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Physiology of Thyroid

Discussion points…….

- Thyroid hormone
- Production of Thyroid Hormones.
- Transport of T3 and T4.
- Regulation of Thyroid Hormones.
- Actions of Thyroid Hormones.

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Thyroid Hormone

- There are two biologically active thyroid hormones:
  - Tetraiodothyronine (T4)- also k/a thyroxine.
  - Triiodothyronine (T3)- Derived from modification of tyrosine.
- Thyroid secretes-
  - 80mg of T4 per day
  - 5mg of T3 per day
- Additional 25mg/day of T3 is produced by peripheral conversion of T4.
- T3 has a much greater biological activity about 10 folds than T4.

Production of Thyroid Hormones

IODINE Metabolism:

- Dietary iodine is absorbed in the GI tract.
  - Taken up by the thyroid gland
  - Or removed from the body by the kidneys.
- 80% of the iodine is lost in urine.
- 20 % is taken up by the Thyroid follicular cells.

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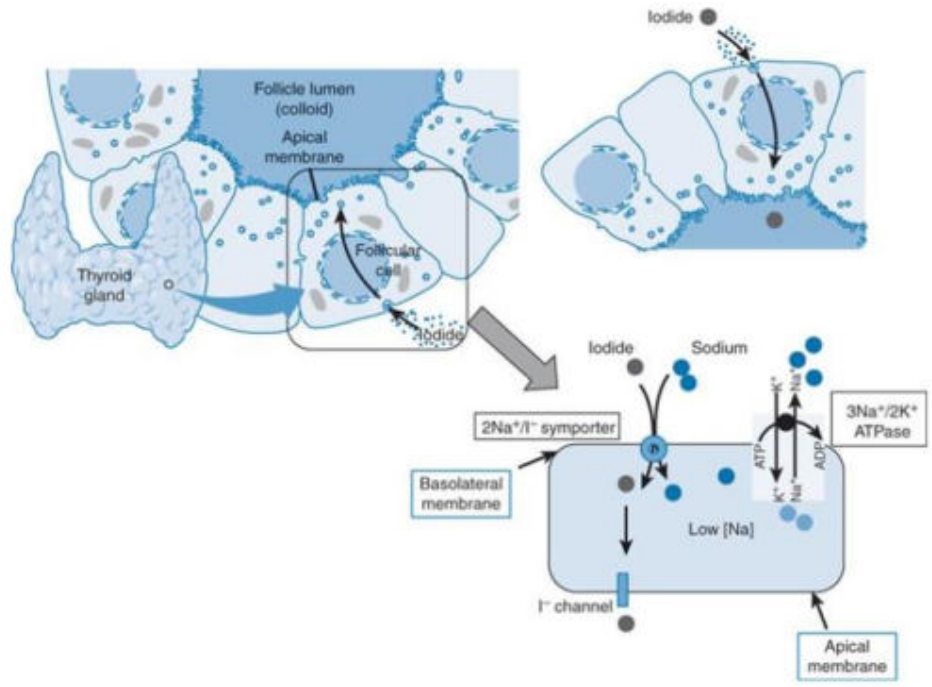
Production of Thyroid Hormones…….

IODINE Metabolism:

- Transport of iodide into follicular cells is dependent upon a Na+/I- co-transport system.
- Iodide(I^-) taken up by the thyroid gland is oxidized by peroxide in the lumen of the follicle.
- Oxidized iodine(I^+) can then be used in production of thyroid hormones.



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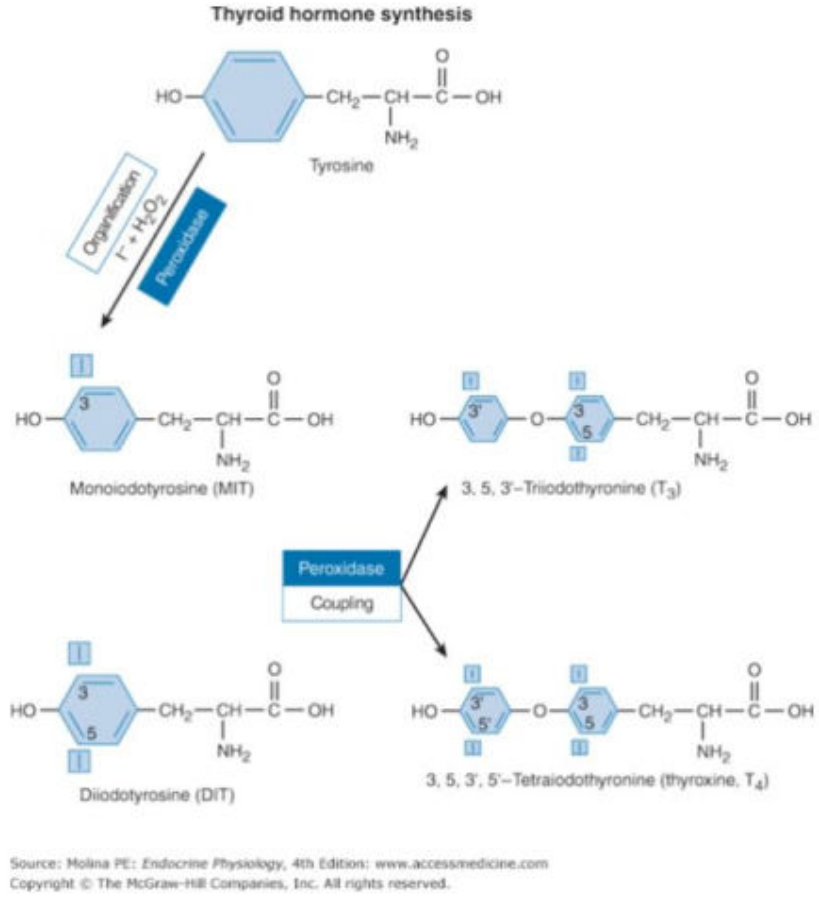
Production of Thyroid Hormones…….

