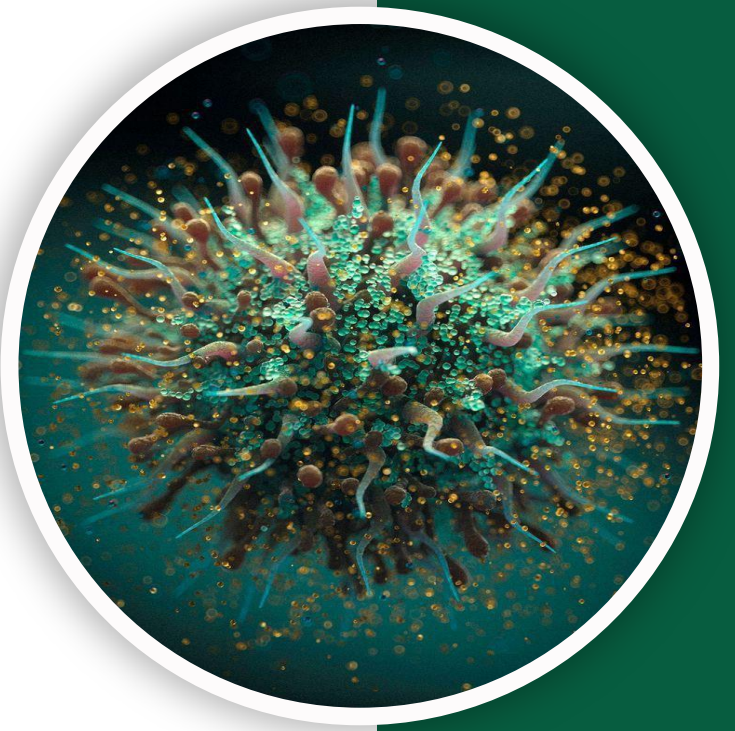
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Pathology | FINAL 4

Disease of the Thyroid Gland Pt.1



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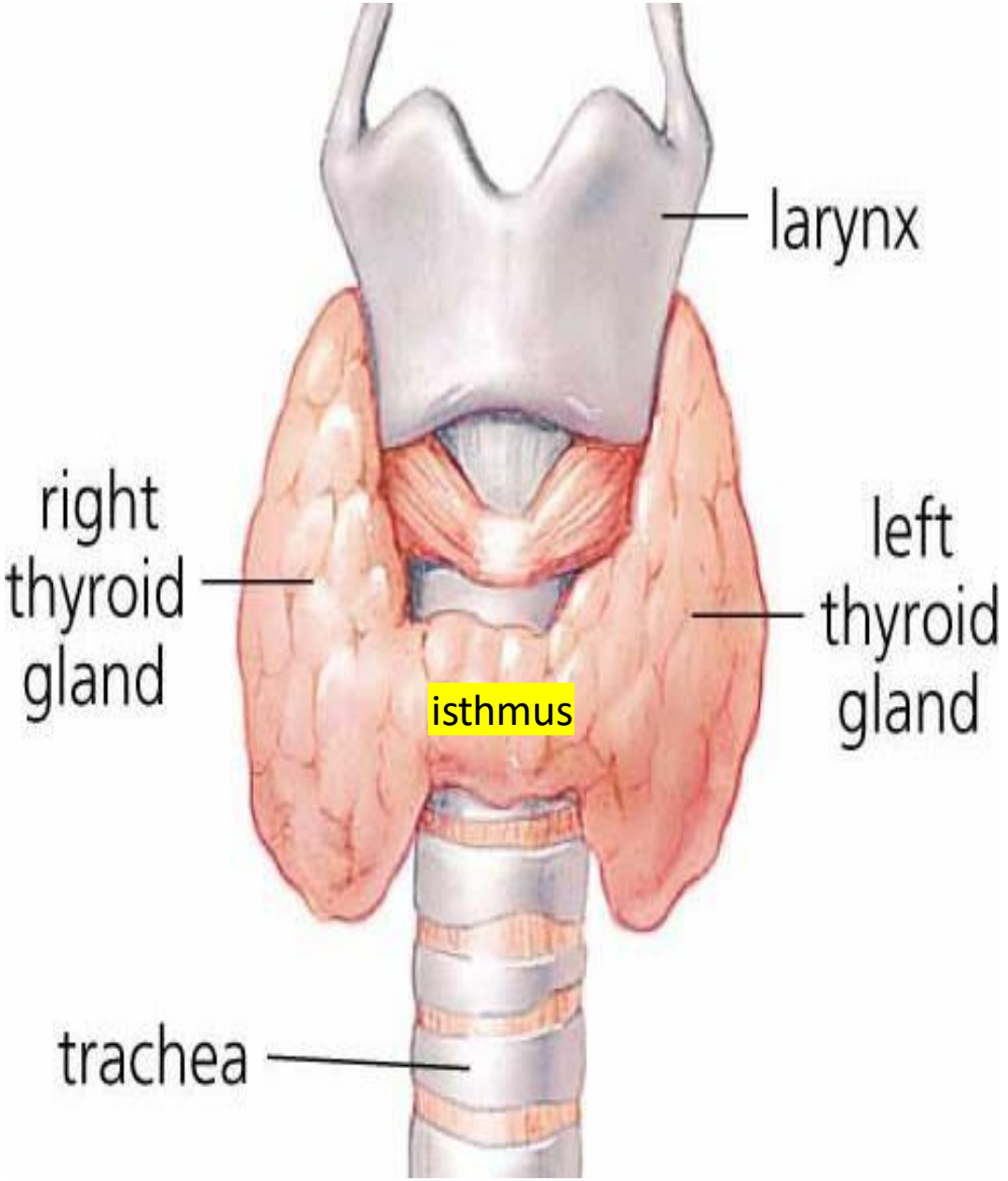
Endocrine System
Thyroid Gland Part 1

Dr Heyam Awad MD, FRCPath

Thyroid gland

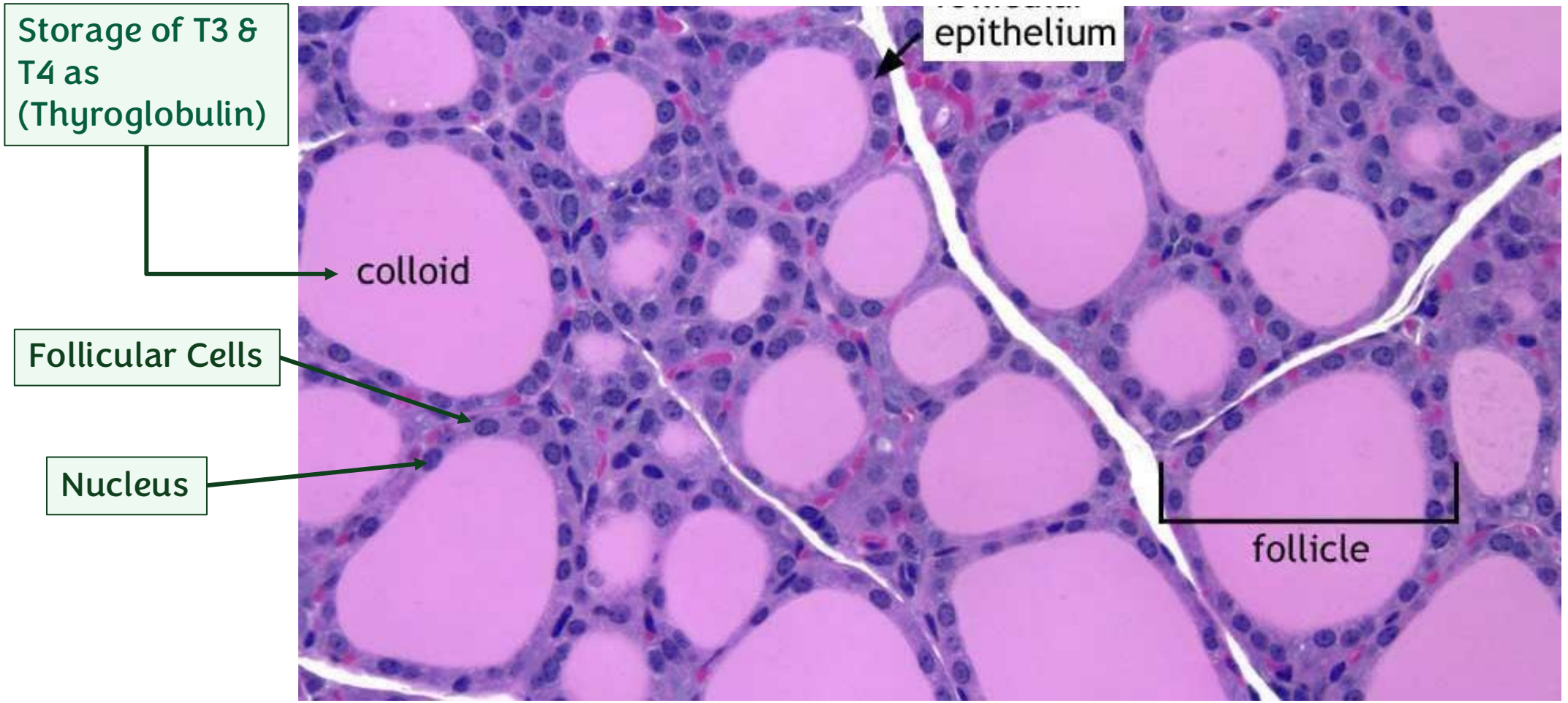
- The thyroid gland consists of **two lobes (right and left) that are connected by the isthmus.**
- The right and left lobes are pear shaped with the apex directed upwards.
- The thyroid is attached to the the larynx; it moves upwards during swallowing. So if you see a neck mass ask the patient to swallow,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



