

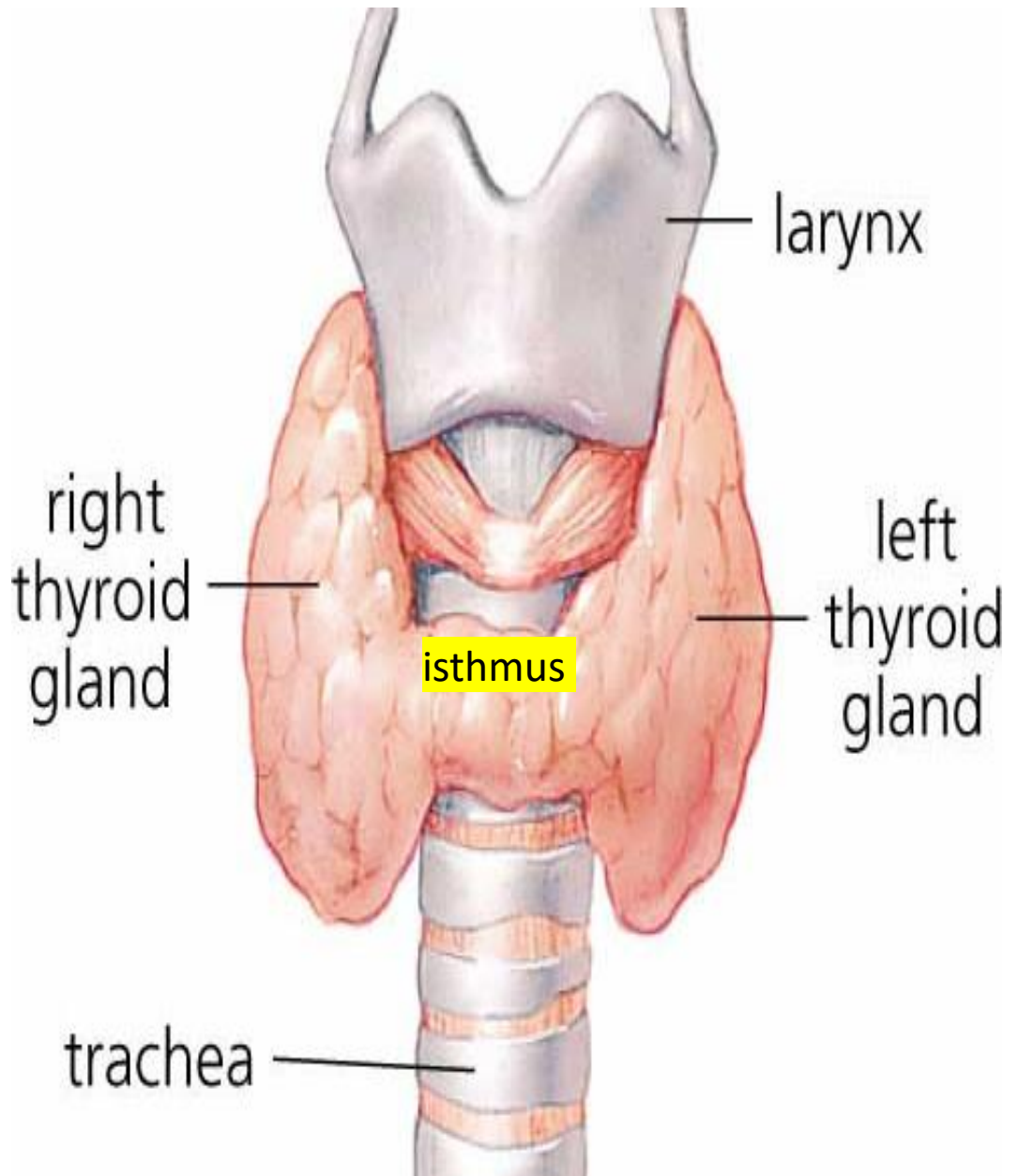
Endocrine system 2019

Thyroid gland part 1

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Thyroid gland

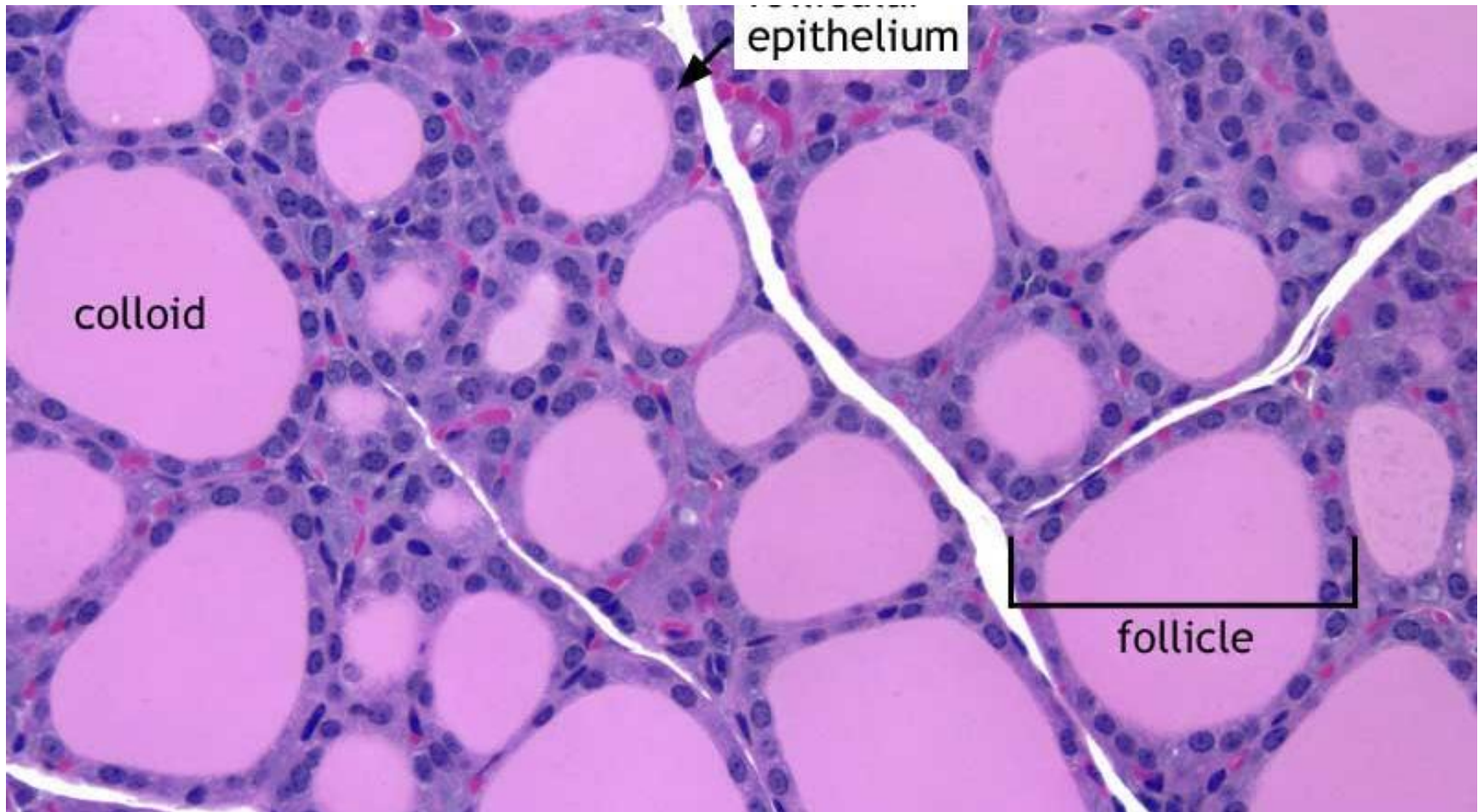
- The thyroid gland consists of two lobes (right and left) that are connected by the isthmus.
- The right and left lobes are pear shaped with the apex directed upwards.
- The thyroid is attached to the larynx: it moves upwards during swallowing. So if you see a neck mass ask the patient to swallow, if the mass moves upwards, then it is from the thyroid.



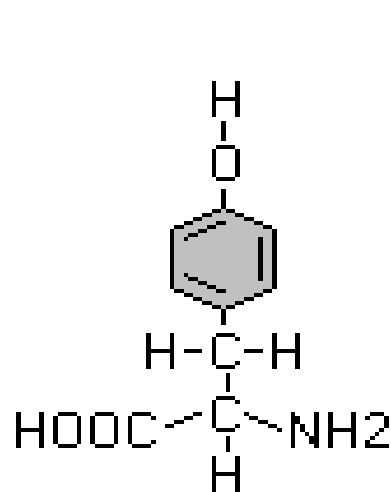
Thyroid gland histology

- The thyroid gland is composed of follicles lined by follicular epithelial cells which are cuboidal to low columnar.
- The follicles contain **colloid** which is composed of **thyroglobulin** which is the iodinated **precursor** protein of thyroid hormones.