Production Of Thyroglobulin:

- Pituitary produces TSH, which binds to follicle cell receptors.
- Follicle cells produce thyroglobulin (glycoprotein).
- Thyroglobulin is released into the colloid space.
- It's tyrosine residues are iodinated by I^+.
- This results in formation of monoiodotyrosine or diiodotyrosine.



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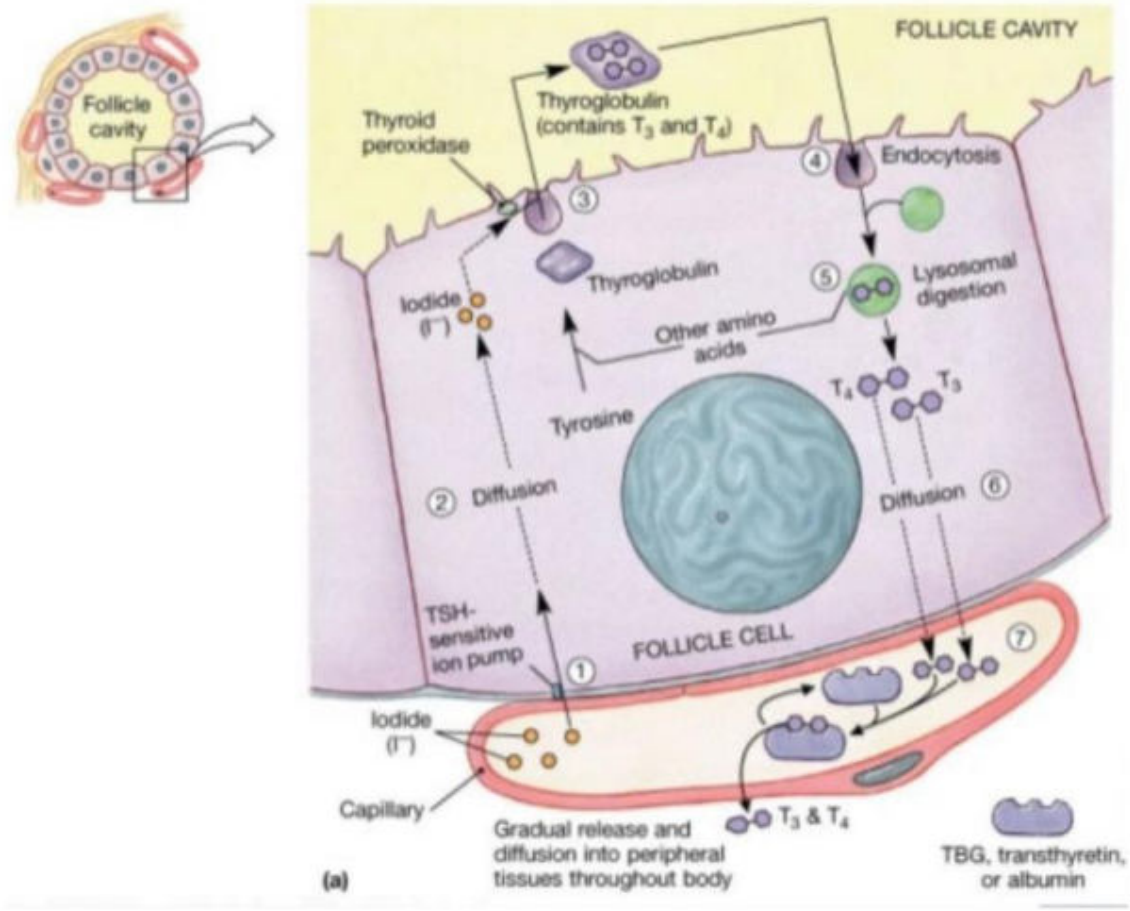
Production of Thyroid Hormones.....

- Thyroid hormone production and release:
  - T4 is approximately 95%.
  - T3 is 5%.



Transport of Thyroid Hormones

- Thyroid hormones are lipid-soluble.
- Found in the circulation associated with binding proteins:
  - Thyroid Hormone-Binding Globulin(TBG) (~70% of hormone)
  - Pre-albumin(Transthyretin) (~15%)
  - Albumin (~15%)
- Less than 1% of thyroid hormone is found free in the circulation.
- Only free and albumin-bound thyroid hormone is biologically available to tissues.

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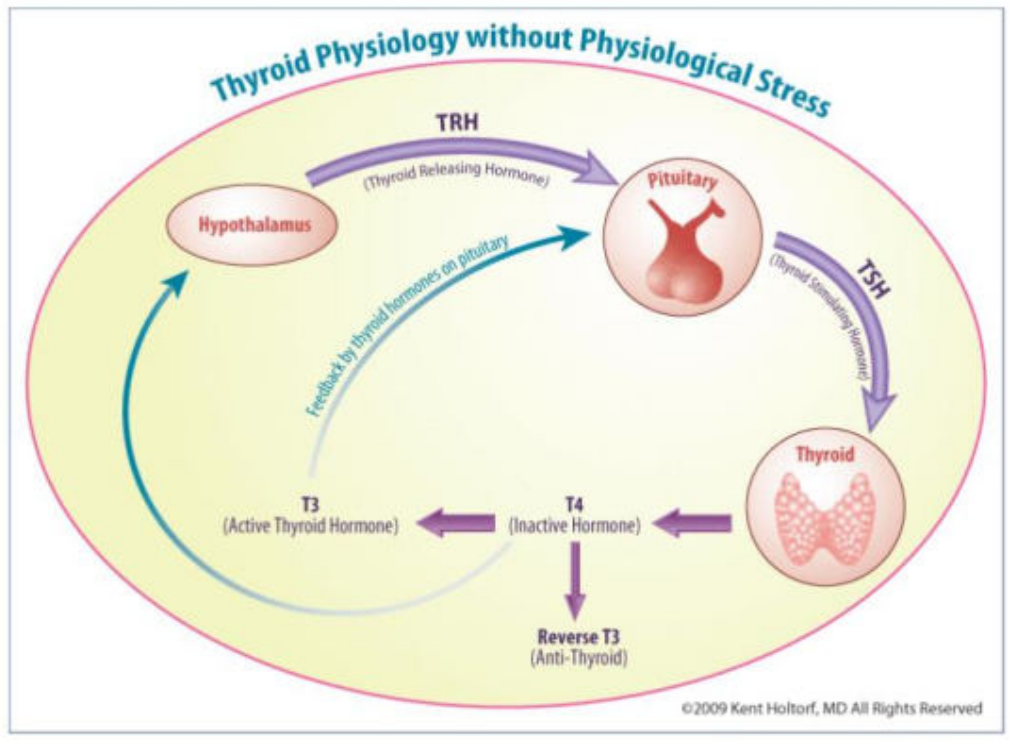
Conversion of T4 to T3