Thyroid gland histology

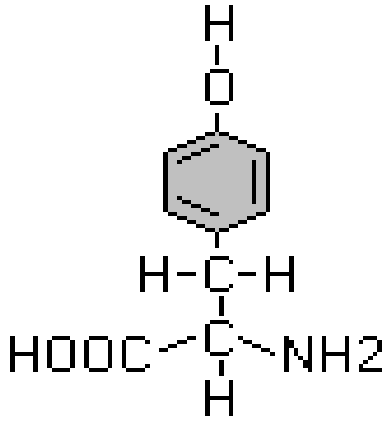
- The thyroid gland is **composed of follicles lined by follicular epithelial cells which are cuboidal to low columnar.**
- The follicles **contain colloid** which is **composed of thyroglobulin** which is the iodinated precursor protein of thyroid hormones.

Histology

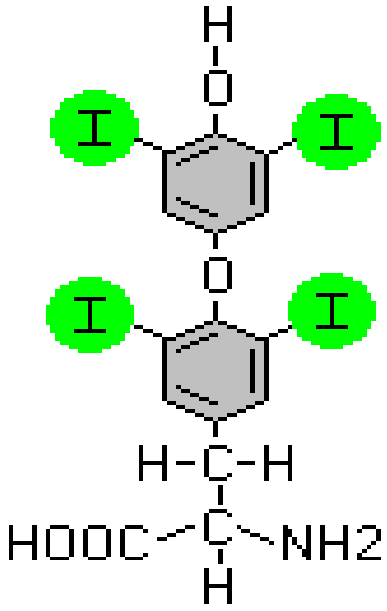

Storage of T3 & T4 as (Thyroglobulin)
epithelium
colloid
Follicular Cells
Nucleus
follicle

Thyroid hormones

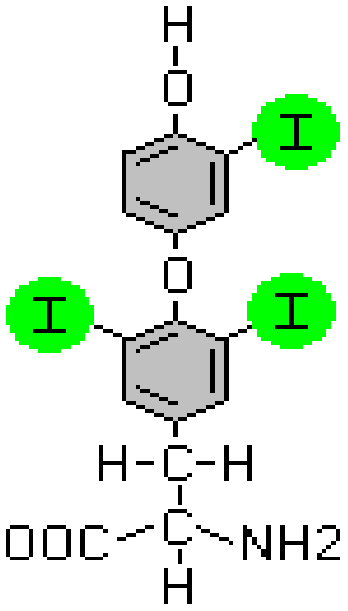
- They are named T3 and T4 depending on how many iodide atom they have.



Tyrosine



Thyroxine (T4)

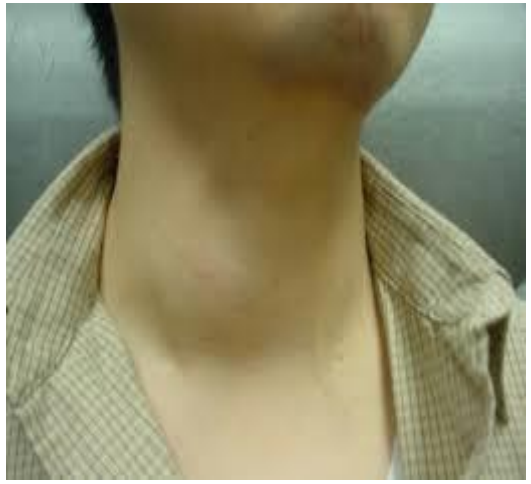


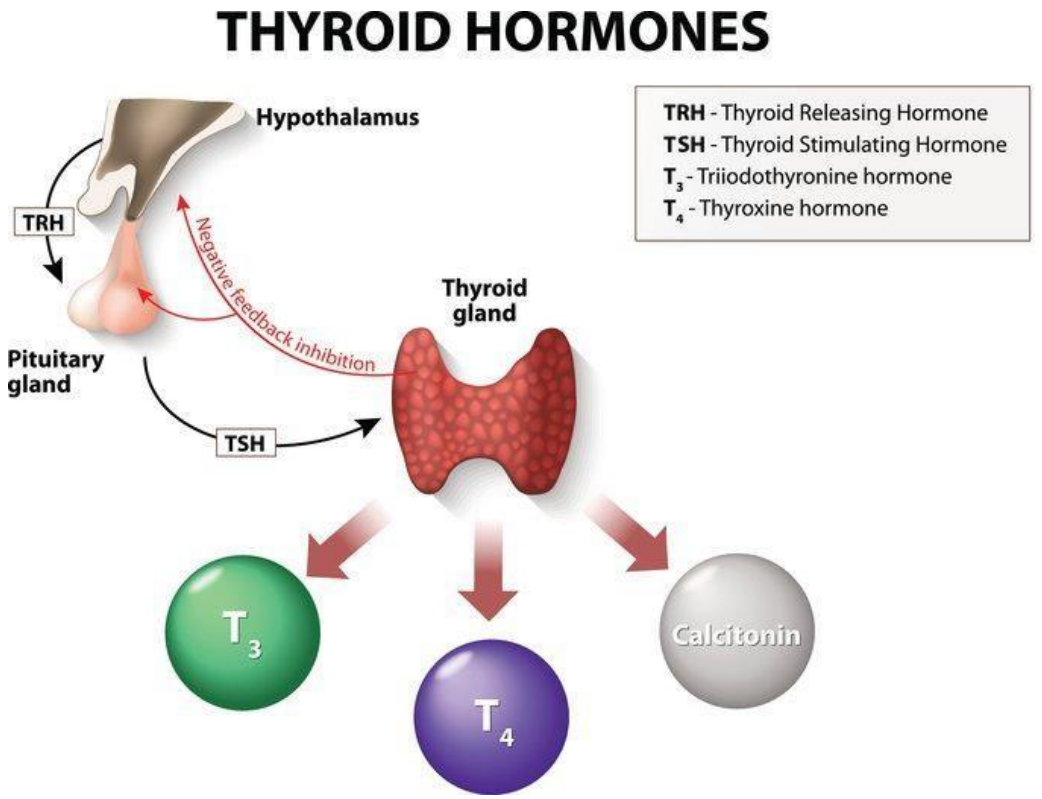
Triiodothyronine (T3)

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)**

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

- Thyroid gland have different cell types that **secrets different hormones** ::
  - Follicular cells secrete : **T3 & T4.**
  - Parafollicular cells secrete (C Cells) : **Calcitonin.**





Diseases of the Thyroid Gland

- **Same general rules of all endocrine glands!** (refer to lecture 1)
- Mass effect. Not related to hormonal abnormalities.
- Hormonal Abnormalities :
  - Hyperthyroidism (thyrotoxicosis).
  - Hypothyroidism.

- Again, there is **no relation between mass effect and level of hormonal production**

  A large thyroid gland does not necessarily mean increased hormone secretion, and a small gland does not necessarily mean decreased secretion.

