

Thyroxine

Increase

- Hyperthyroidism
- Factitious hyperthyroidism
- Pitutary TSH secreting pitutary tumor
- Raised TBG

Decrease

- Primary hypothyroidism
- Secondary/pitutary hypothyroidism
- Severe non thyroidal illness
- Decrease TBG

Free T_4

- Small fraction of total T_4 unbound to protein
- Metabolically active form
- 0.05% of total T4
- Do not get affected by TBG levels or NTI
- Measurement useful in conditions where TBG levels are affected
- Normal levels:0.89- 1.76ng/dL

TBG(Thyroid binding globulin)
Main sr.carrier protein for both T4 & T3
(13-39ug/dL)

Increase

- Drugs:Clofibrate,estrogen,O.c Pills,Heroin.methadone
- Genetic
- Acute & chronic hepatitis
- Pregnancy
- Acute intermittent porphyria
- Angioneurotic edema
- Hyperproteinemia

Decrease

- Drugs:Androgens ,glucocorticoids,phenytoin,larg e doses of salicylates
- Malnutrition
- Hypoproteinemia,nephrotic syndrome
- Acromegaly,cushing`s syndrome
- Liver failure
- Sepsis

Thyroglobulin

Synthesised & secreted by thyroid follicles(30ng/ml)

Reflects throid mass,thyroid injury & TSH receptor stimulation

Tg ↑
- Grave`s disease
- Thyroiditis
- Nodular goitre

Indications :Monitoring recurrence of certain variants of thyroid Ca

Thyroid dysgenesis in Congenital hypothyroidism

Follow up of patients with thyroid malignancy

Thyroid Autoantibodies

- Diagnosing autoimmune diseases
- Autoantibodies :**Tg,Thyroid microsomal Ag,** TSH receptor, non Tg colloid antigen,TSH,T4

Anti Tg antibodies

Methods: Agar gel diffusion precipitation test
Tanned red cell haemagglutination tests(TRCH test)
ELISA
Immunoflourescence of tissue section
RIA
Positive: Hashimoto`s thyroiditis,Grave`s disease,myxedema,nontoxic goitre,thyroid ca,pernicious anaemia

Thyroid tests

Detect antibodies to thyroid tissue (Anti thyroid antibodies)

Found in Hashimoto's thyroiditis (95% of patients) and Grave's disease (55% of patients)

Adults without thyroid disease (10% of adults)

In Grave's disease, hyperthyroidism is caused by antibodies activating TSH receptors

In thyroiditis, hypothyroidism is caused by antibodies competitively binding to TSH receptors thus blocking the TSH from eliciting the response

Radioiodine uptake studies

Correlates with functional activity of thyroid gland

- Tracer dose of I^{131} orally followed by measurement of amount of radioactivity over thyroid gland at 2 hrs and again at 24hrs
- Normal radioactive uptake 20 to 40 % of administered dose at 24 hr