- T4 is converted to T3 in peripheral tissues by the enzyme 5'monodeiodinase.
- Large amount of T4 (25%) is converted to T3 in peripheral tissues.
- Conversion takes place mainly in the Liver and Kidneys.

  T3 formed is then released to the blood stream.

  Equal amount of "Reverse T3" may also be formed (no biological activity).

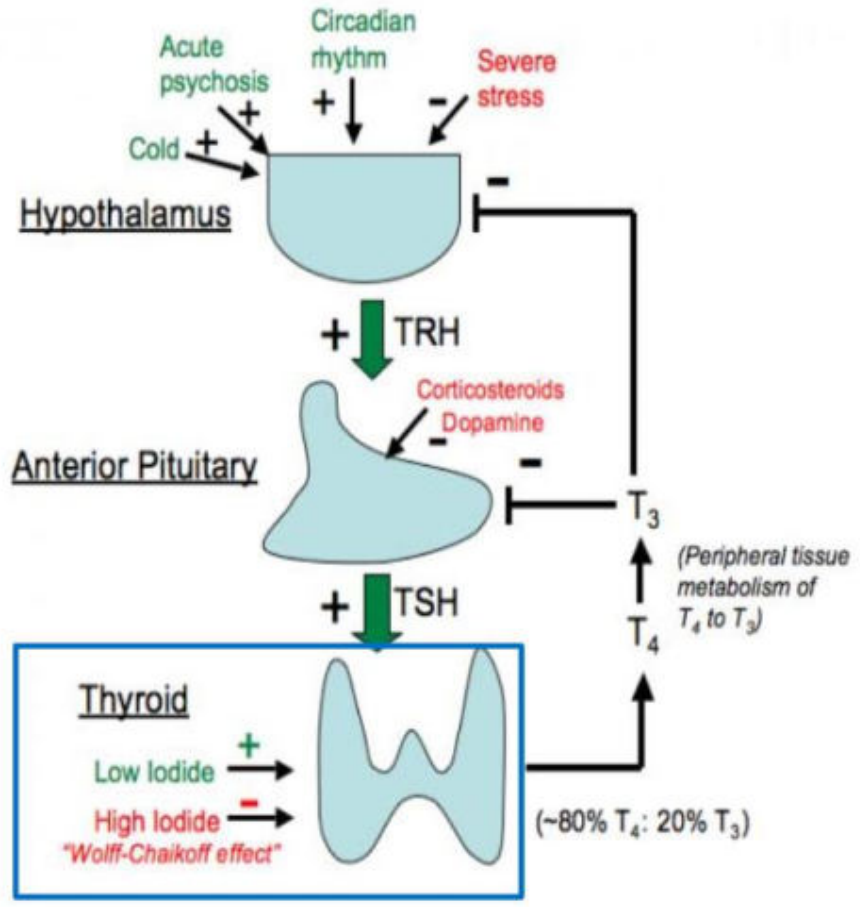


Regulation of Thyroid Hormones

- Thyroid hormone synthesis and secretion is regulated by two main mechanisms:

  Regulation by the Hypothalamus and Anterior Pituitary.

  "Auto Regulation" mechanism, which reflects the available levels of iodine.



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Regulation of Thyroid Hormones.....

Auto Regulation of Thyroid Hormone production.

. Rate of iodine uptake and incorporation into thyroglobulin is influenced by the amount of iodide available: -

Low iodide levels increase iodine transport into follicular cells

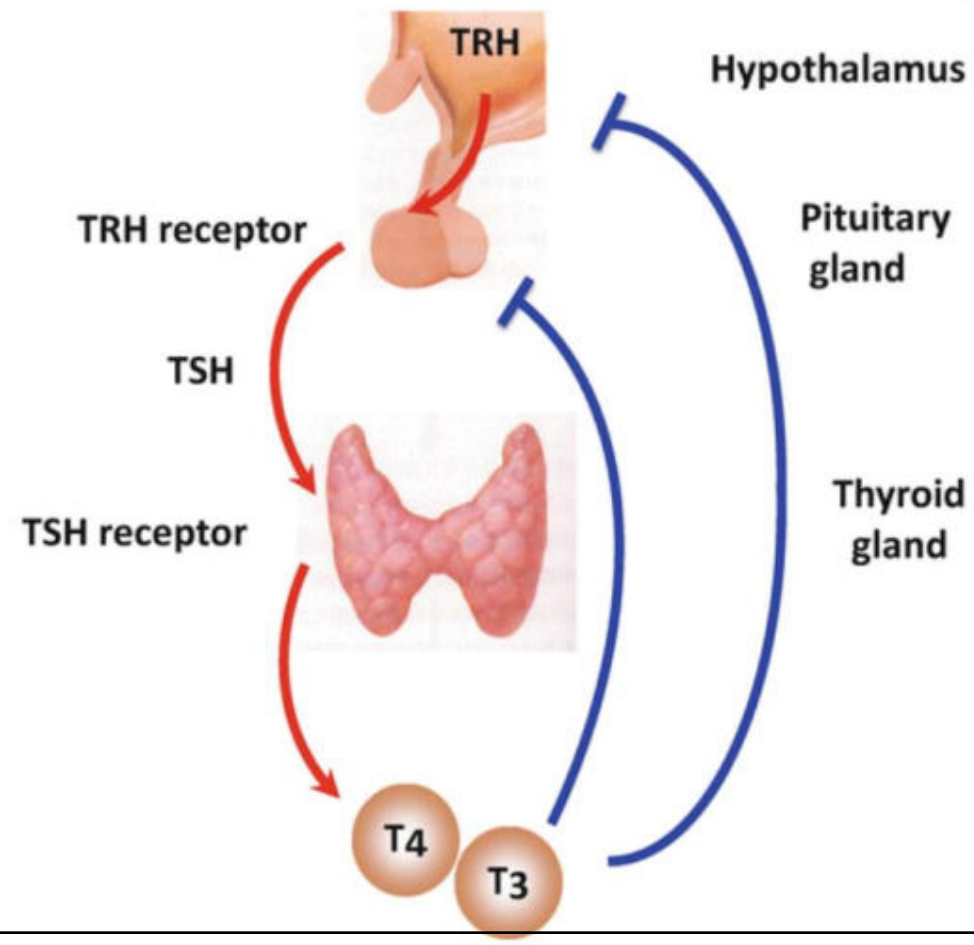
High iodide levels decrease iodine transport into follicular cells