Thyroid Diseases

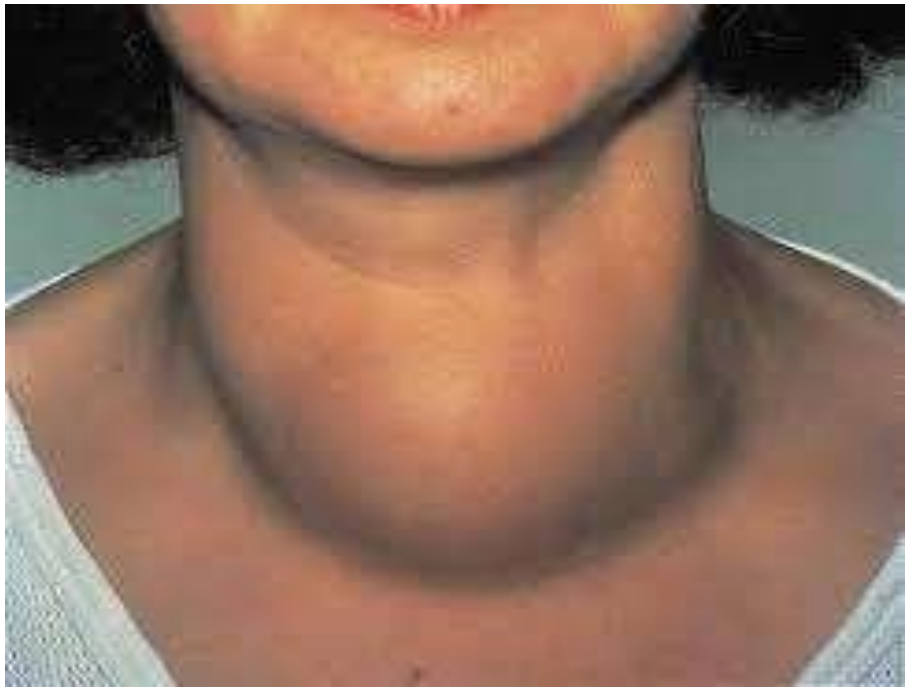
1. **Mass effect**: enlargement can be due to:
   - Inflammation, neoplasms, autoimmune diseases. (details later)
   - Thyroid enlargement, due to any cause is called: **goiter.**

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

➢ **Hormonal Abnormalities :**

2. **Hyperthyroidism (thyrotoxicosis).**
3. **Hypothyroidism.**

Goiter: **enlarged thyroid.. Regardless of the cause.**



Clinical Manifestations of Hyperthyroidism (Thyrotoxicosis)

- Thyroid hormones **increase basal metabolic rate (BMR)**, **increase appetite, increase breakdown of fat and glucose.**
- Also **increase heart rate**, cause hypertension.
- **Increase body temperature.**
- **Flushing of the skin.**
- **Excessive sweating.**
- SO, if these hormones are increased you expect to see a wide range of symptoms.

Causes of Hyperthyroidism

Toxic = hot = Secretory
Non-toxic = Cold = Non-Secretory

A. Diffuse toxic (Secretory) hyperplasia (Graves disease) — **The most important cause.**
B. Hyperfunctioning (Toxic) multinodular goiter
   Multinodular goiter **usually** presents with normal thyroid hormone levels, and **only rarely** becomes hyperfunctioning, leading to hyperthyroidism.
C. Hyperfunctioning (toxic) adenoma "Functioning adenoma"
D. TSH-secreting pituitary adenoma (rare)
E. Ectopic secretion of thyroid hormones from non-thyroidal tissue.. So thyroid function is normal.

Clinical Manifestations of Thyrotoxicosis

A. **Constitutional symptoms :** warm **flushed skin, heat intolerance** (feel hot in cold temperature and can't handle heat in hot temp), excessive sweating and **weight loss despite increased appetite (due to increased BMR).**

B. **Malabsorption, and diarrhea** (because of increased intestinal motility)

C. **Tachycardia** and elderly patients may develop to arrythmia and 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 (eye lids are widely opened due to over stimulation of levator muscles).

F. **50% develop proximal muscle weakness** (thyroid myopathy). – Hypothyroidism may cause muscle weakness: Since it increase lipid & glucose destruction So the proteins is the only source of energy which may be destructed & causes muscle weakness.

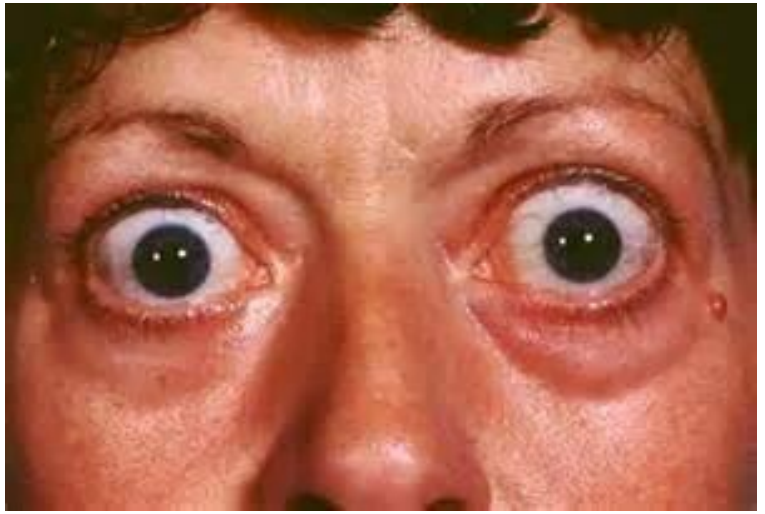
Eye changes in Thyrotoxicosis:

- In Graves' disease, **exophthalmos is present.** Whereas in other causes of thyrotoxicosis, the typical finding is a wide, staring gaze.

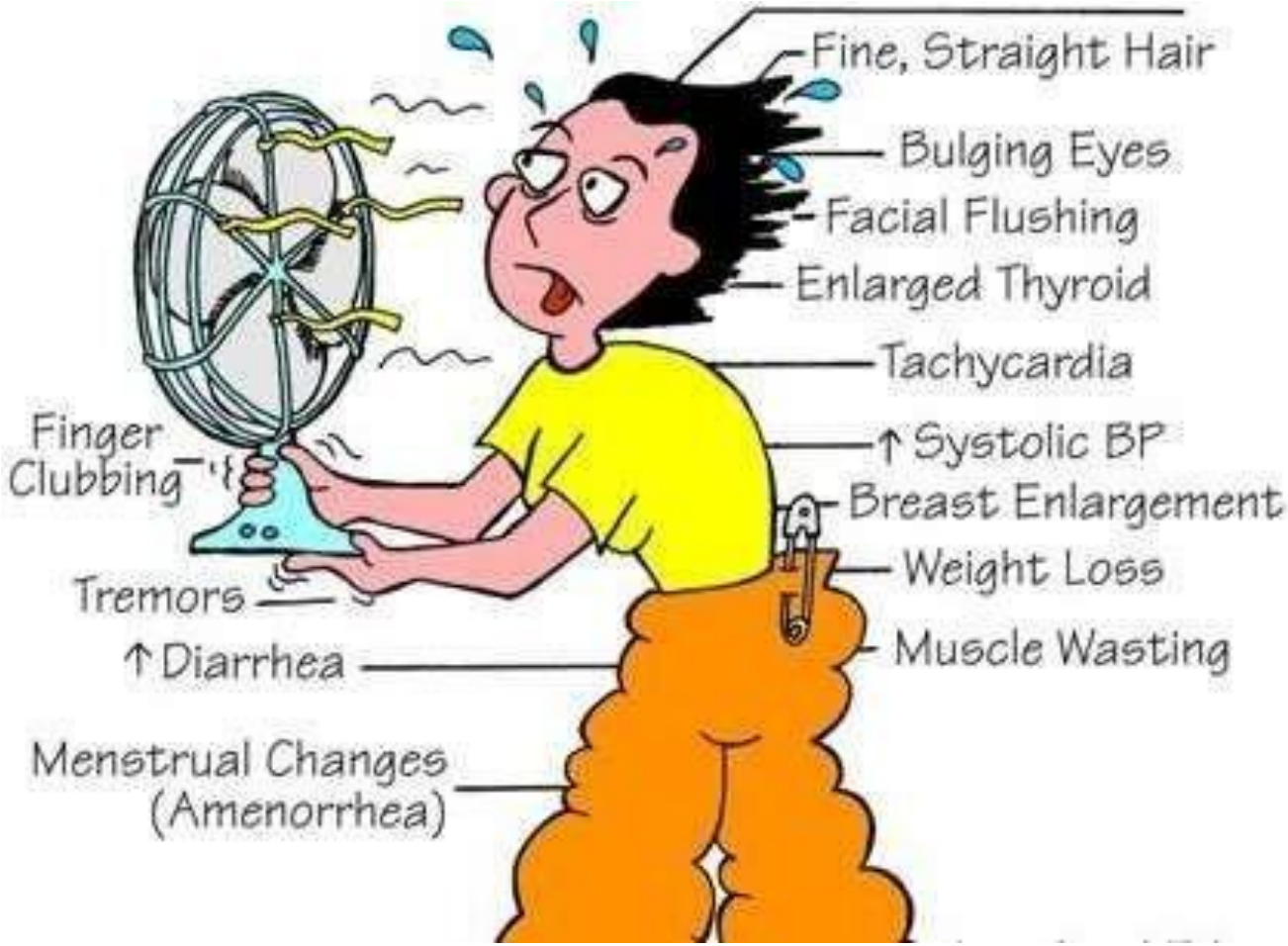
- **Exophthalmos** is the actual physical forward bulging of the eyeball out of the eye socket.
- **wide staring gaze (lid retraction** or Dalrymple sign) is an abnormal widening of the eye opening where the upper eyelid is pulled high, showing the white of the eye above the iris, often without the eyeball itself being pushed forward