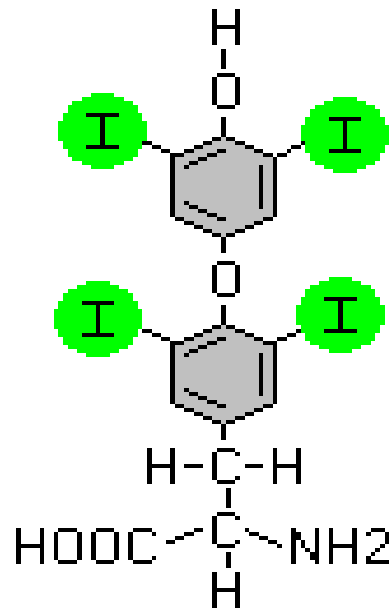
Histology



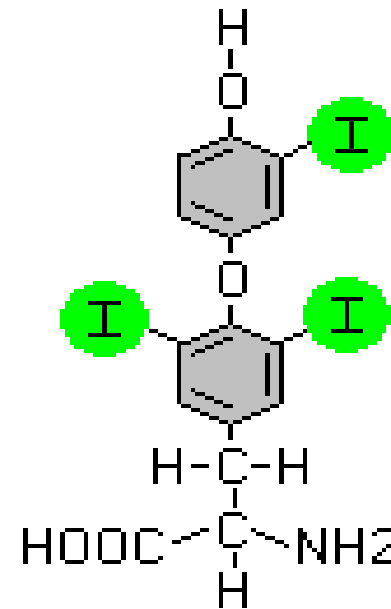
Thyroid hormones



Tyrosine



Thyroxine (T₄)



Triiodothyronine (T₃)

Note that thyroid hormones are derived from tyrosine. The main two are T₃ and T₄. Note relation to iodide atom (T₃: 3 iodine atoms and T₄ ; 4 atoms)

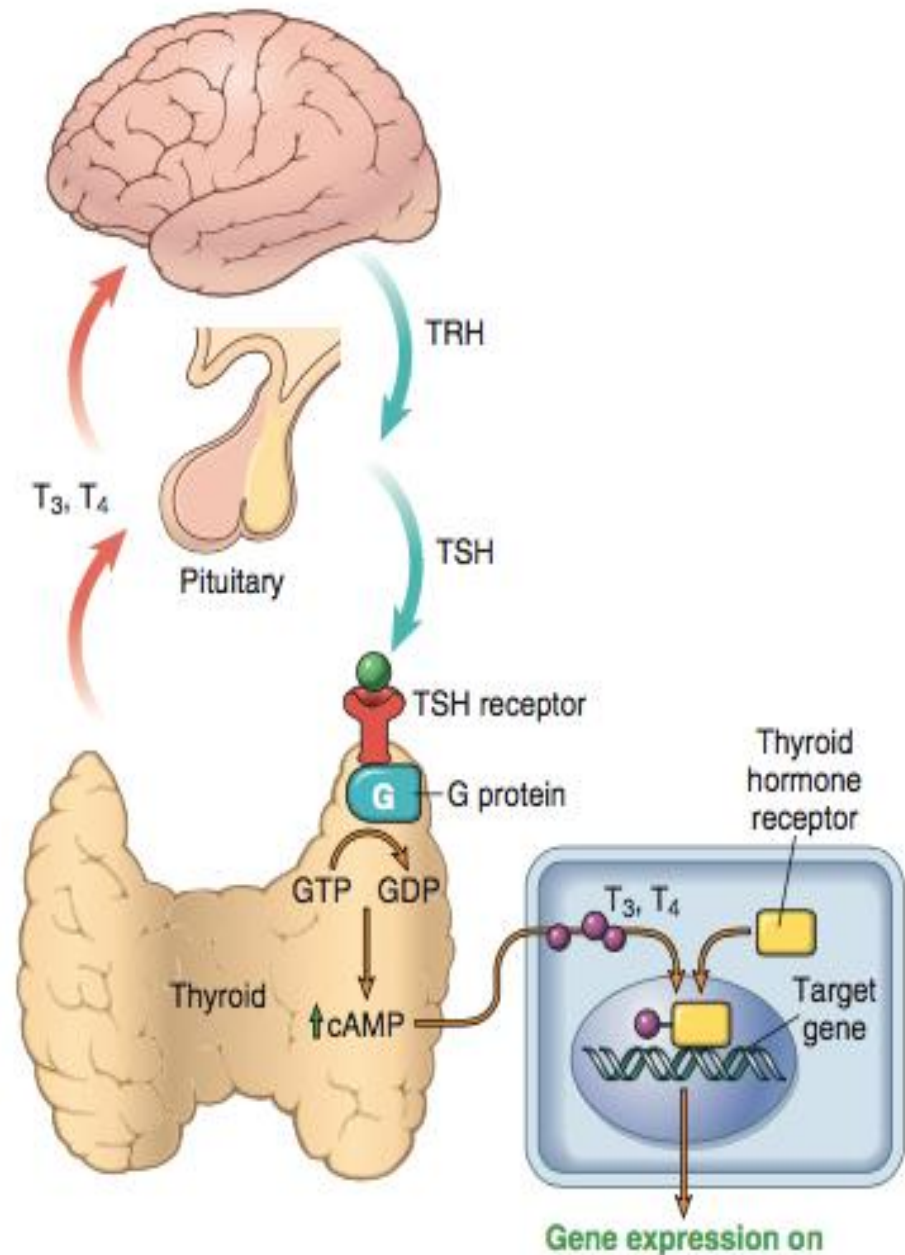
A bit of physiology!

Homeostasis of thyroid hormones

- **TRH** from the hypothalamus causes release of **TSH** from the pituitary .
- TSH binds to its **receptor** on thyroid follicular cells causing activation and conformational change in the receptor, allowing it to associate with a stimulatory **G-protein**.
- activation of stimulatory G-protein results in an increase in intracellular **cAMP** levels, which stimulates thyroid hormone synthesis and release.
- Thyroid follicular epithelial cells convert thyroglobulin into **thyroxine (T4)** and lesser amounts of **triiodo thyronine (T3)**.
- T4 and T3 are released into the systemic circulation, where most of them are bound to circulating plasma proteins, such as T4-binding globulin, for transport to peripheral tissues. **Some free (not bound to proteins) T3 and T4 stay in circulation.**
- In the periphery, the majority of free T4 is deiodinated to T3; **T3 binds to thyroid hormone nuclear receptors in target cells with 10-fold greater affinity than T4 and has greater activity.**
- Binding of thyroid hormone to its **nuclear thyroid hormone receptor (TR)** creates a hormone-receptor complex that regulates the **transcription** of a subset of cellular genes.
- This produces diverse cellular effects, including increased carbohydrate and lipid catabolism and protein synthesis in a wide range of cell types. The net result of these processes is an **increase in the basal metabolic rate.**

Thyroid hormone homeostasis

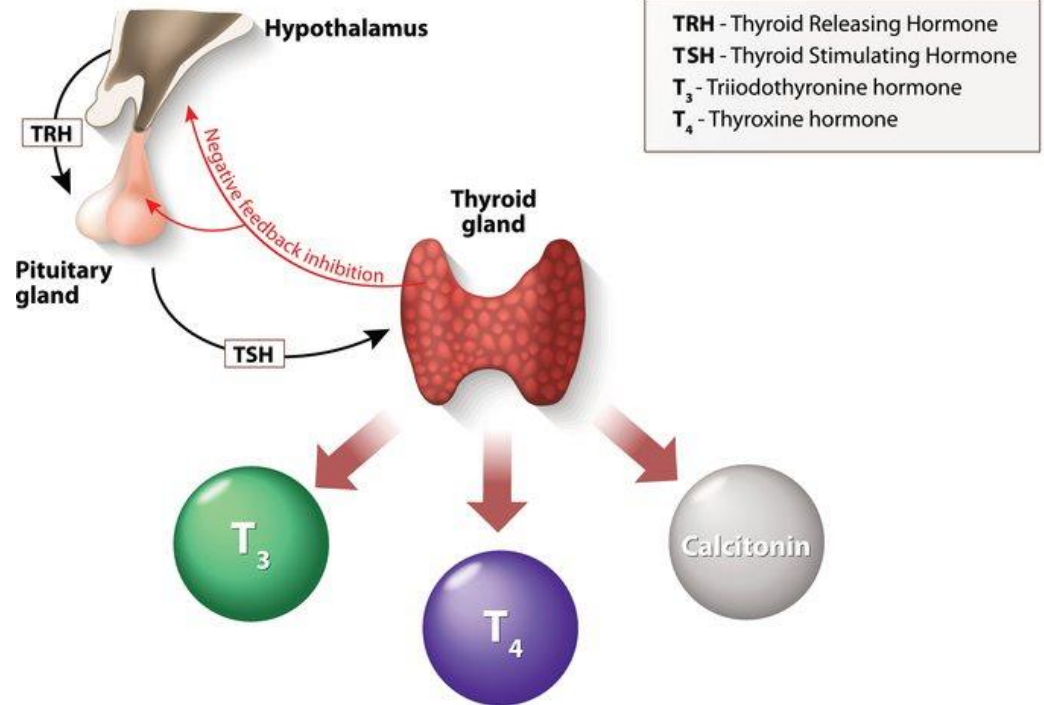
- TRH released from hypothalamus stimulates TSH release from the pituitary.
- TSH binds to its receptors on the thyroid follicular cells.
- this binding stimulates G protein which stimulates cAMP.
- cAMP aids the conversion of thyroglobulin to active hormones (T₃ and T₄)
- in target cells, T₄ converted to T₃ (more active and has more affinity to bind to receptors).
- T₃ binds to a thyroid nuclear receptor (TR).
- in the nucleus, the T₃-TR complex causes gene transcription.
- this causes increased catabolism of carbs and lipids but increased protein synthesis.
- net effect: increased metabolic rate.



Note that the thyroid gland also secretes calcitonin, from C cells= parafollicular cells.



THYROID HORMONES



Diseases of thyroid gland

Same general rules of all endocrine glands!(
refer to lecture 1)

- Mass effect.
- Hyperthyroidism (thyrotoxicosis).
- Hypothyroidism.
- Again, there is **no relation between mass effect and level of hormonal production**

Thyroid diseases

1. ***Mass effect:*** enlargement can be due to: inflammation, neoplasms, autoimmune diseases. (details later)

Thyroid enlargement, due to any cause is called: **goiter**.

AGAIN: enlarged gland doesn't necessarily mean increased hormone production.

2. ***Hyperthyroidism and thyrotoxicosis.***
3. ***Hypothyroidism.***

Goiter: enlarged thyroid.. Regardless of the cause.



Increased thyroid hormone= thyrotoxicosis

- *Thyrotoxicosis means: increased thyroid hormone, **regardless of the cause** of the increase.
- *Hyperthyroidism is the most common cause of thyrotoxicosis and it means there is **actual increase** in thyroid hormone production **from the thyroid gland**.

NOTE: 1. **actual increase** excludes relative increase in cases of thyroiditis where there is destruction of the gland causing increased release (not production) of thyroid hormones... so there is **a relative** net increase in T3 & T4.. Here we have thyrotoxicosis but no hyperthyroidism

2. **from the thyroid gland**: this excludes **ectopic** production of thyroid hormones

HOWEVER, this is philosophical!! In clinical practice most people use the two terms to mean the same thing!!!!