Thus, there is negative feedback regulation of iodide transport by iodide.

Regulation of Thyroid Hormones.....

. Neuroendocrine Regulation of Thyroid hormones:

Hypothalamo-pituitary-thyroid axis.



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Regulation of Thyroid Hormones.....

- Influence of TRH:

  TRH is a hypothalamic releasing factor.

  Travels through the pituitary portal system

  Act on Anterior Pituitary Thyrotrophic cells.

  - TRH acts through G protein-coupled receptors
  - Activates the IP3 (Ca^{2+}) and DAG (PKC) pathways

  Cause increased production and release of TSH.

Regulation of Thyroid Hormones.....

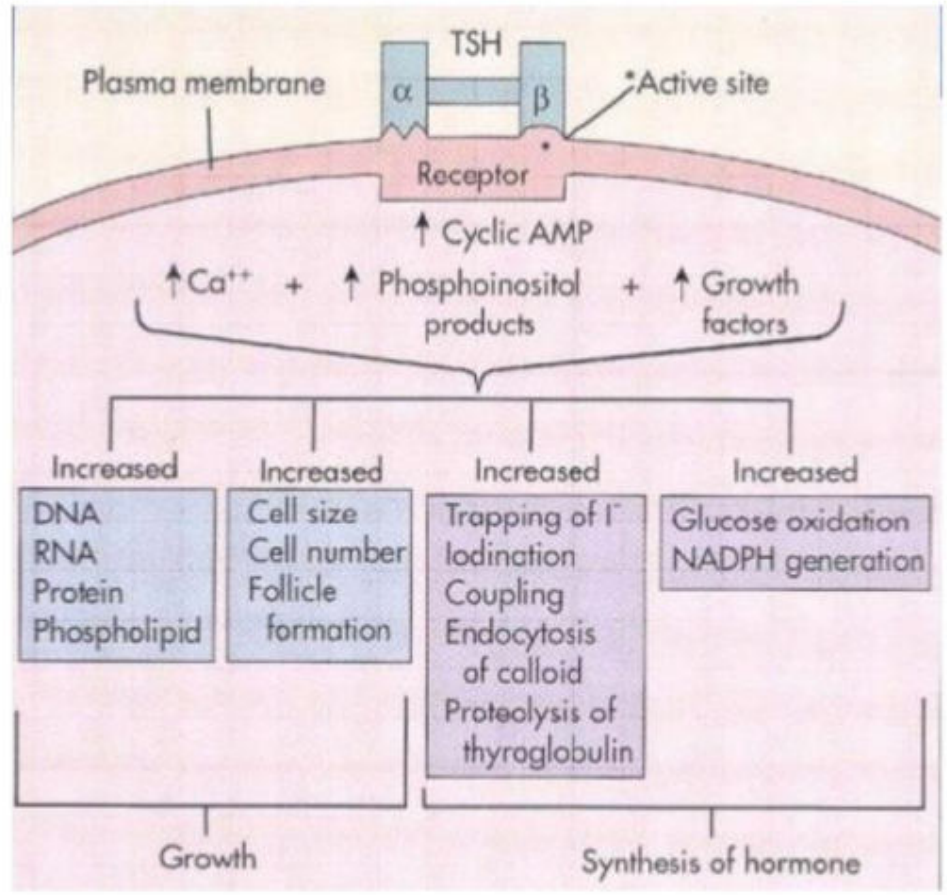
- Role of TSH-

  TSH (glycoprotein) composed of two subunits:

  - Alpha subunit (common to LH, FSH, TSH, hCG)
  - Beta subunit- specific for receptor binding and biological activity.

  Action of TSH on Thyroid:

  - TSH acts on follicular cells of the thyroid.
  - Increases iodide transport into follicular cells
  - Increases production and iodination of thyroglobulin
  - Increases endocytosis of colloid from lumen into follicular cells



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Regulation of Thyroid Hormones.....