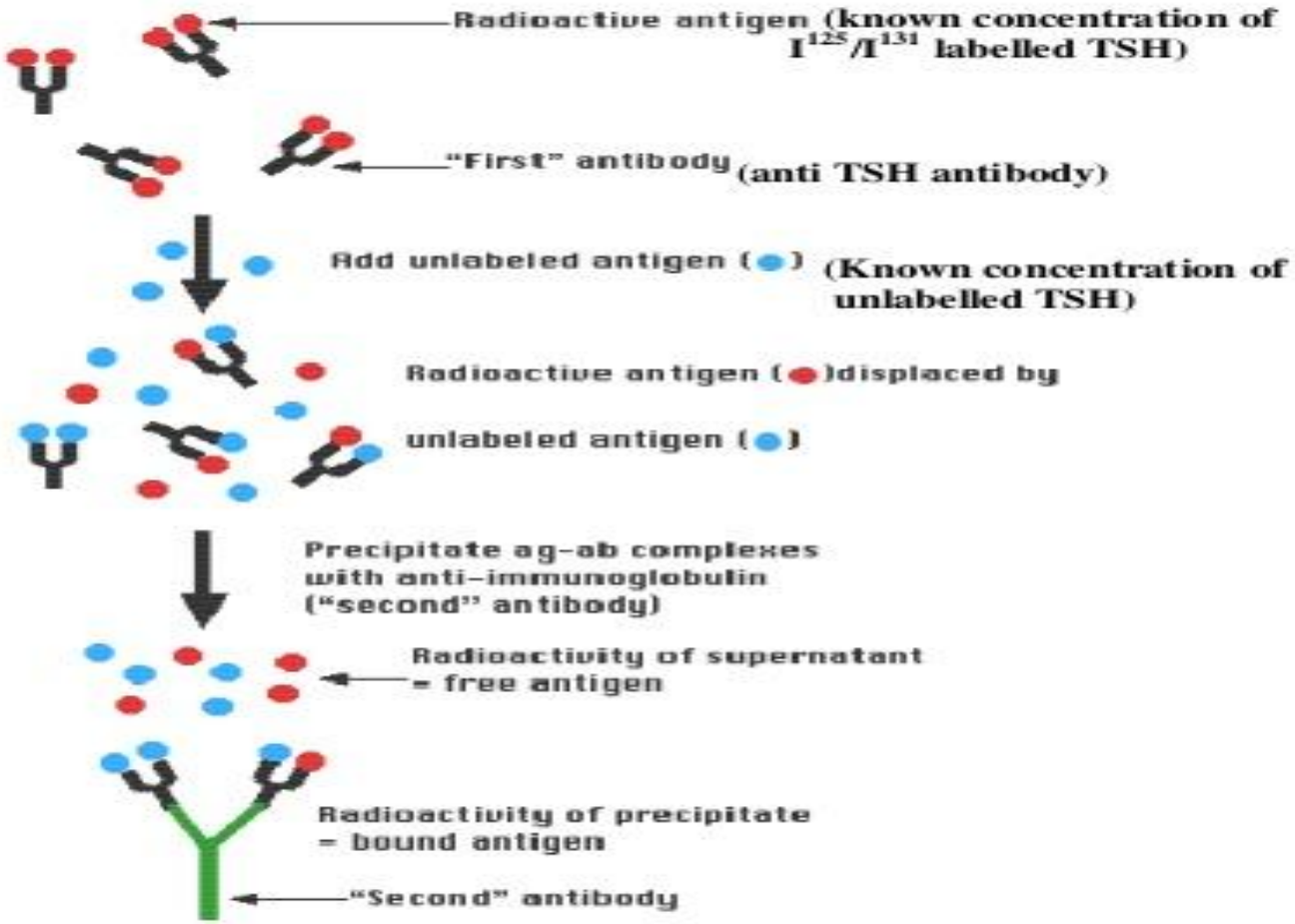
- Increased Uptake :
  - hyperthyroidism due to grave`s disease,
  - toxic MNG,
  - toxic adenoma,
  - TSH secreting tumor

Decreased uptake:

- hypothyroidism
- subacute thyroiditis,
- large I_2 doses, thyroid hormone
- factitious hyperthyroidism

Method: (Radioimmunoassay)(RIA)

The technique was introduced in 1960 by Berson and Yalow as an assay for the concentration of insulin in plasma. It represented the first time that hormone levels in the blood could be detected by an in vitro assay.



- A mixture is prepared of
  - radioactive antigen
    - Because of the ease with which iodine atoms can be introduced into tyrosine residues in a protein (TSH here), the radioactive isotopes ^{125}I or ^{131}I are often used.
  - antibodies ("First" antibody) against that antigen.
- Known amounts of unlabeled ("cold") antigen (known unlabelled TSH) are added to samples of the mixture. These compete for the binding sites of the antibodies.