A. Thyrotoxicosis Associated with hyperthyroidism (Thyroid hyperfunction):

1. **Primary**

- a. Diffuse toxic hyperplasia (Graves disease)
- b. Hyperfunctioning (Toxic) multinodular goitre.
- c. Hyperfunctioning (toxic) adenoma

2. **Secondary** -- TSH-secreting pituitary adenoma (rare)

B. Thyrotoxicosis not associated with hyperthyroidism : less common

- Excessive release of pre-formed hormones in thyroiditis (just increased release with no increased overall production)
- Ectopic secretion of thyroid hormones.. So thyroid function is normal.

Clinical manifestations of thyrotoxicosis

- Thyroid hormones increase basal metabolic rate, increase appetite, increase breakdown of fat and glucose
- Also increase heart rate, cause hypertension
- Increase body temperature
- SO if these hormones are increased you expect to see a wide range of symptoms.

Clinical manifestations of thyrotoxicosis

- a. Constitutional symptoms : warm flushed skin, heat intolerance and excessive sweating ,weight loss despite increased appetite.
- b. Malabsorption, and diarrhoea (because of increased intestinal motility)
- c. Tachycardia and elderly patients may develop heart failure due to aggravation of pre-existing heart disease
- d. Nervousness, tremor, and irritability.
- e. A wide, staring gaze and lid lag because of sympathetic overstimulation of the levator palpebrae superioris
- f. 50% develop proximal muscle weakness (thyroid myopathy).
- g. Thyroid storm .. See next

Thyroid storm

- Abrupt onset of severe hyperthyroidism
- This condition occurs most commonly in individuals with Graves disease and it is a medical emergency because significant numbers of untreated patients die of cardiac arrhythmias
- Usually occurs in untreated or undertreated people

Thyroid storm

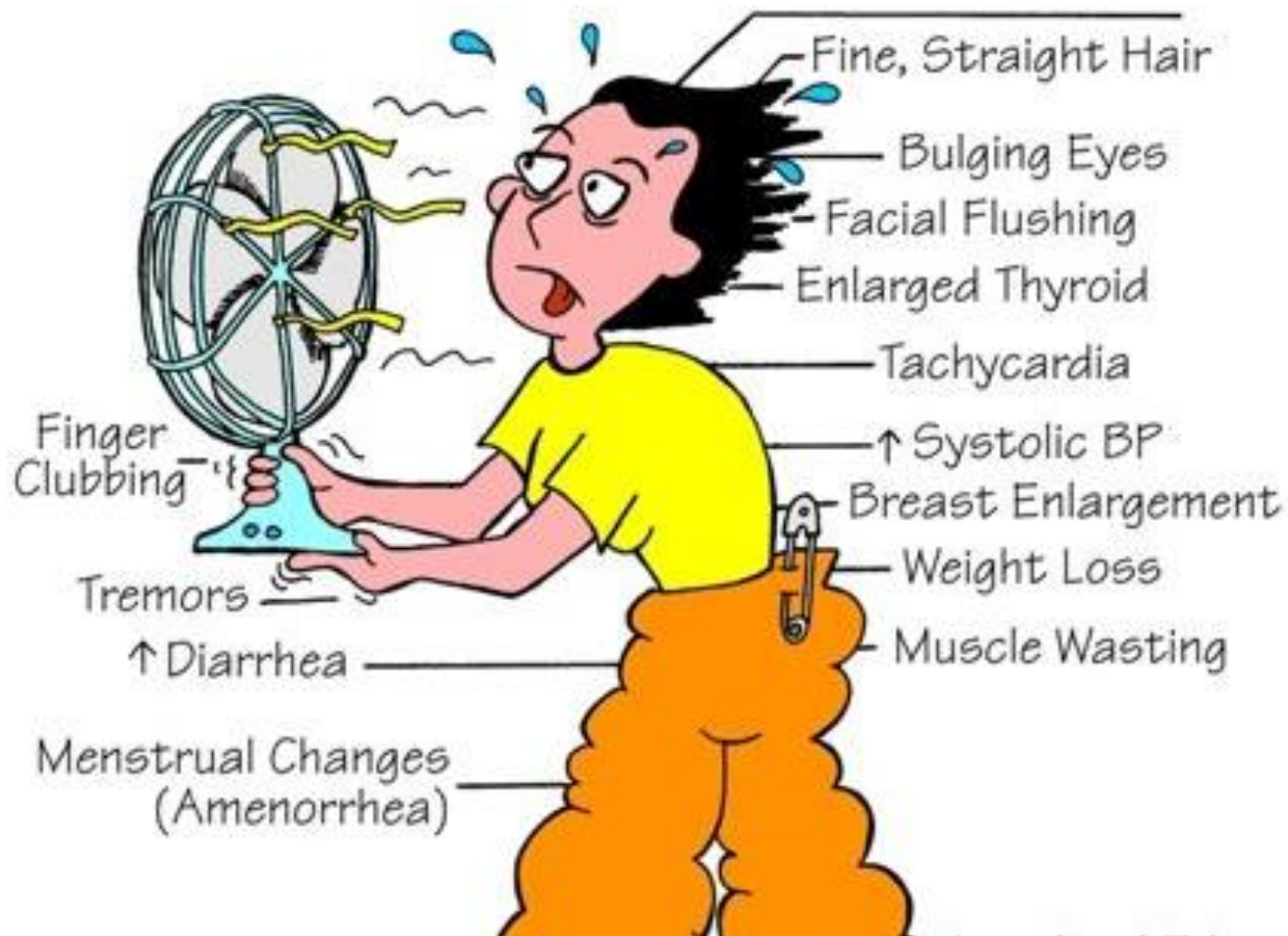
People with hyperthyroidism may develop thyroid storm after experiencing one of the following:

- trauma
- surgery
- severe emotional distress
- stroke
- diabetic ketoacidosis
- congestive heart failure
- pulmonary embolism

SO: make sure you control their thyroid hormone levels if they have one of the above. If they undergo surgery make sure you correct their hormonal levels **before** the surgery



hyperthyroidism



Lab tests

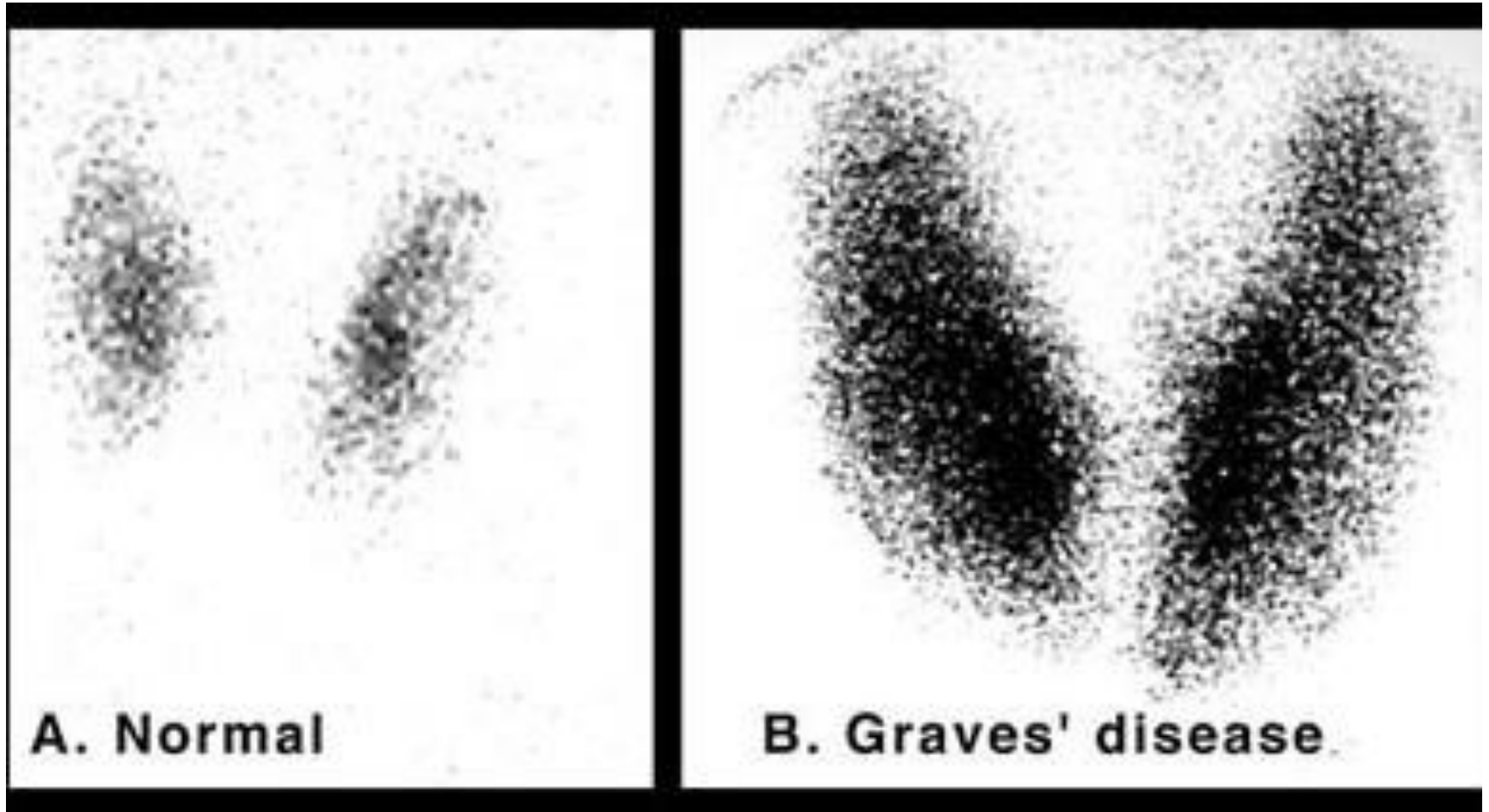
- *The measurement of **serum TSH** is the most useful single screening test for hyperthyroidism, because TSH levels are decreased even at the earliest stages, when the disease may still be subclinical*

- Once the diagnosis of thyrotoxicosis has been confirmed measurement of **radioactive iodine** uptake by the thyroid gland is valuable in determining the etiology

For example, such scans may show :

- a. Diffusely increased (whole-gland) uptake in Graves disease,
- b. Increased uptake in a solitary nodule in toxic adenoma
- c. Or decreased uptake in thyroiditis.