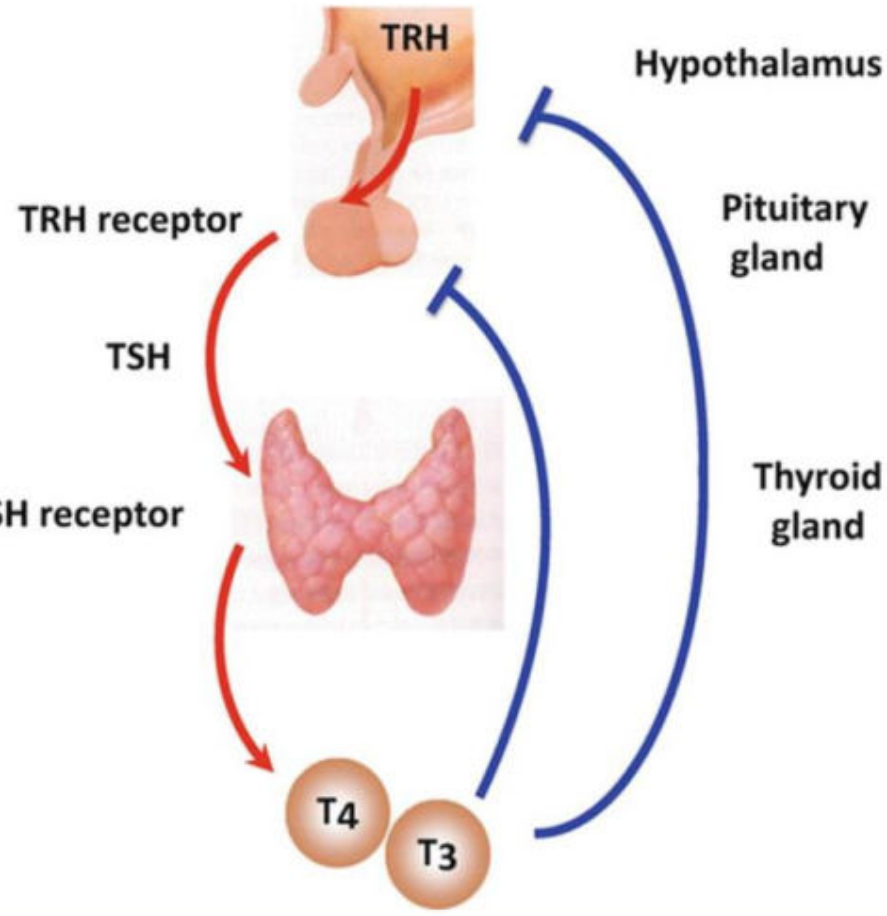
- Regulation of TSH release from the anterior pituitary:

  TSH release is influenced by-

  - Hypothalamic TRH.
  - Thyroid hormones themselves.

  Thyroid hormones exert NEGATIVE FEEDBACK on TSH release:

  - Inhibition of TSH synthesis.
  - Decrease in pituitary receptors for TRH.



Regulation of Thyroid Hormones.....

- Other Factors Regulating Thyroid Hormone levels:

  Diet:

  - High carbohydrate diet- increases T3 levels, resulting in increased metabolic rate (diet-induced thermogenesis).
  - Low carbohydrate diet- decrease T3 levels, resulting in decreased metabolic rate.

  Cold Stress: increases T3 levels in other animals, but not in humans.

  Any condition that increases body energy requirements (e.g., pregnancy, prolonged cold) stimulates hypothalamus.

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Actions of Thyroid Hormones

1. Essential for normal growth of tissues, including the nervous system.
   - Lack of TH during development results in short stature and mental deficits (cretinism).
2. Thyroid hormone stimulates or increase Basal Metabolic Rate(BMR).
3. Required for GH and prolactin production and secretion
4. Required for GH action
5. Increases intestinal glucose reabsorption (glucose transporter)
6. Increases mitochondrial oxidative phosphorylation (ATP production)
7. Increases activity of adrenal medulla (sympathetic; glucose production)
8. Induces enzyme synthesis

❖Result: stimulation of growth of tissues/increased metabolic rate/Increased heat production (calorigenic effect)

Actions of Thyroid Hormones.....

.Effects of Thyroid Hormone On Nutrient sources:

Effects on PROTEIN synthesis and degradation:

- Low level of TH- increased protein synthesis (low metabolic rate; growth)
- High level- increased protein degradation (high metabolic rate; energy)

Effects on CARBOHYDRATES:

- low doses of TH- increase glycogen synthesis (low metabolic rate; storage of energy)
- high doses- increase glycogen breakdown (high metabolic rate; glucose production

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Actions of Thyroid Hormones.....

.One Major Target Gene Of T3:

Na+/K+ ATPase Pump:

- Pumps sodium and potassium across cell membranes to maintain resting membrane potential
- Activity of the Na+/K+ pump uses up energy, in the form of ATP
- About 1/3rd of all ATP in the body is used by the Na+/K+ ATPase

T3 increases the synthesis of Na+/K+ pumps, markedly increasing ATP consumption (BMR increases).

T3 also acts on mitochondria to increase ATP synthesis (size and number of mitochondria will increase).

The resulting increased metabolic rate increases thermogenesis (heat production).

Actions of Thyroid Hormones.....

.Thyroid hormone actions which increase oxygen consumption

Increase mitochondrial size, number and key enzymes.

Increase plasma membrane Na-K ATPase activity.

Increase futile(ineffective) thermogenic energy cycles.

Decrease superoxide dismutase activity.

.Effects of thyroid hormones on the cardiovascular system

Increase heart rate

Increase force of cardiac contractions

Increase stroke volume

Increase Cardiac output

Up-regulate catecholamine receptors

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Actions of Thyroid Hormones.....

.Effects of thyroid hormones on the Respiratory System:

Increase resting respiratory rate

Increase minute ventilation

Increase ventilatory response to hypercapnia and hypoxia

.Effects of thyroid hormones on the Renal System:

Increase blood flow

Increase glomerular filtration rate(GFR)

.Effects of thyroid hormones on Oxygen-carrying Capacity:

Increase RBC mass

Increase oxygen dissociation from hemoglobin

Actions of Thyroid Hormones.....

. Effects of thyroid hormones on intermediary metabolism

Increase glucose absorption from the GI tract

Increase carbohydrate, lipid and protein turnover

Down-regulate insulin receptors

Increase substrate availability

. Effects thyroid hormones in growth and tissue development:

Increase growth and maturation of bone.

Increase tooth development and eruption.

Increase growth and maturation of epidermis, hair follicles and nails.