Exophthalmos

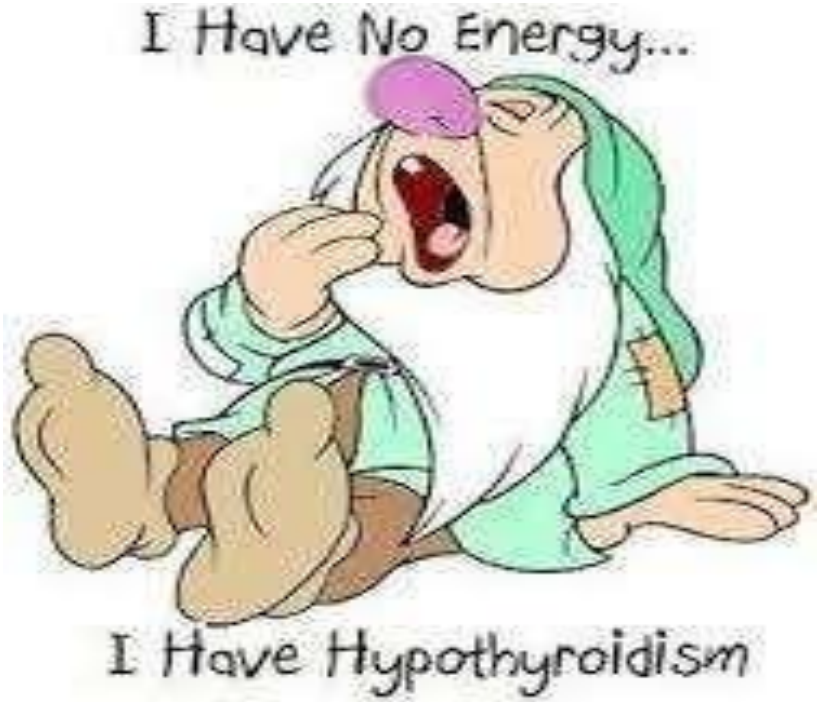
Wide, staring gaze



Hyperthyroidism



Hypothyroidism



Hypothyroidism

- **Primary causes**:
  A. **Worldwide**, the most common cause of hypothyroidism is **dietary deficiency of iodine**.
  B. In most **developed** countries **(countries having sufficient amounts of iodine)**, **autoimmune diseases predominate** such as **Hashimoto thyroiditis**
  C. **Genetic defects** (Rare) such as *Thyroid dysgenesis or* congenital biosynthetic defect (dyshormogentic goitre).

- **Secondary causes**: Pituitary or hypothalamic disorder.

Hypothyroidism

Hypothyroidism depends on age:

- In Early childhood → Cretinism → Affect the CNS development.
- In Older children & adults → Myxedema = Accumulation of fluid & lipids under the skin.

- **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.

Cretinism

- Definition: Refers to hypothyroidism developing in infancy or early childhood

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

Clinical Features of Cretinism

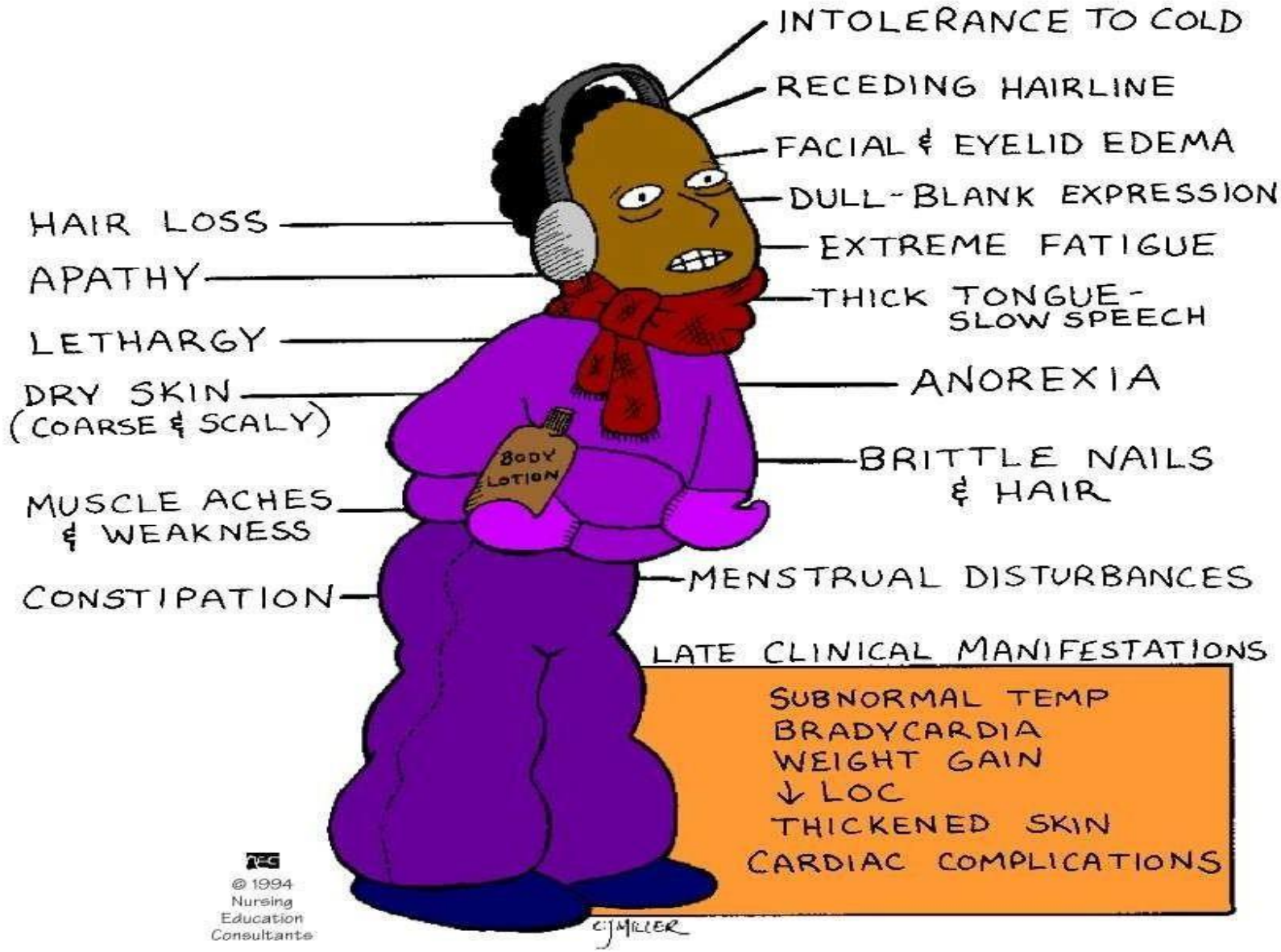
- **Impaired** development of **skeletal system- short stature.**
- Coarse facial features, **protruding tongue, umbilical hernia.**
- **Central nervous system problems , with mental retardation**
- In addition to normal hypothyroidism clinical features (myxedema) – less destruction of fat → accumulation of fat under the skin + attracting water towards it.

Myxedema or Gull Syndrome:

A. Cold intolerance **(decreased BMR)** and obesity **(less fat destruction).**
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. – opposite to hyperthyroidism which is causing diarrhea.
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
Hair dry, coarse, sparse
Lateral eyebrows thin
Periorbital edema
Puffy dull face with dry skin

HYPOTHYROIDISM



Thyroiditis

- Definition: Inflammation of the thyroid gland
- Several types:
  1. Chronic Lymphocytic (Hashimoto) Thyroiditis
  2. Subacute Granulomatous (de Quervain Syndrome) 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.
- **Clinical Presentation**: Middle aged women + Associated with other autoimmune diseases + hypothyroidism (you may see transient hyperthyroidism in the initial stage (why? You will know soon)).

- **Most** autoimmune diseases show:
  - Genetic predisposition
  - A tendency to occur in families.
  - Associated with other autoimmune diseases.

Immunological Definitions

- **Cellular immunity**: Mediated mainly by **T- lymphocytes** ($CD4^+$ helper T cells produce **cytokine (mainly IFN- gamma) which cause inflammation and destruction**, $CD8^+$ Killer cytotoxic Tcells **directly destroy cells**).

- **Humoral immunity**: Mediated mainly by **B-lymphocytes turn to** plasma cells (which produce antibodies), which **initiate the destruction of cells.**

❑ **Summary :**

- **T-lymphocyte**
  → T-helper → CD4 cells
  → T-killer → CD8 cells, cytotoxic killer cell
- **B-lymphocyte**
  → turn to plasma cells
  → produce antibodies
  → destruct the cell (follicular epithelial cell)

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.