Iodine scans.. Black color shows how much iodine the gland is taking.. More iodine means more activity in producing hormones

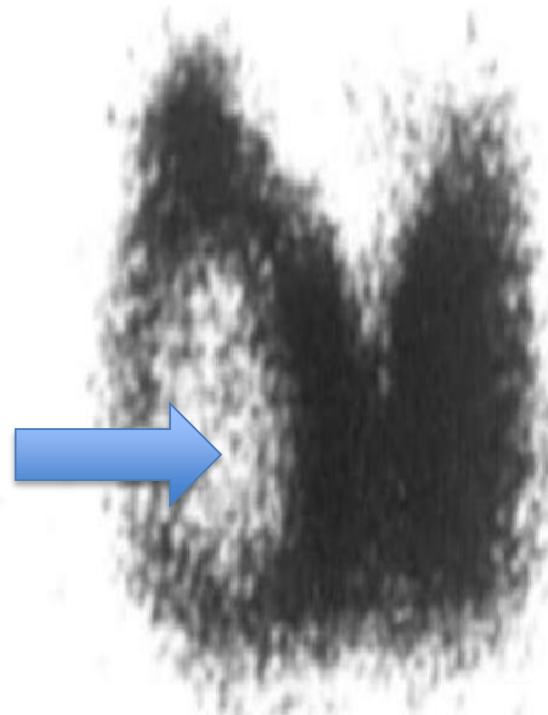


Iodine scans

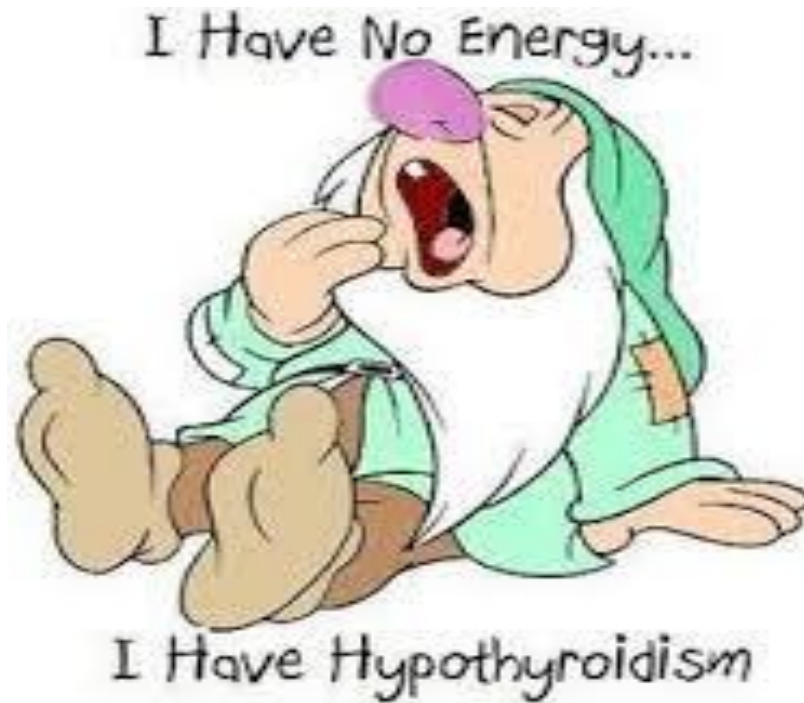
The white color (arrow) indicates that there is less iodine uptake than normal; this is a cold nodule.

In clinical practice: cold nodule means a non-functioning one (no or decreased iodine uptake)

Hot nodule=
hyperfunctioning: more iodine uptake than normal.



hypothyroidism



HYPOTHYROIDISM

Primary causes

- a. - **Worldwide**, the most common cause of hypothyroidism is **dietary deficiency of iodine**.
- b. In most **developed** countries, autoimmune diseases predominate such as **Hashimoto** thyroiditis
- c. **Genetic** defects such as *Thyroid dysgenesis* or congenital biosynthetic defect (dyshormogenic goitre).

Secondary causes: Pituitary or hypothalamic disorder.

hypothyroidism

It causes two clinical syndromes.

- **Cretinism**.. Hypothyroidism in infancy and early childhood
- **Myxedema**... hypothyroidism in older children and adults.
- The difference of features of hypothyroidism among these age groups is because thyroid hormones are vital early in life for brain and body development.

Decreased thyroid hormones during pregnancy

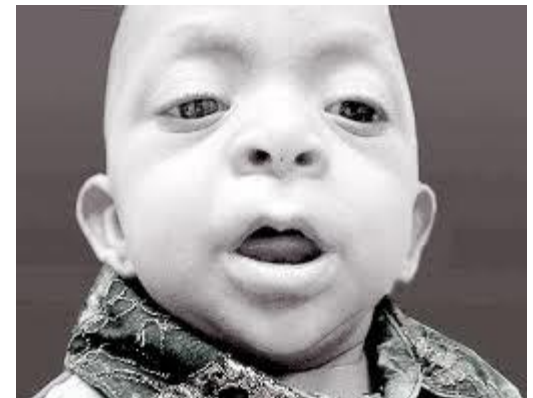
- Normally, maternal hormones that are critical to fetal brain development, including T3 and T4, **cross the placenta**.
- If maternal thyroid deficiency is present before the development of the fetal thyroid gland, mental retardation is severe.
- Reduction in maternal thyroid hormones later in pregnancy, after the fetal thyroid has developed, allows normal brain development.

Cretinism :Refers to hypothyroidism developing in infancy or early childhood

1. Endemic cretinism: in dietary iodine deficiency is endemic, including mountainous areas (the Himalayas)
2. Sporadic cretinism. Caused by **enzyme defects** that interfere with thyroid hormone synthesis

Clinical features of cretinism include:

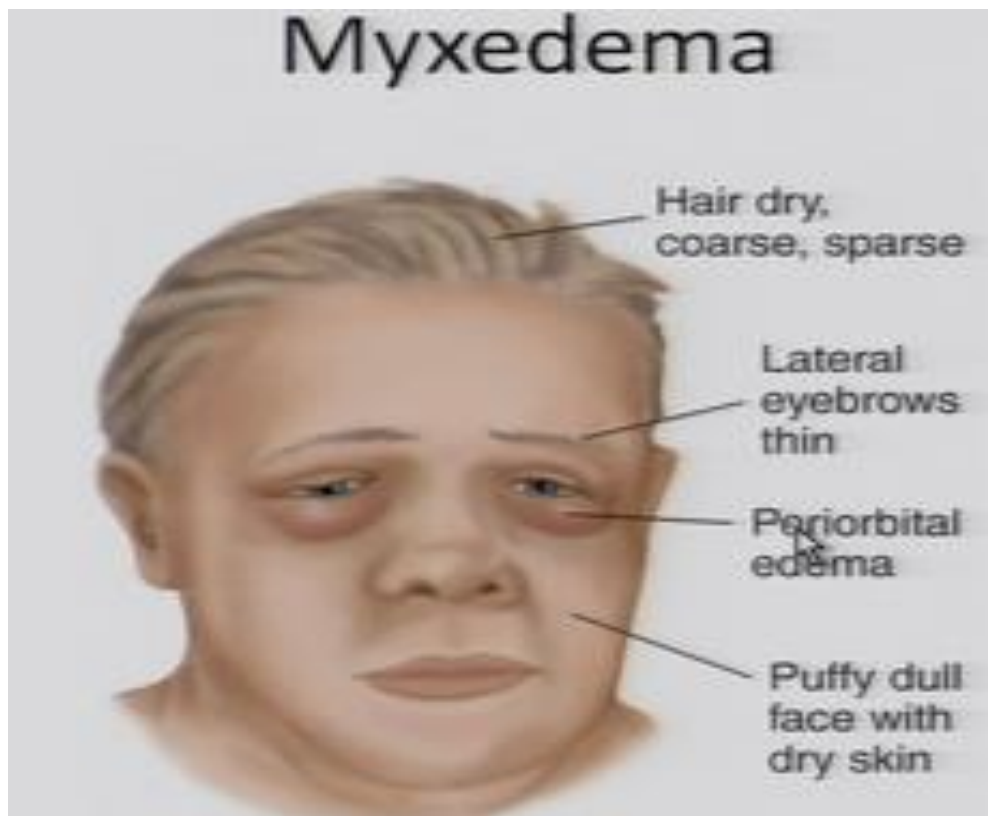
- Impaired development of skeletal system- short stature,
- Coarse facial features, protruding tongue, umbilical hernia.
- Central nervous system problems , with mental retardation