Increase rate and force of skeletal muscle contraction.

Inhibits synthesis and increases degradation of mucopolysaccharides in subcutaneous tissue.

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Thyroid function test

Thyroid function tests

.Biochemical tests used to investigate thyroid function:

Tests that establish whether there is thyroid dysfunction-

- TSH
- T4
- T3

Tests to know the cause of thyroid dysfunction-

- Thyroid auto-antibody
- Serum thyroglobulin measurements
- Thyroid enzyme activities

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Thyroid function tests……

- TSH:

  The single most sensitive, specific and reliable test of thyroid status.

- Total T4 and Total T3:

  More than 99% of T4 and T3 circulate in plasma bound to protein.

  Both change if [TBG] alters (e.g. in pregnancy).

- Free T4 and Free T3:

  Free thyroid hormone concentrations are independent of changes in TBGs.

  More reliable for diagnosis of thyroid dysfunction.

Thyroid function tests……

- Indications of TFT:

  Diagnosing thyroid disorder in symptomatic person

  Screening new-born for hypothyroidism

  Monitoring thyroid replacement therapy in hypothyroidism patients

  Diagnosis & monitoring female infertility patients

  Screening adults for thyroid disorders

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Thyroid function tests……

- 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

  Methods of TSH estimation

  - Radioimmunoassay/ Immunometric assay/ Chemiluminiscent & flourescent techniques.

  Normal values: TSH 0.4 to 4mU/L

Thyroid function tests……

- 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.

- Free T4:

  Small fraction of total T4 unbound to protein

  Metabolically active form and (0.05%) of total T4

  Do not get affected by TBG levels.

  Measurement useful in conditions where TBG levels are affected

  Normal levels: 0.89- 1.76ng/dL

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Thyroid function tests……

- Free and Total T3

  Normal plasma level T3 are very low.

  Metabolically more active, shorter half life, faster turn over.

  Free T3 – (0.5%) of total and useful with altered protein level.

  T3 level: 80 to 180ng/dl and fT3 level: 1.5 – 4.1pg/mL.

  Measured by immunoassays.

  Uses:

  - Diagnosis of T3 thyrotoxicosis
  - Early diagnosis of hyperthyroidism

Thyroid function tests……

- Thyroglobulin:

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

  Reflects thyroid mass, thyroid injury & TSH receptor stimulation

  Raised level- 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

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Thyroid function tests……

- Thyroid Autoantibodies:

  Diagnosing autoimmune diseases

  Autoantibodies-

  - Anti-Tg antibody
  - Anti-microsomal antibody
  - TSH-Receptor antibody (inhibitory or stimulatory)
  - non Tg colloid antigen

Thyroid function tests……

- Anti-Tg antibodies:

  Methods:

  - Agar gel diffusion precipitation test
  - Tanned red cell haem agglutination tests(TRCH test)
  - ELISA/ Immunofluorescence of tissue section/ RIA

  Positive:

  - Hashimoto`s thyroiditis
  - Grave`s disease
  - Myxoedema
  - Nontoxic goitre
  - Thyroid ca
  - Pernicious anaemia

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Thyroid function tests……

- Anti-microsomal Abs (also k/a Anti-TPO Abs):

  Methods:

  - CFT
  - Immunofluorescence tests
  - TRCH assay/ ELISA/ RIA

  Positive:

  - Grave`s disease
  - Hashimoto`s thyroiditis

  More frequently positive for autoimmune diseases than Tg Ab.

Thyroid function tests……

- Thyroid receptor antibody:
  - 2-Types:
    - TBI- Grave`s disease.
    - TSIgs- Grave`s disease/ Predicting relapse or remission in hyperthyroidism/ development of neonatal hyperthyroidism.

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Thyroid function tests……

- Thyroid scan

  Advantages:

  - Distinguishes diffuse glandular activity from patchy pattern seen in goitre
  - Functional classification of nodules: *Warm, Hot, Cold*
  - In association with thyroid suppression regimes, TSH dependent or autonomous nature of hot nodules
  - Information regarding size, shape, position of gland
  - Identification & localisation of functioning thyroid tissue in ectopic or metastatic sites
  - Helps on differentiating various causes of thyrotoxicosis