Pathogenesis of Hashimoto Thyroiditis (Summary)

1. **Cytokine-mediated damage**

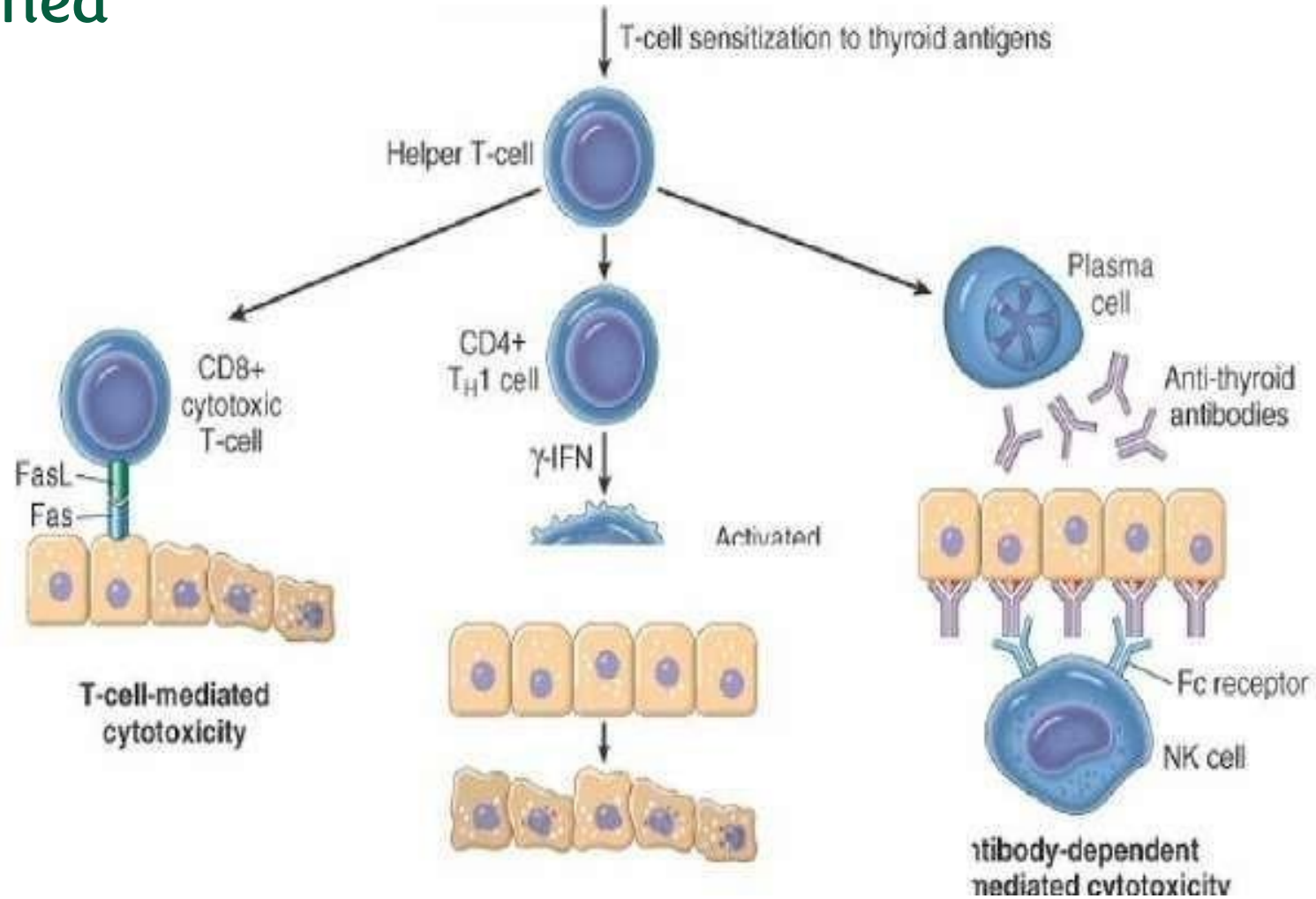
2. ↑ T-cell activation
   → ↑ inflammatory cytokines, especially **IFN-γ**
   → macrophage recruitment/activation
   → **follicular damage**

3. **Antibody-mediated damage**
   1. **Anti-thyroglobulin + anti-TPO antibodies** bind thyroid antigens
      → **ADCC**
      → thyroid cell destruction.

4. **T-cell cytotoxicity**
   1. T cells directly attack thyroid follicular cells
      → **cell death and thyroid destruction**

HASHIMOTO

Already Explained



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,** diffuse enlargement of the entire 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),** which happens in all thyroiditis.

- 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.

Clinically

- **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.

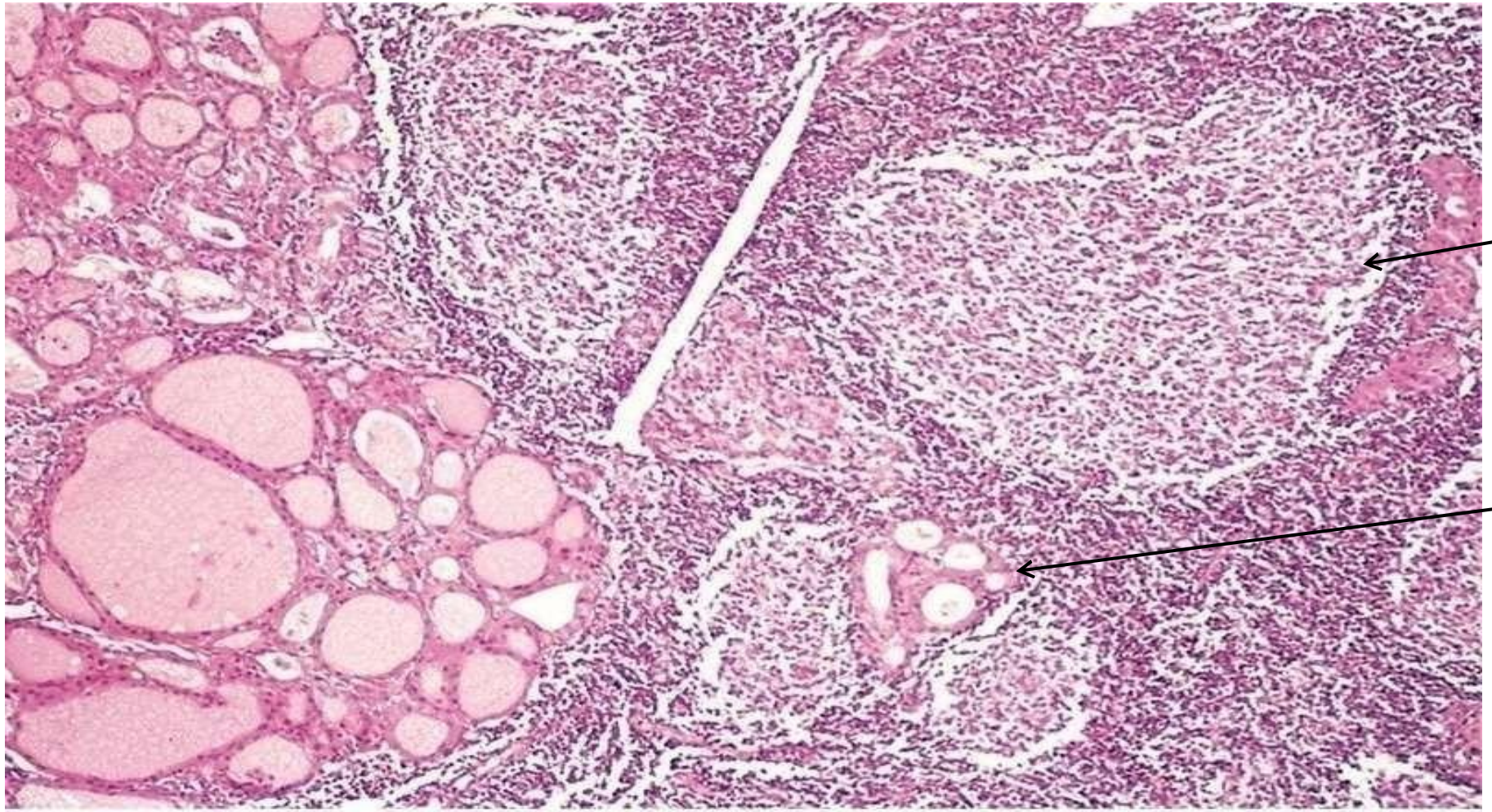
Clinically:

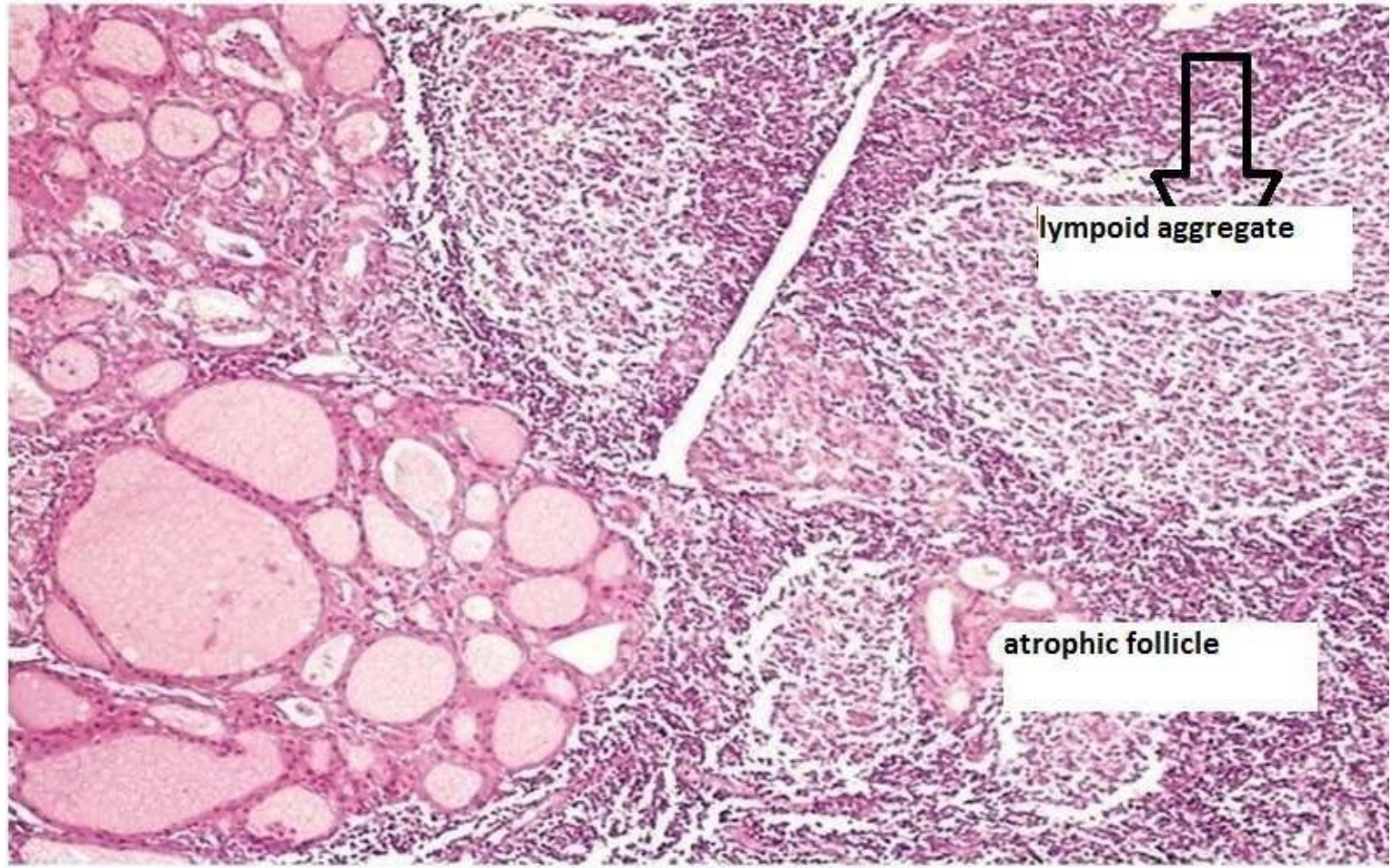
- Women.
- Middle aged.
- Other autoimmune diseases.
- **Painless** (Most important) enlargement of the thyroid gland.
  - **Important to distinguish it from subacute granulomatous thyroiditis.**

Pathological Features of Hashimoto Thyroiditis

- Gross (macroscopic) features:
  - Diffuse and symmetric enlargement of the thyroid
- 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. Hurthle cells have numerous mitochondria.

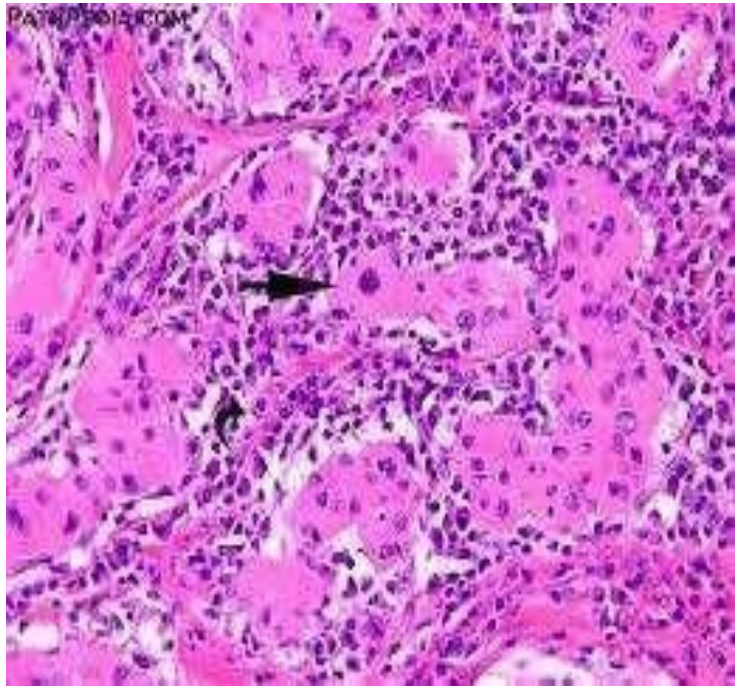
Hashimoto’s Thyroiditis

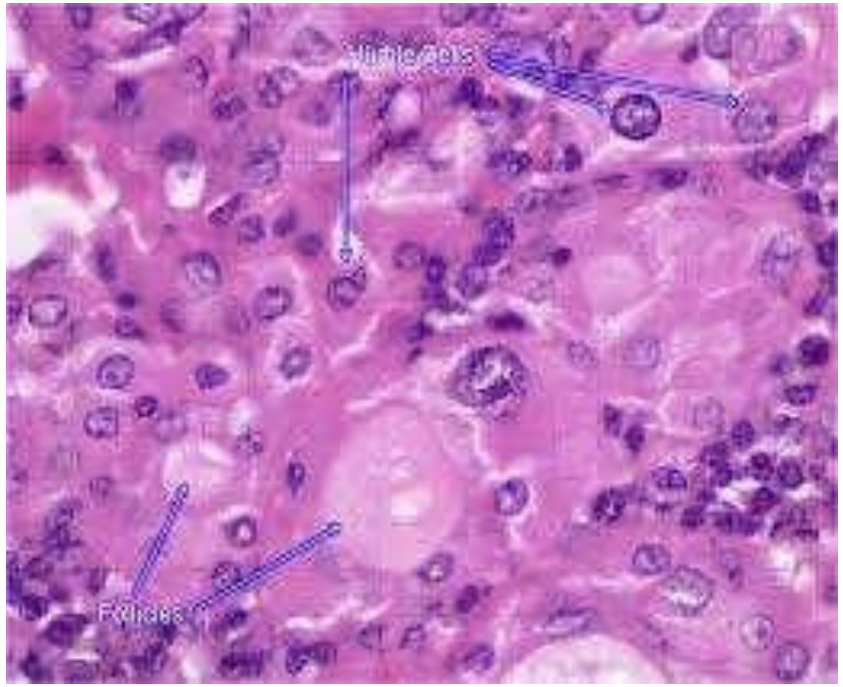




Kumar et al: Robbins Basic Pathology, 9e.

<u>Hurthle cells:</u> large cells with **large nuclei and** abundant eosinophilic cytoplasm, due to increased mitochondria





- These are follicular cells attempting to compensate for hypothyroidism **but are unsuccessful**.
- They develop abundant cytoplasmic organelles, especially mitochondria, **which increase eosinophilic staining**.

Further notes on previous slide

❑ **Why mitochondria causes cytoplasm to be eosinophilic (more eosinophilic)?**
✓ due to binding of eosinophilic stain to arginine and lysine residues on the mitochondria.

❑ **Important Lab Questions:**
✓ What are the histological features of Hashimoto thyroiditis?

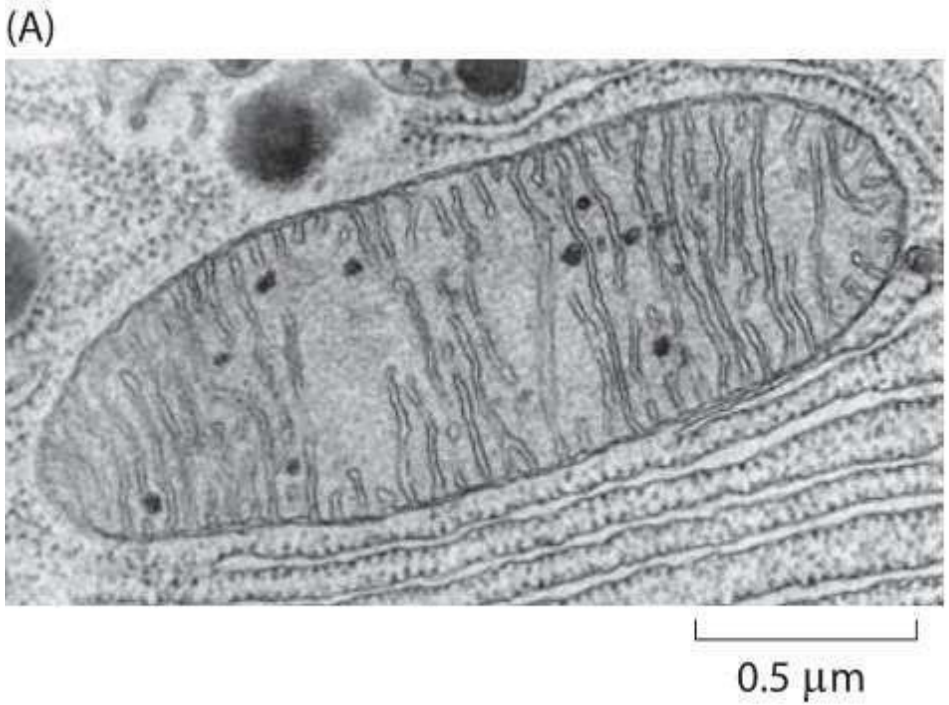
❑ **Important Question:** Why does the cell increase its mitochondria numbers?!
✓ Maybe to increase the ATP production and to compensate the ↓ in BMR.
✓ Some theories suggest that they can produce thyroid hormones. (We don't know :))