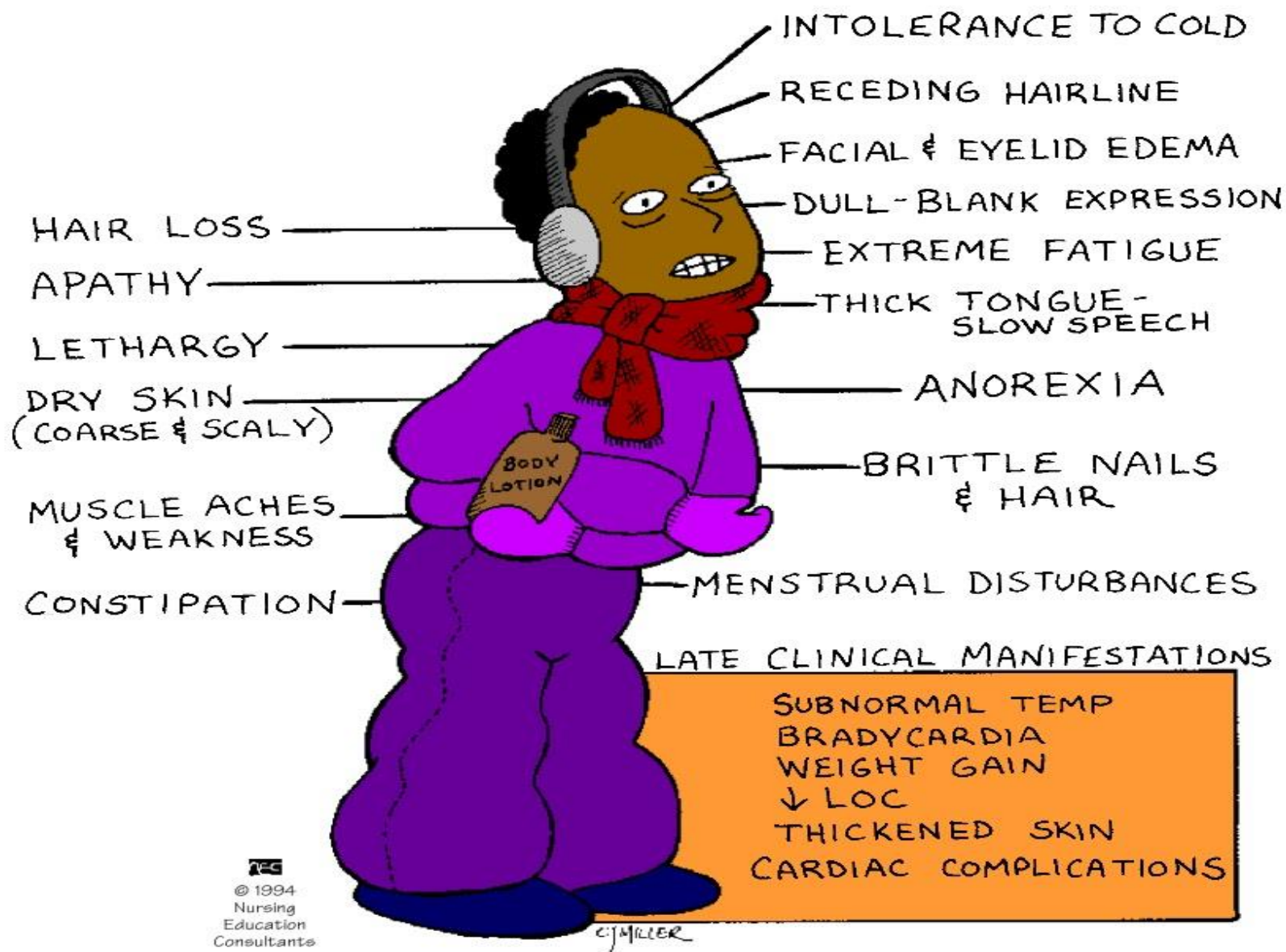
Myxedema. or Gull syndrome :

- a. cold intolerance and obesity
- b. Generalized apathy and mental sluggishness that in the early stages of disease may mimic depression
- c. Broadening and coarsening of facial features
- d. Enlargement of the tongue, and deepening of the voice.
- e. Bowel motility is decreased, resulting in constipation.
- f. Pericardial effusions are common; in later stages, the heart is enlarged, and heart failure may supervene.
- g. Mucopolysaccharide-rich edematous fluid accumulates in skin, subcutaneous tissue, and number of visceral sites

Myxedema



HYPOTHYROIDISM



Lab tests

*Serum **TSH** is the most sensitive screening test .*

- a. The serum TSH is increased in primary hypothyroidism
- b. The TSH is not increased in persons with hypothyroidism caused by primary hypothalamic or pituitary disease.
- c. Serum T_4 is decreased hypothyroidism of any origin.

Thyroiditis.

- = inflammation of the thyroid gland
- Several types:
- 1. Chronic Lymphocytic (Hashimoto) Thyroiditis
- 2. Subacute Granulomatous (de Quervain) Thyroiditis
- 3. Subacute Lymphocytic Thyroiditis
- 4. Riedel thyroiditis

1.Hashimoto thyroiditis.. Named after
a Japanese doctor.



Chronic Lymphocytic (Hashimoto) Thyroiditis

- *Is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient.*
- It is characterized by gradual thyroid failure secondary to **autoimmune** destruction of the thyroid gland
- It is most prevalent between the ages of 45 and 65 years and is more common in **women** than in men

***NOTE: ALL THYROID DISEASES ARE MORE IN WOMEN**

- It can occur in children and is a major cause of non-endemic goiter in children

What do we mean by autoimmune destruction?

- Normally, our B and T lymphocytes undergo maturation within the **t**hymus (**T** cells) and **b**one marrow (**B** cells)
- During this maturation phase, the lymphocytes that have receptors recognizing our own antigens are deleted (they die by apoptosis)
- So, only lymphocytes that are self tolerant (cannot recognize self antigens as foreign) are released to circulation and deposited into tissues.
- This means our lymphocytes will not attack our antigens (proteins)
- This is called self tolerance.
- If this mechanism fails, one will have lymphocytes that recognize self proteins as foreign antigens and will attack them. This results in autoimmune diseases.
- T lymphocytes can attack our cells directly causing direct killing (T cell mediated cytotoxicity), or via producing cytokines that destroy our cells.
- B lymphocytes attack cells by antibodies = antibody mediated cytotoxicity.

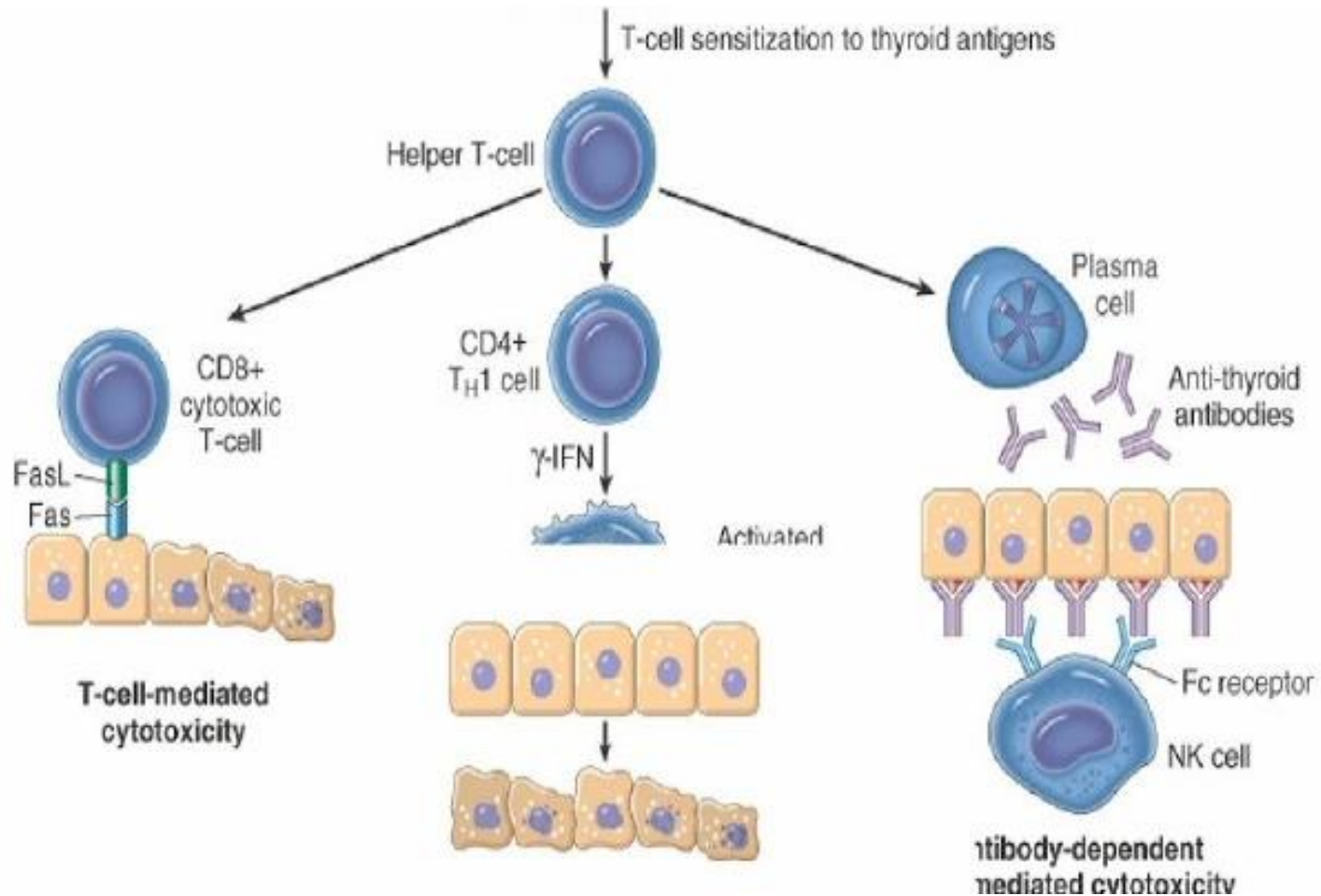
PATHOGENESIS of Hashimoto thyroiditis :-

Caused by breakdown in self-tolerance to thyroid antigens

- Circulating **autoantibodies** against thyroid antigens are present in the vast majority of patients
- Multiple immunologic mechanisms may contribute to thyroid damage.