Thyroid function tests……

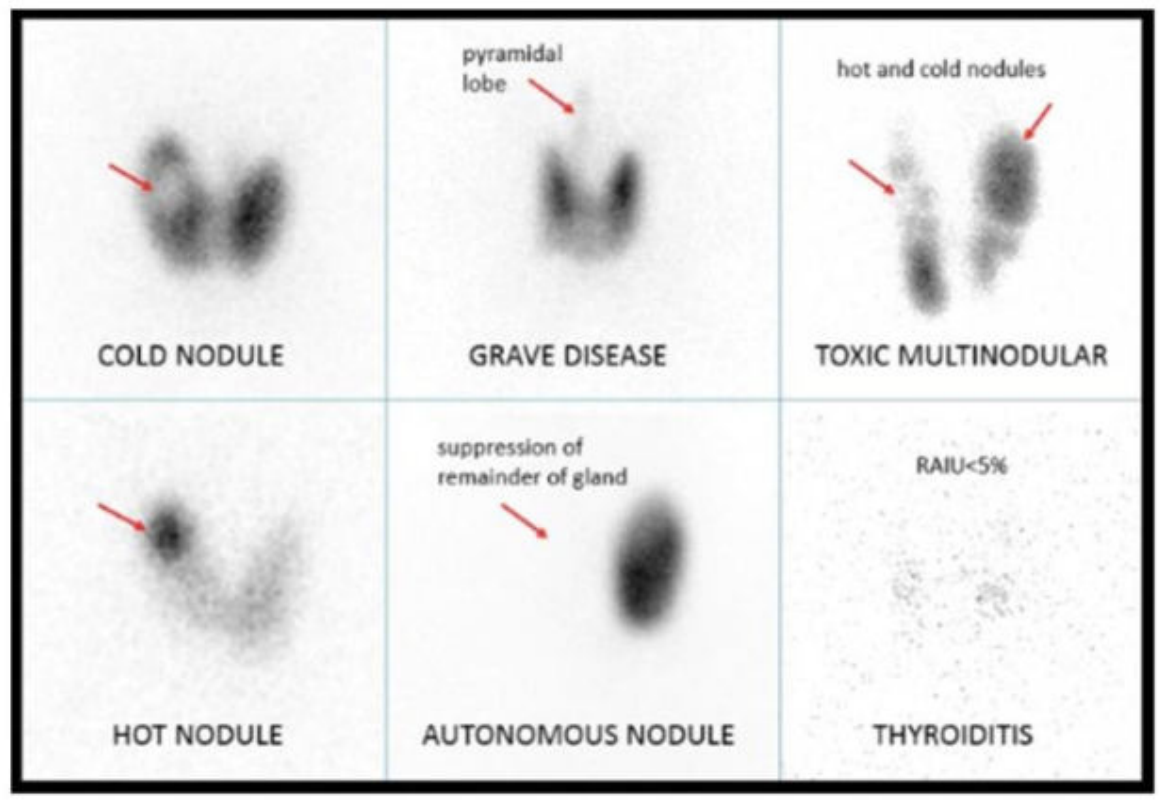
- Thyroid scan

  ➢ Indications:

  - Thyroid nodule
  - Diffuse or multinodular goitre
  - Clinical hyper- or hypothyroidism
  - Evaluation of substernal mass
  - R/O Ectopic thyroid tissue
  - Subacute thyroiditis, early phase

  ➢ Contraindications:

  - Pregnancy
  - Lactation



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Thyroid function tests……

- Whole body scan I-131:

  Post-operative evaluation for thyroid remnant or functioning metastasis

  Follow up patients after I-131 ablation or I-131 treatment

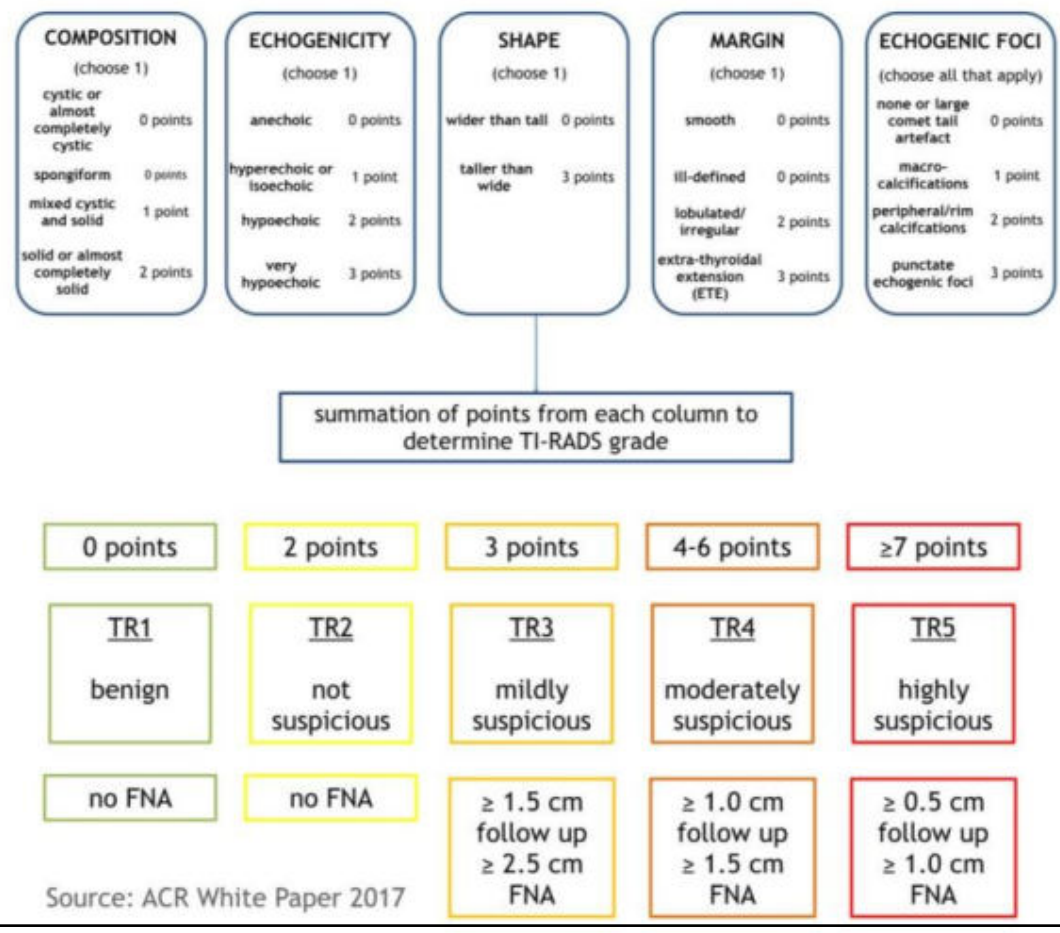
  Serum Tg rising

  Suspected tumour recurrence

  Suspected functioning metastases (either local or distant metastases)

Radiological imaging

- Ultrasound
  - ➢Scoring-
    - five categories of ultrasound findings.
  - ➢Higher the score
    - Higher the TR (TI-RADS) level
    - and likelihood of malignancy.