(v) Antithyroid antibodies

Antibodies used:

Anti microsomal antibody Anti thyroid peroxidase antibody (anti TPO)	Hashimoto
Anti TSH receptor antibody	Grave's

Uses:
For diagnosis and monitoring of autoimmune thyroid disorders

TRH stimulation tests

Uses: Confirms diagnosis of secondary hypothyroidism
Evaluation of suspected hypothalamic disease

Procedure:

TRH injected iv(200 0r 500ug) followed by measurement of serum TSH at 20 & 60 min

Interpretation:

Peak response in **normal** 4 times elevation of TSH

Primary hypothyroidism: exaggerated & prolonged response

Secondary hypothyroidism: blunted response

Tertiary hypothyroidism: response is delayed

TSH stimulation test

Use: Differentiates primary from secondary hypothyroidism

Procedure: After 24hr RIU studies,3 injections of TSH, each 5 USP units are given at 24 hrs interval
24hr RIU is measured after 42 hrs after final TSH dose.

Interpretation:
In primary hypothyroidism, failure of stimulation of gland
In secondary hypothyroidism, stimulation of gland showing increased RIU.

Tests based on metabolic effects of thyroid hormones

BMR:

Between 5% & 20% normal

- Euthyroid state : -10% to 10% of normal
- Hyperthyroidism:50% to 75%
- Hypothyroidism: < -20%

Sr. CHOLESTROL LEVEL:

- 260mg% hypothyroidism

Sr. CREATINE LEVEL

- 0.6mg% hyperthyroidism

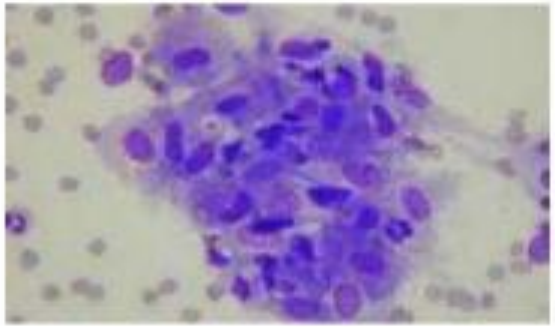
Sr. URIC ACID LEVEL:

Myxedema 6.5 to 11mg%

Sr. CK LEVELS⇧ & HYPERCALCEMIA

Summary

Disease	Total serum T4	Total serum T3	T3 resin uptake	Free T4 index	Radioactive iodine uptake test	TSH
Hypothyroidism	↓	↓	↓	↓	↓	↑ 1^0 ↓ 2^0, 3^0
Hyperthyroidism	↑	↑	↑	↑	↑	↓
T3 toxicosis	No change	↑	No change	No change	No change ↑	↓
Euthyroid sick syndrome	No change ↓	↓	↑	variable	No change	No change



FNAC thyroid

Indications:

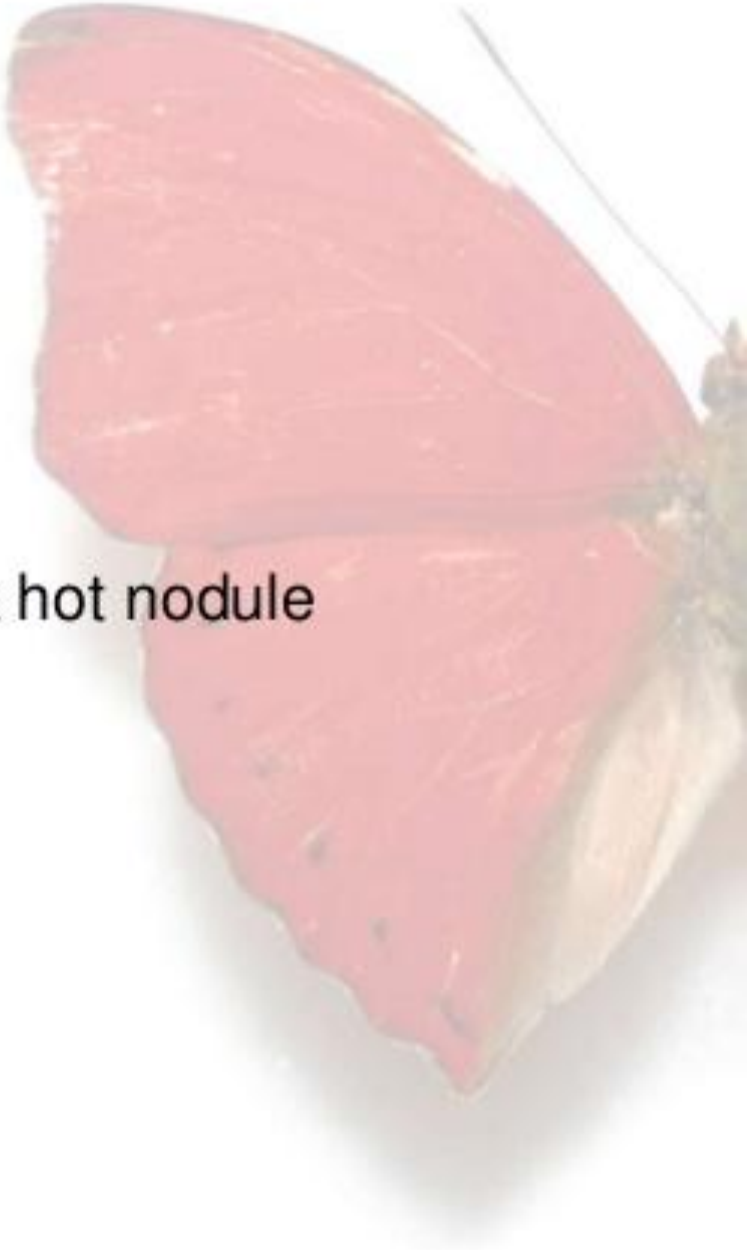
- Diagnosis of diffuse non toxic goitre
- Diagnosis of solitary or dominant thyroid nodule
- Confirmation of clinically obvious malignancy
- To obtain material for special laboratory investigations aimed at defining prognostic parameters.

Main limitation: Inability to distinguish between between follicular adenoma & carcinoma.

Contraindications: No

Complications:

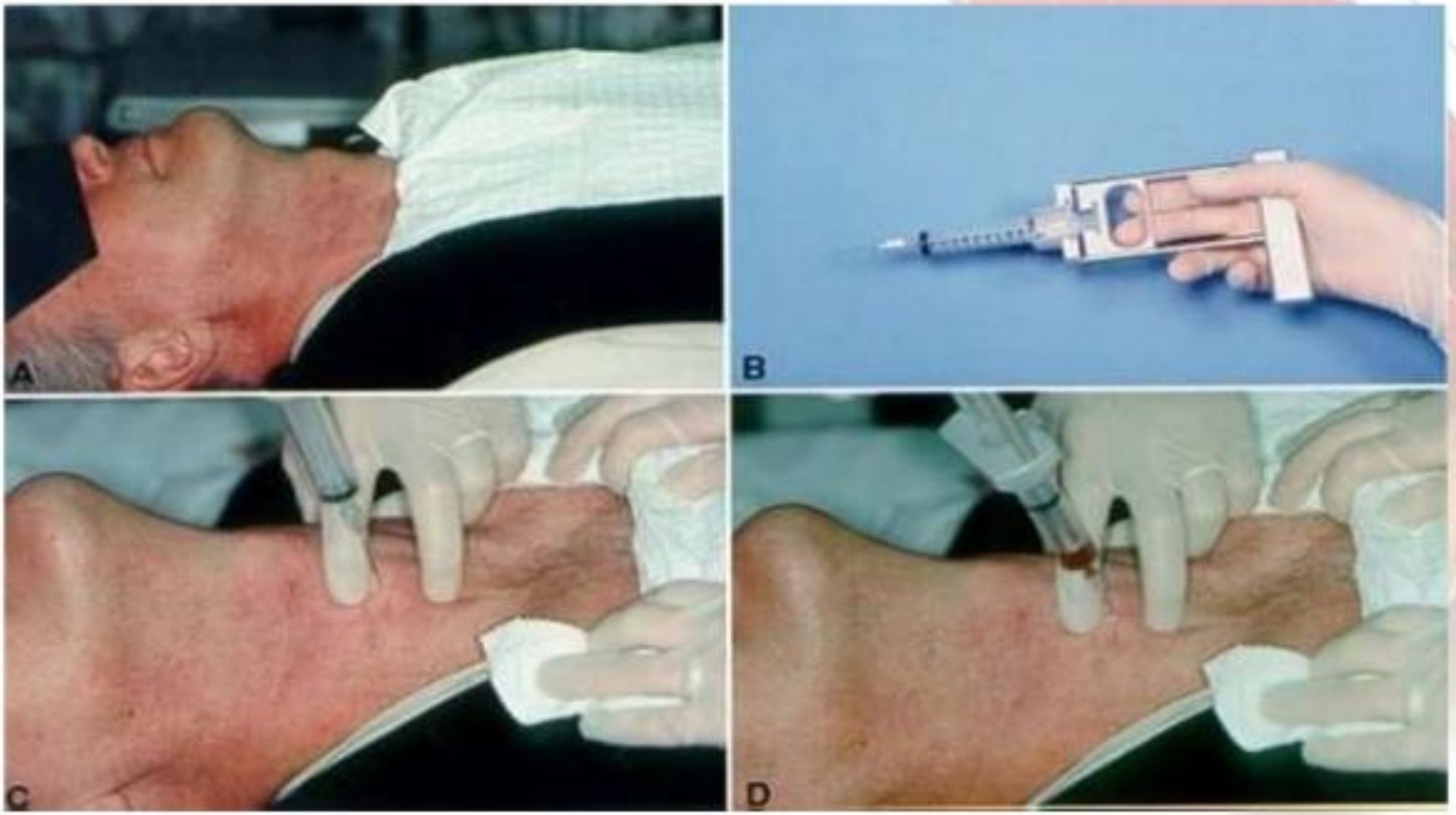
- Local h`age & haematoma.
- Transient laryngeal nerve paresis.
- Tracheal puncture
- Rarely,needling causes formation of a hot nodule



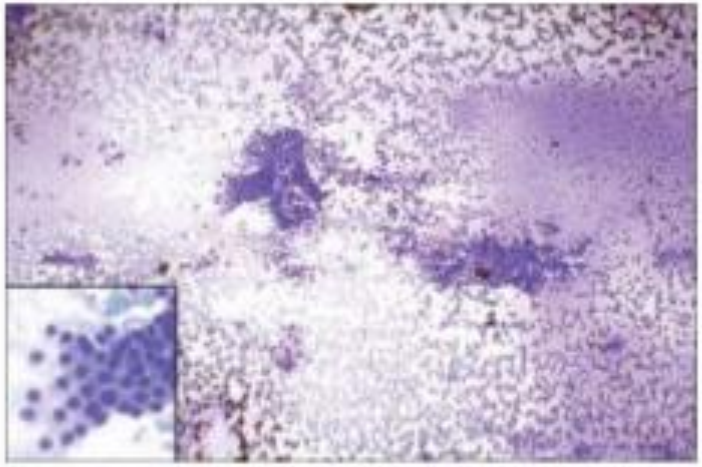
Materials

- Syringes & syringe holder(pistol)
- 22-25 guage needle
- Cotton Swabs
- Alcohol bottles for wet fixation

FNAC aspiration technique



FNAC non aspiration technique



Sample adequacy

- Six groups of follicular cells, each containing 10 to 20 cells on two separate slides
- Presence of colloid indicates benign nature

Bethesda system of reporting FNAC thyroid

1.Non diagnostic/Unsatisfactory

Cyst fluid only

Virtually acellular specimen

Other(obscuring blood,clotting artifacts)

2.Benign

Consistent with Benign follicular nodule(adenomatous,collloid nodule)

Consistent with lymphocytic(hashimoto`s thyroiditis) with proper clinical context

Consistent with granulomatous (subacute thyroiditis)

Other

3.Atypia of undetermined significance/Follicular lesion of undetermined significance