- I. **Cytokine-mediated** cell death: Excessive T cell activation leads to the production of inflammatory cytokines such as IFN- γ in the thyroid with resultant recruitment and activation of macrophages and damage to follicles .
- II. Binding of anti-thyroid antibodies (antithyroglobulin, and antithyroid peroxidase antibodies), followed by **antibody-dependent cell-mediated cytotoxicity**
- III. **T cell mediated cytotoxicity.**

HASHIMOTO



▪

HASHIMOTO

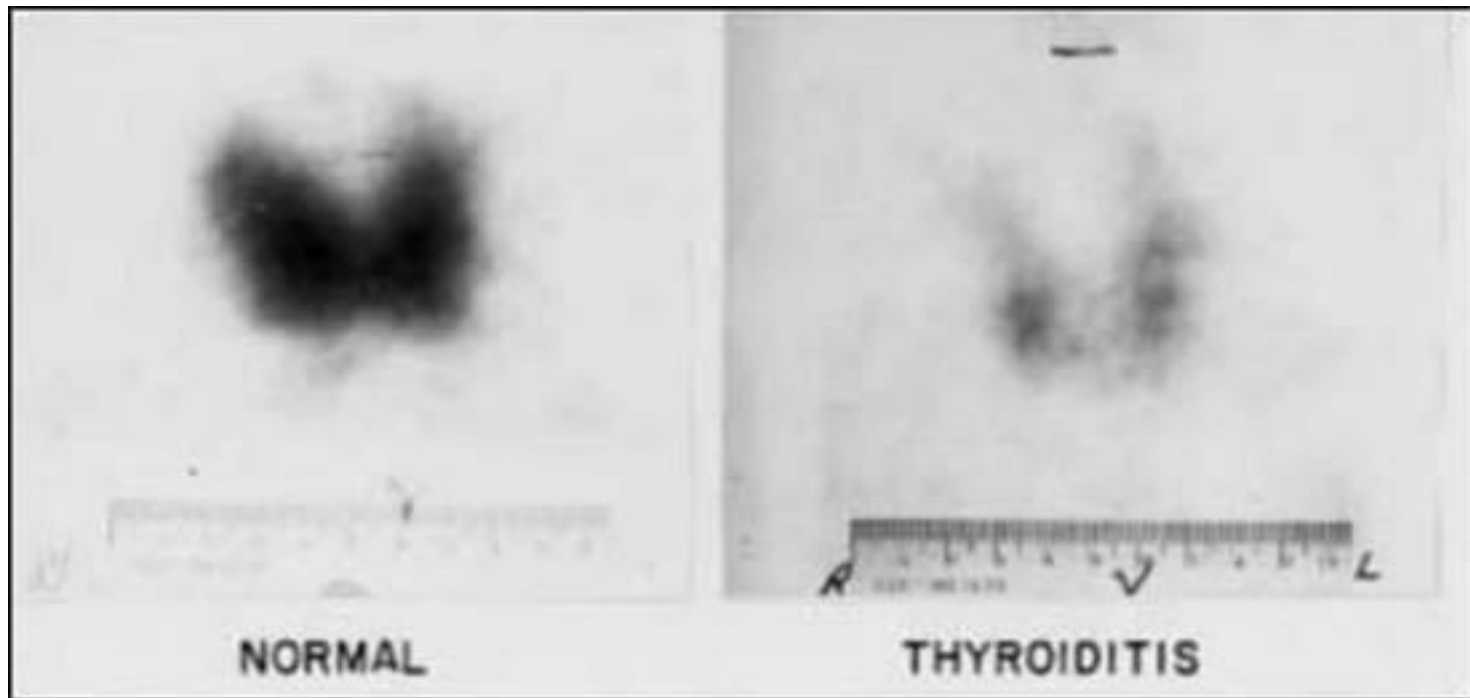
- A significant genetic component is supported by the
 - a. Concordance of disease in 40% of monozygotic twins,
 - b. the presence of circulating antithyroid antibodies in 50% of asymptomatic siblings of affected patients .

- **Clinically** ,

1. ***Painless thyroid enlargement associated with some degree of **hypothyroidism**,***
2. - In the usual clinical course, hypothyroidism develops gradually; however, it *may be preceded by transient thyrotoxicosis* due to disruption of thyroid follicles ,and secondary release of thyroid hormones (*hashitoxicosis*).

SO: at the beginning of the disease the destruction by autoimmune antibodies might cause increased release of thyroid hormones from the destructed follicles but later there is so much destruction and no new colloid is formed, resulting in hypothyroidism

Decreased iodine uptake in Hashimoto thyroiditis



- Patients with Hashimoto thyroiditis often :
 1. Have *other autoimmune diseases*
 2. Are at *increased risk for the development of B cell non-Hodgkin lymphomas* within the thyroid gland.

Note:

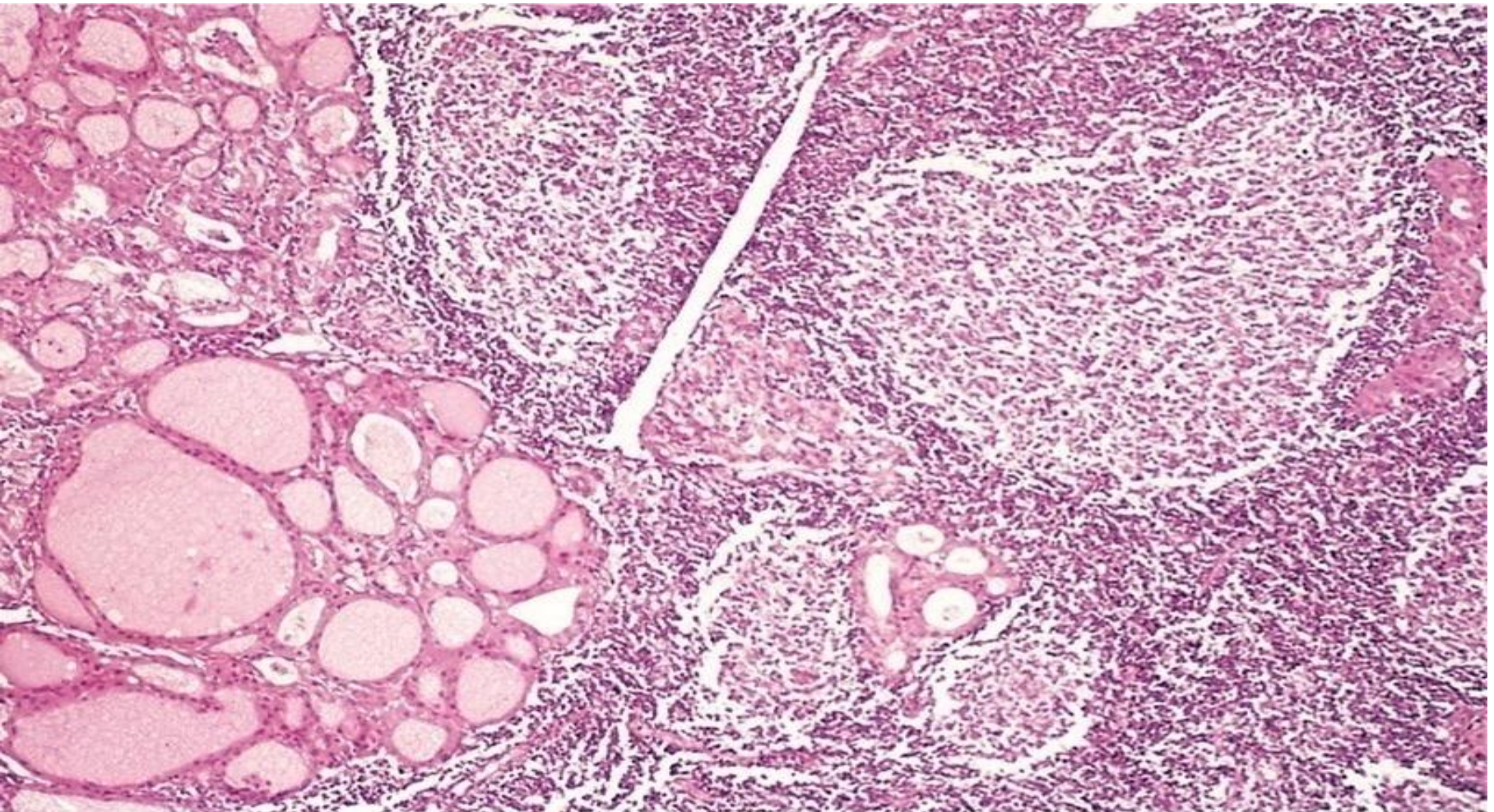
- The relationship between Hashimoto disease and thyroid epithelial cancers remains controversial, with some morphologic and molecular studies suggesting a predisposition to papillary carcinomas

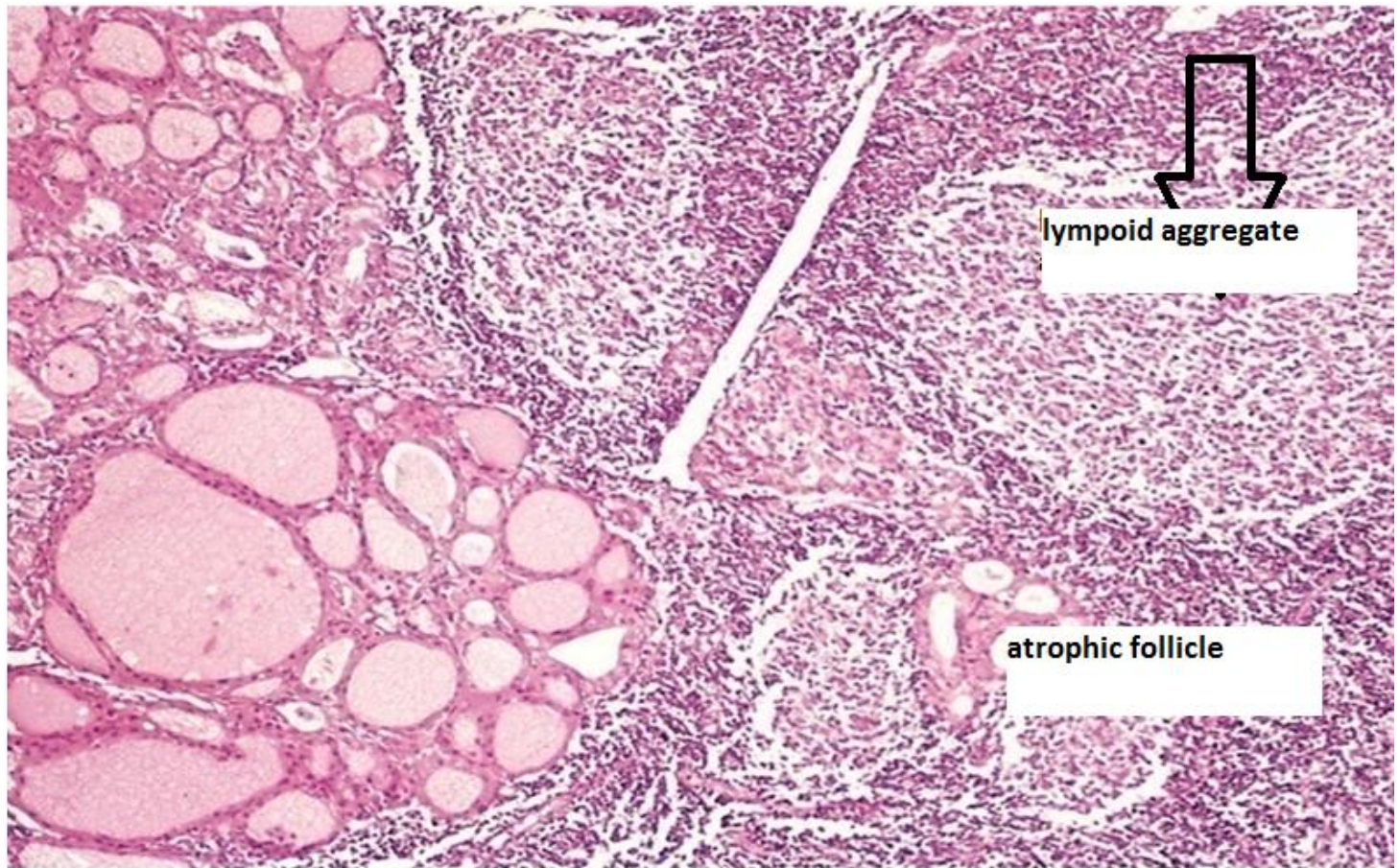
- Gross(macroscopic) features:
 - **Diffuse** and **symmetric** enlargement of the thyroid but localized enlargement may be seen in some cases to raise suspicion for neoplasm