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Cytology of thyroid

- FNAC thyroid:

  Indications:

  - Diagnosis of diffuse non toxic goitre
  - Diagnosis of solitary or dominant thyroid nodule
  - Confirmation of clinically obvious malignancy

  Complications:

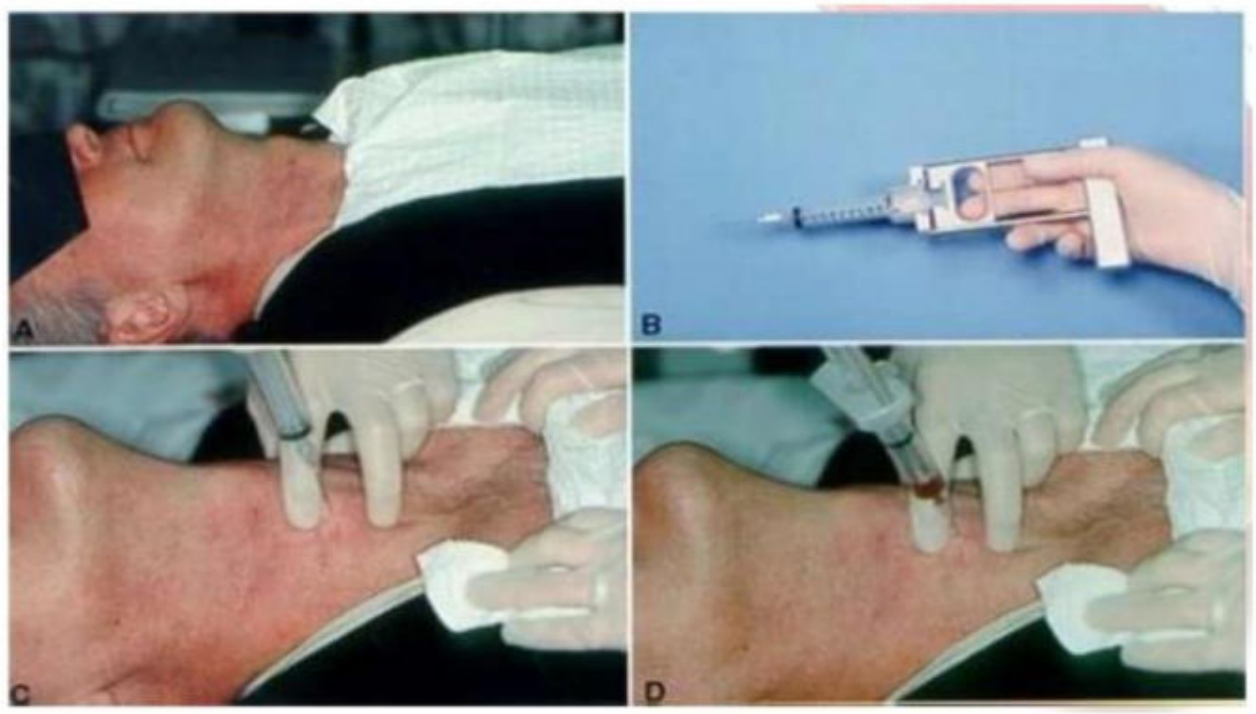
  - Local haemorrhage & haematoma.
  - Transient laryngeal nerve paresis.
  - Tracheal puncture
  - Rarely, needling causes formation of a hot nodule

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

Cytology of thyroid….

- FNAC thyroid

  - Procedure:
    - Materials-
      - Syringes & syringe holder(pistol)
      - 22-25 gauge needle
      - Cotton Swabs
      - Alcohol bottles for wet fixation



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Cytology of thyroid….

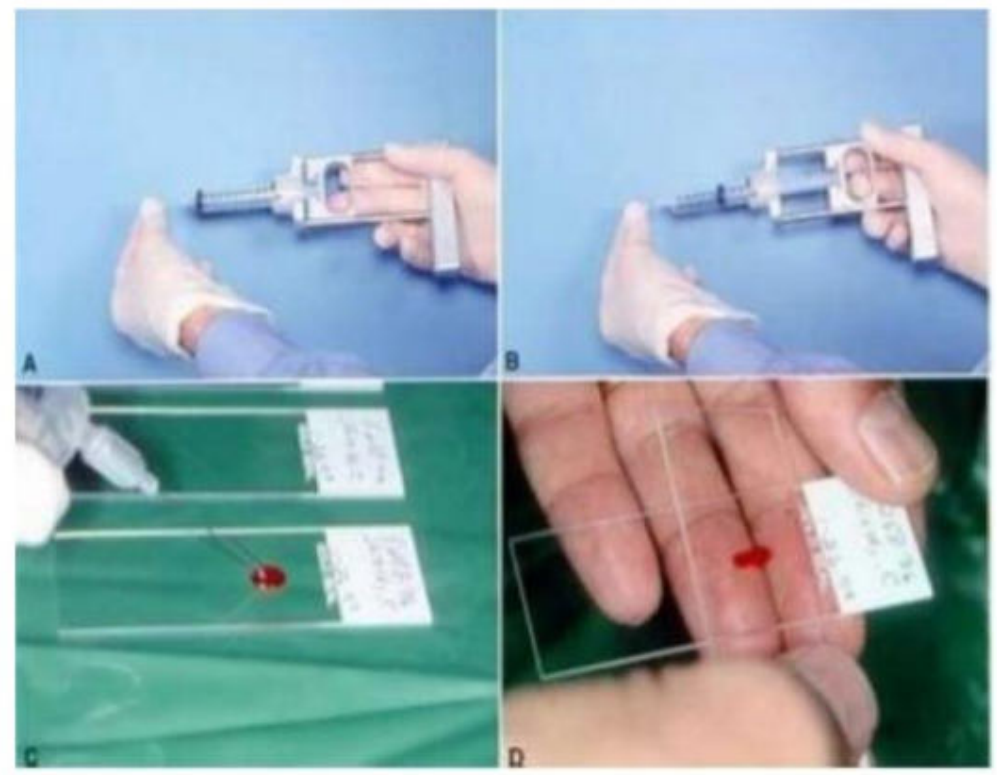
- FNAC thyroid:

  Smearing, fixation & staining

  - Rapid smearing
  - Air dried stained with giemsa
  - Alcohol fixed smears stained with Pap

  Sample adequacy

  - Six groups of follicular cells
  - Each containing 10 to 20 cells on two separate slides



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