4.Follicular neoplasm or suspicious for follicular neoplasm

Specify if hurthe(oncocytic type)

5.Suspicious for malignancy

Suspicious for papillary,medullary,metastatic,lymphoma,other

6.Malignant

Papillary thyroid Ca,poorly differentiated ca,medullary thyroid ca,undifferentiated ca,Squamous cell ca,Ca with mixed features,metastatic carcinoma,NHL,other

Approach to a case of thyroid enlargement

DIFFUSE

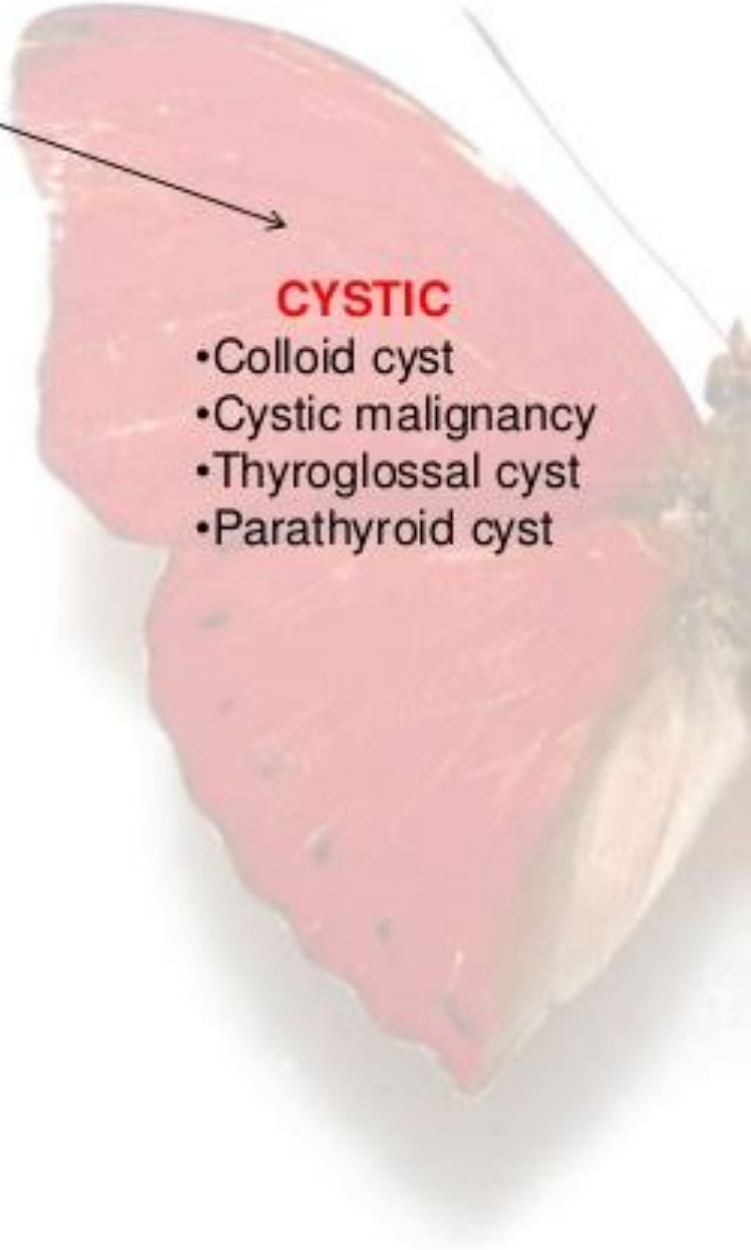
- Acute suppurative thyroiditis
- Subacute thyroiditis
- Hashimoto`s thyroiditis
- Adenomatous /colloid goitre
- Painless /silent thyroiditis
- Grave`s disease
- Invasive fibrosis

NODULAR

- Follicular
- Medullary
- Papillary
- Toxic nodule

CYSTIC

- Colloid cyst
- Cystic malignancy
- Thyroglossal cyst
- Parathyroid cyst



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Thank you ☺