Microscopic examination reveals

1. Infiltration by small **lymphocytes, plasma cells, and well-developed germinal centers**
2. **The thyroid follicles are atrophic**
3. Some follicles are lined by epithelial cells with abundant eosinophilic, cytoplasm, termed **Hürthle cells** and **these Hurthle cells have numerous mitochondria**

Hashimoto thyroiditis

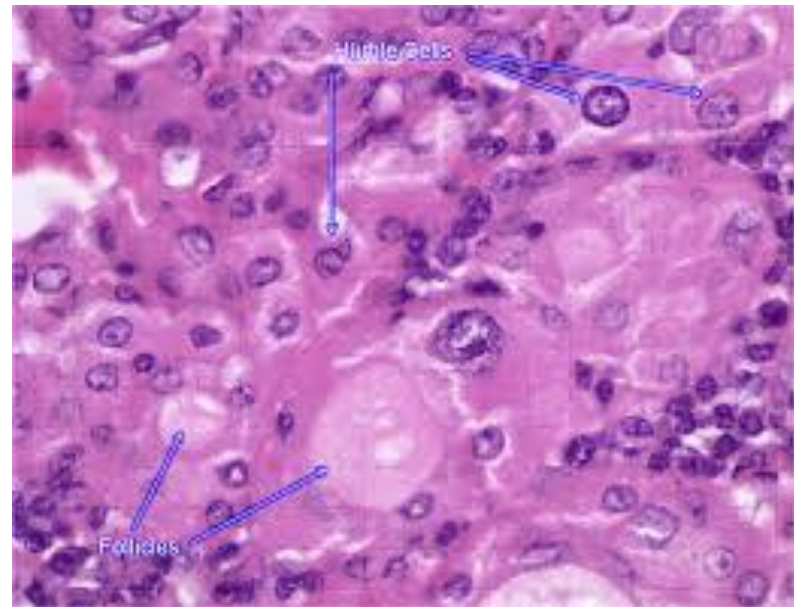
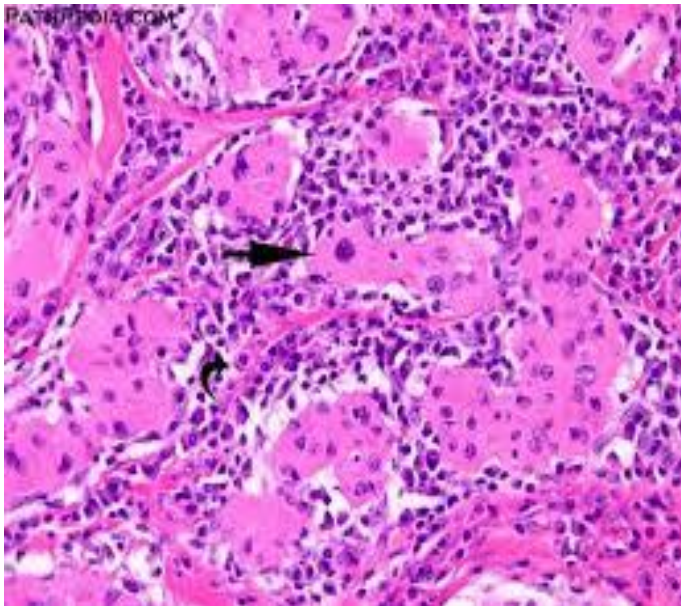




lymphoid aggregate

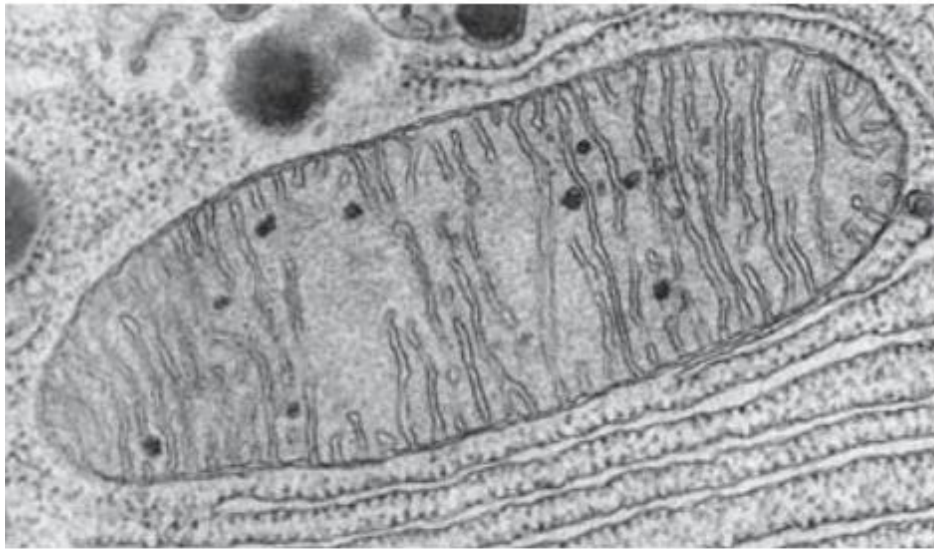
atrophic follicle

Hurthle cells: large cells with abundant eosinophilic cytoplasm, due to increased mitochondria



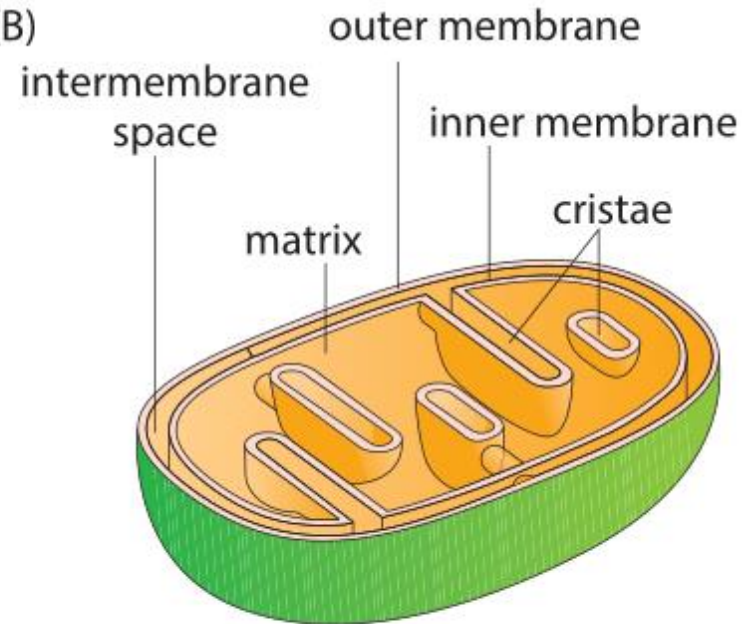
Hurthle cell cytoplasm is full of mitochondria

(A)



0.5 μm

(B)



3-D view of mitochondrion

2. Subacute Granulomatous (de Quervain)

Thyroiditis

- Is much less common than Hashimoto disease
- Is most common between the ages of 30 and 50 and,
- More frequently in women than in men.
- Is believed to be caused by a **viral infection** and a majority of patients have a history of an upper respiratory infection just before the onset of thyroiditis.

Gross- The gland has intact capsule, and may be unilaterally or bilaterally enlarged.

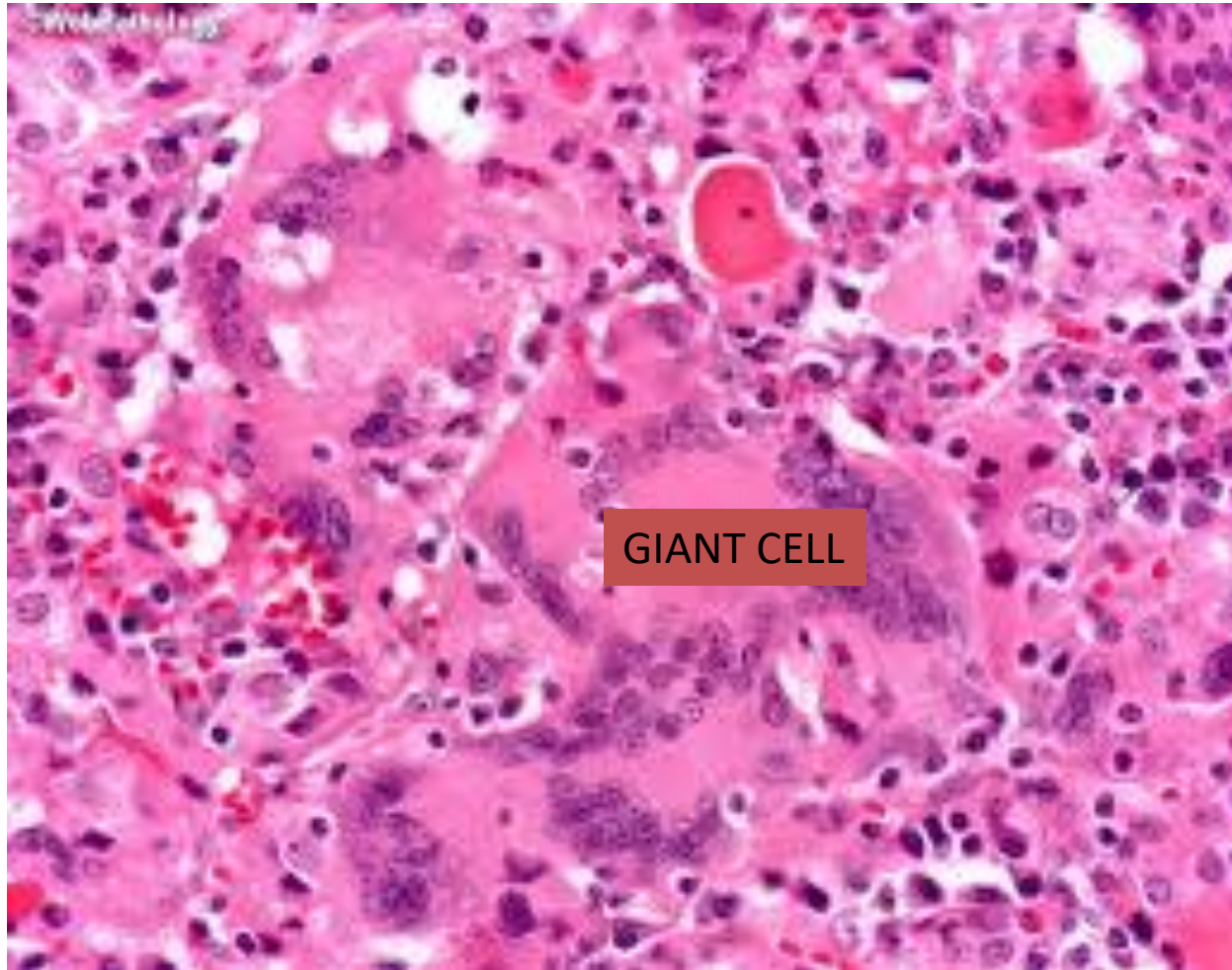
- Clinical Features :

- Acute onset characterized by neck **pain** (with swallowing)
- **Fever, malaise** (tiredness), and **variable enlargement** of the thyroid.
- **Transient hyperthyroidism** may occur as a result of disruption of follicles and release of excessive hormones.
- **The leukocyte count is increased.**
- With progression of disease and gland destruction, a transient hypothyroid phase may ensue.
- The condition typically is **self-limited**, with most patients returning to a euthyroid state within 6 to 8 weeks

Histologic examination reveals

1. Disruption of thyroid follicles, with extravasation of colloid leading to a neutrophilic infiltrate, which is replaced by lymphocytes, plasma cells, and macrophages.
2. The extravasated colloid provokes a **granulomatous** reaction with giant cells that contain fragments of colloid.
3. Healing occurs by resolution of inflammation and fibrosis.

Subacute granulomatous thyroiditis



3. Subacute Lymphocytic Thyroiditis :

- Also is known as *silent or painless* thyroiditis;
- And in a subset of patients the onset of disease follows - pregnancy (*postpartum thyroiditis*).
- Most likely to be *autoimmune* because circulating antithyroid antibodies are found in a majority of patients
- It mostly affects middle-aged women, who present with a *painless* neck mass or features of thyrotoxicosis

4. Riedel thyroiditis,:

A rare disorder of unknown etiology,

- Characterized by extensive fibrosis involving the thyroid and adjacent structures simulating a thyroid neoplasm
- May be associated with idiopathic fibrosis in other parts of the body, such as the retroperitoneum
- The presence of circulating antithyroid antibodies in most patients suggests an autoimmune etiology

Case study

- Mrs A is a 45 year old lady who had a history of SLE (systemic lupus erythematosus) . She suffers from constipation and tiredness. Although it was a hot July day you notice that she wears a coat and gloves!

- What else you like to ask her?
- Is the SLE relevant in her case?

Answers

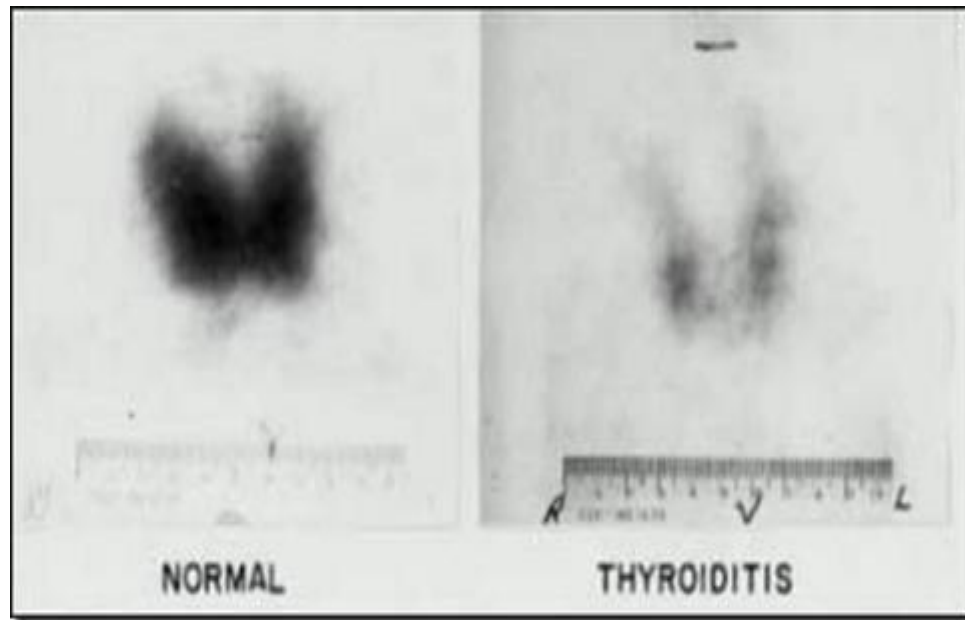
- This patient seems to have some symptoms of hypothyroidism... so start by taking full clinical history: ask about other features of hypothyroidism.
- Yes, SLE is important. SLE is an autoimmune disease and in general there are associations with autoimmune diseases (several occur in the same patient) so: this raises the possibility of an autoimmune thyroid disease.

- On physical examination you find her thyroid to be diffusely enlarged and painless.
- What will you do next?
- Blood tests?
- Iodine scan?
- Fine needle aspiration (FNA) ?
- Histology?

Answers

- On physical examination you find her thyroid to be diffusely enlarged and painless: this description along with the hypothyroidism should raise the possibility of Hashimoto. The SLE history supports this assumption.
- What will you do next?
- Blood tests? Sure. Check TSH, T3 and T4
- Iodine scan? Can be done but not really necessary in clinical practice. Iodine scans are used mainly to investigate hyperthyroidism. If done in Hashimoto they will show decreased uptake.
- FNA? Sure. It's easy and less expensive than histology.
- Histology? Yes, especially if FNS not conclusive.

Iodine scan



Thyroid FNA

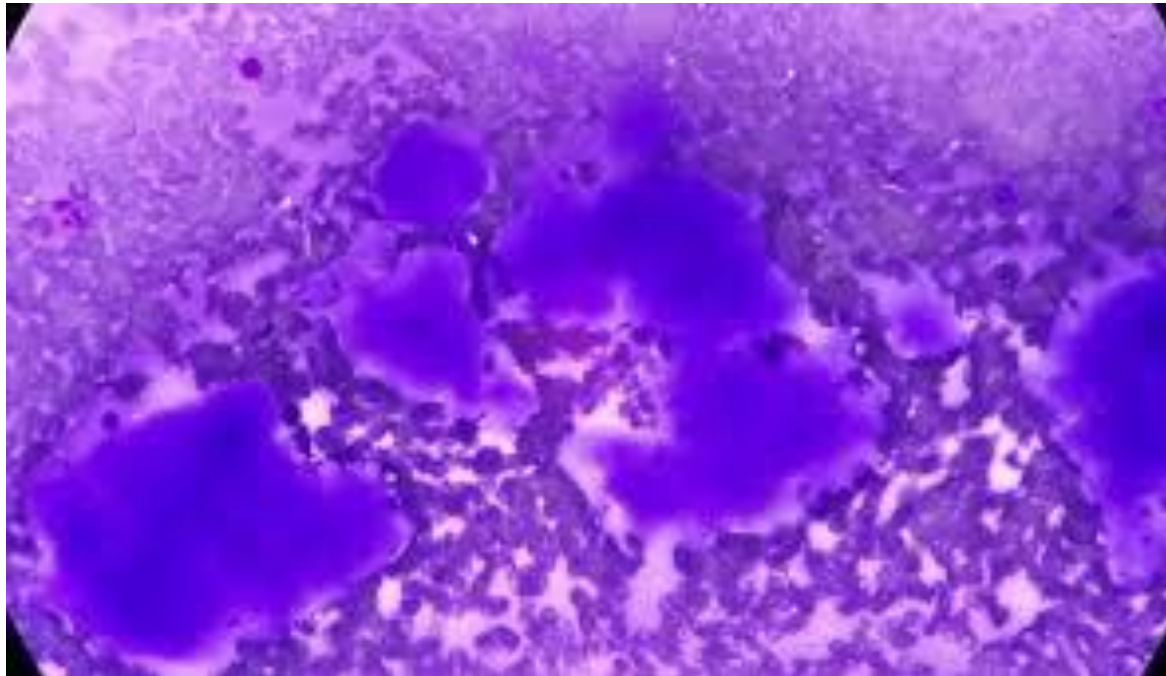


FNA

- This is an easy, quick, relatively cheap way to diagnose thyroid diseases.
- Cells are taken by the needle and put on a slide then stained.
- In FNA we examine cells only not tissue.
- Colloid can be seen in FNA. **See next slide**
- In case of Hashimoto we will see Hurthle cells and lymphocytes.

Colloid as seen on FNA

- The blue color is the colloid. The red cells in the pic are RBCS from blood(when you put the needle some blood will come out(



Question

- Mr M is a 30 year old man who had an upper respiratory tract infection 3 months ago after which he developed neck pain and fever
- You found his thyroid to be tender and enlarged.
- TSH was increased, free T3 decreased.
- What is your diagnosis?

Answer

- This patient had a thyroid disease following a viral infection plus Pain and fever as well as hypothyroidism.
- These features are seen in **Subacute Granulomatous (de Quervain) Thyroiditis**



Thank you!