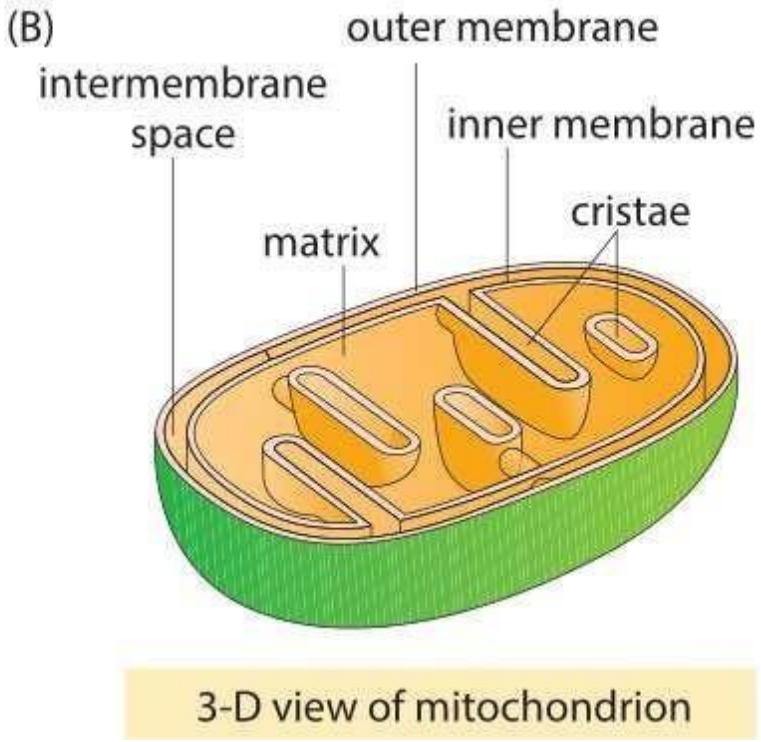
❑ **If you remember necrosis:**
- there will be a coagulation of proteins.
- increase in proteins density (closer to each other) with causes more eosinophilia to bind to proteins → more eosinophilic staining.

Same thing with mitochondria : ↑ Mitochondria → ↑ proteins → ↑ eosinophilia.

❑ **Important Note:**
✓ Hurthel cell does not mean Hashimoto but Hashimoto's necessary to have hurthle cells.

Hurthle cell cytoplasm is full of mitochondria





2. Subacute Granulomatous (de Quervain) Thyroiditis

- Granulomatous **means** inflammation with giant cells, usually caused by a **viral infection** rather **than autoimmune destruction.** It presents with **painful (important to distinguish it from Hashimoto thyroiditis)** enlargement of the thyroid, fever, and is self-limited, with a high WBC count.
- 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.

2. Subacute Granulomatous (de Quervain) Thyroiditis

Mechanism:

- Viral infection → Destruction of follicular lining epithelial cells → Extravasation of colloid (Colloid is a foreign material to macrophages) → Macrophages phagocytosis

So, Cause of granuloma : is extravasation of colloid.

Important: Painful enlargement of the thyroid gland important for distinguishing it from → Hashimoto.

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.

Clinical Features (Summary)

Important clinical features of subacute granulomatous thyroiditis:

- Viral infection
  → fever, malaise
  → increase WBC count
  → painful enlargement of the thyroid gland
  → self limited

- This is also seen in other forms of thyroiditis.

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.

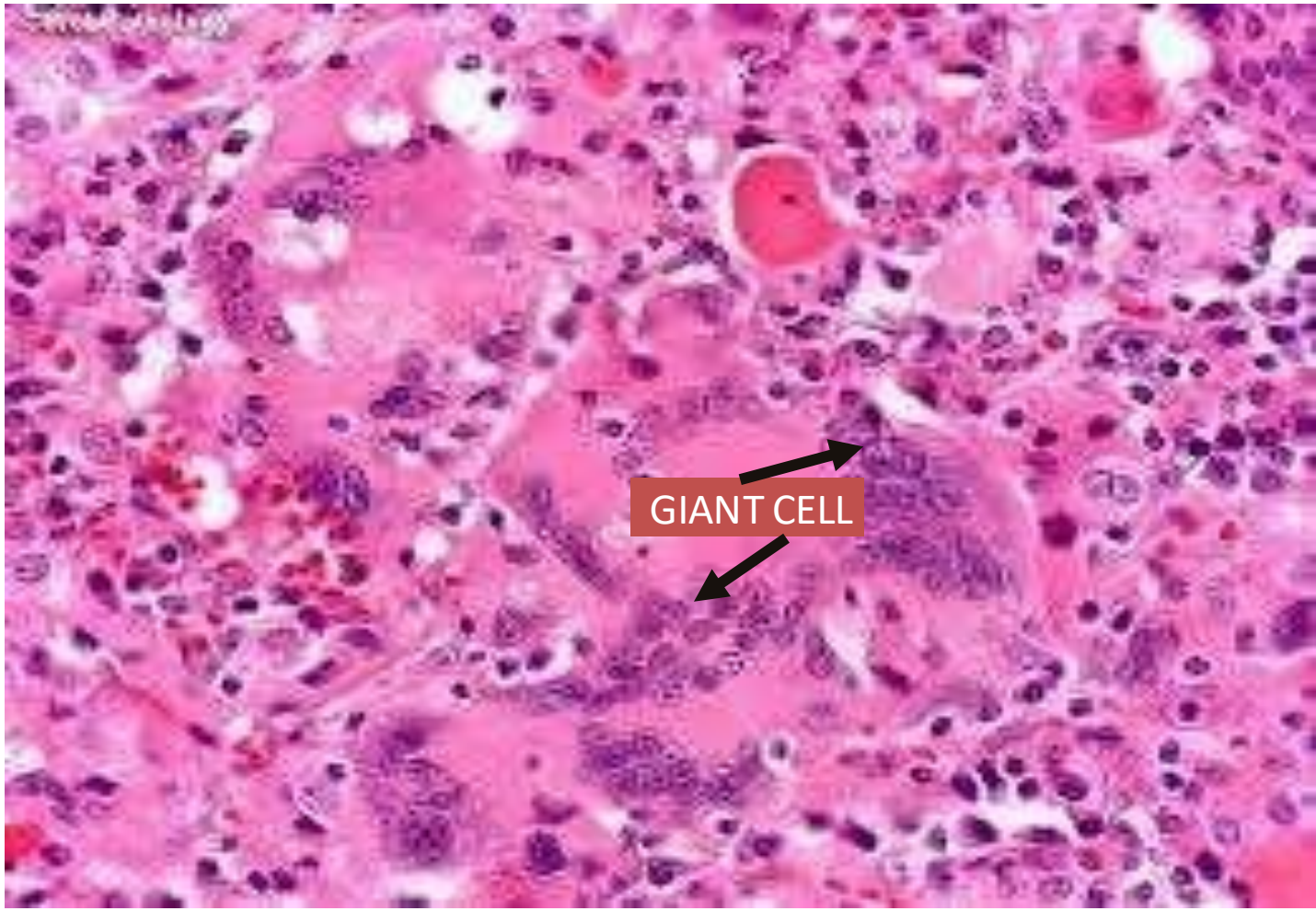
Histologic Examination Reveals

Important histological features:

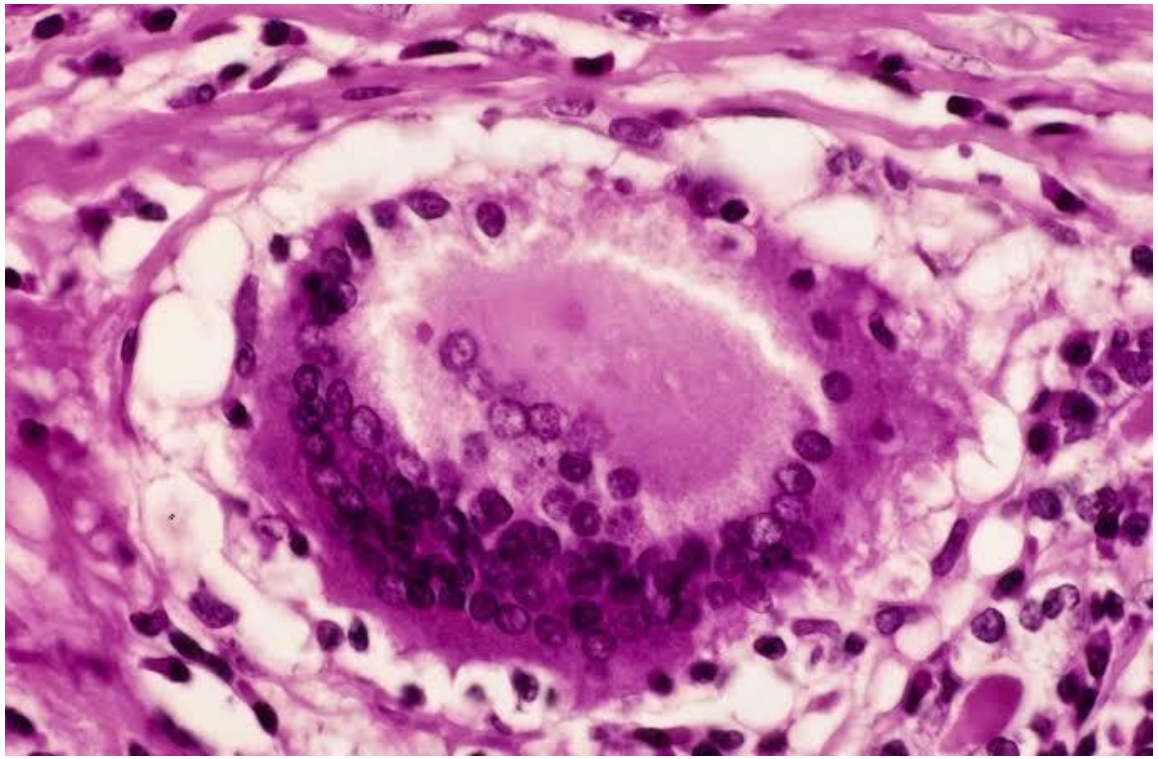
- Destruction.
- Presence of **Giant cells & granuloma**.
- Gaint Cells : Large multinuclear cells, because of fusion of many macrophages, The show same cytoplasm and several nuclei.
- Gaint Cells are **More prominent and common** for recognition of the disease than granulomas (when diagnosing this disease histologically, look for Gaint cells not granuloma.

Subacute granulomatous thyroiditis

- **Granuloma:** an aggregate of histiocytes, some of which fuse to form giant cells.
- **Giant cell:** a large cell with abundant cytoplasm and multiple nuclei.
- Giant cells clump together to phagocytose foreign bodies. In this case, the foreign body is colloid, which is normally found within thyroid follicles. When follicles are destroyed, colloid escapes into the surrounding tissue, triggering granuloma formation.



Giant cell in subacute granulomatous thyroiditis



3. Subacute Lymphocytic Thyroiditis

- **Uncommon**
- Also is known as *silent* or *painless* thyroiditis;
- And in a subset of patients the onset of disease follows pregnancy (*postpartum thyroiditis*).
- Idiopathic, 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

❑ **Subacute lymphocytic thyroiditis**

- Sometimes considered variant of Hashimoto.
- Similar to Hashimoto thyroiditis except for 2 things:

1) No Hurthle cells.
2) Mostly post-partum (following pregnancy).

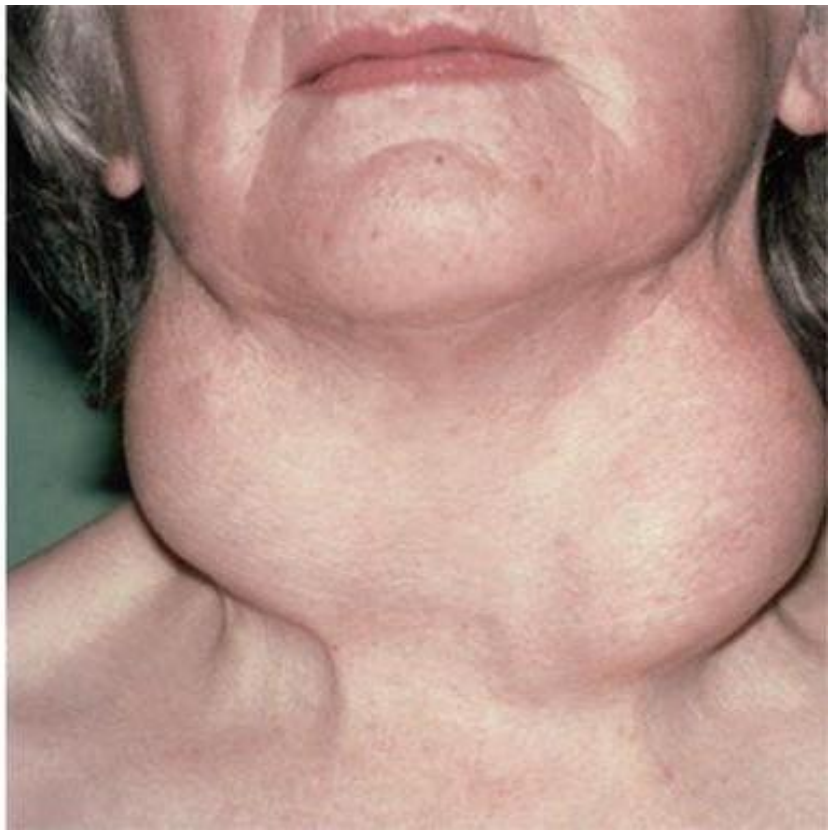
4. Riedel Thyroiditis

- A rare disorder of **unknown** etiology.
- Characterized by extensive fibrosis, not inflammation, involving the thyroid and adjacent structures simulating a thyroid neoplasm, so it should be examined by a pathologist to exclude malignancy.
- 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.

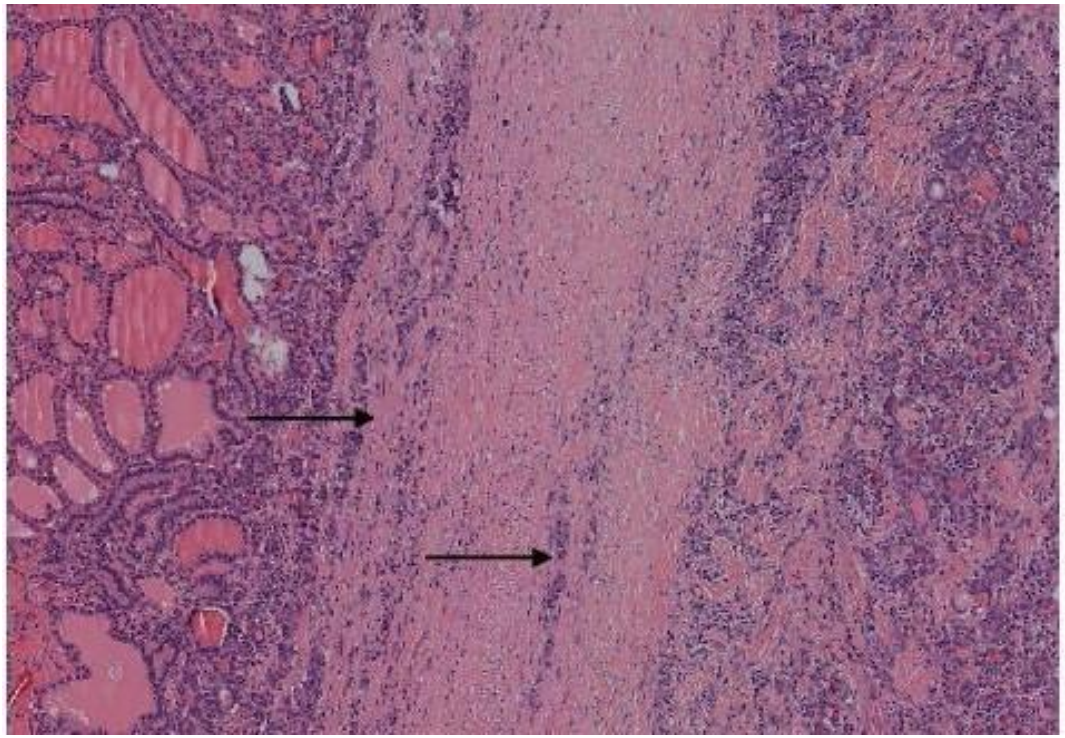
- **Riedel thyroiditis** not an actual inflammation.
- Very important clinically since it mimics malignancy → hard fixed mass.
- It is not malignant but is fibrotic.
- Associated with fibrosis in other places in the body.

RIEDEL'S

Thyroiditis



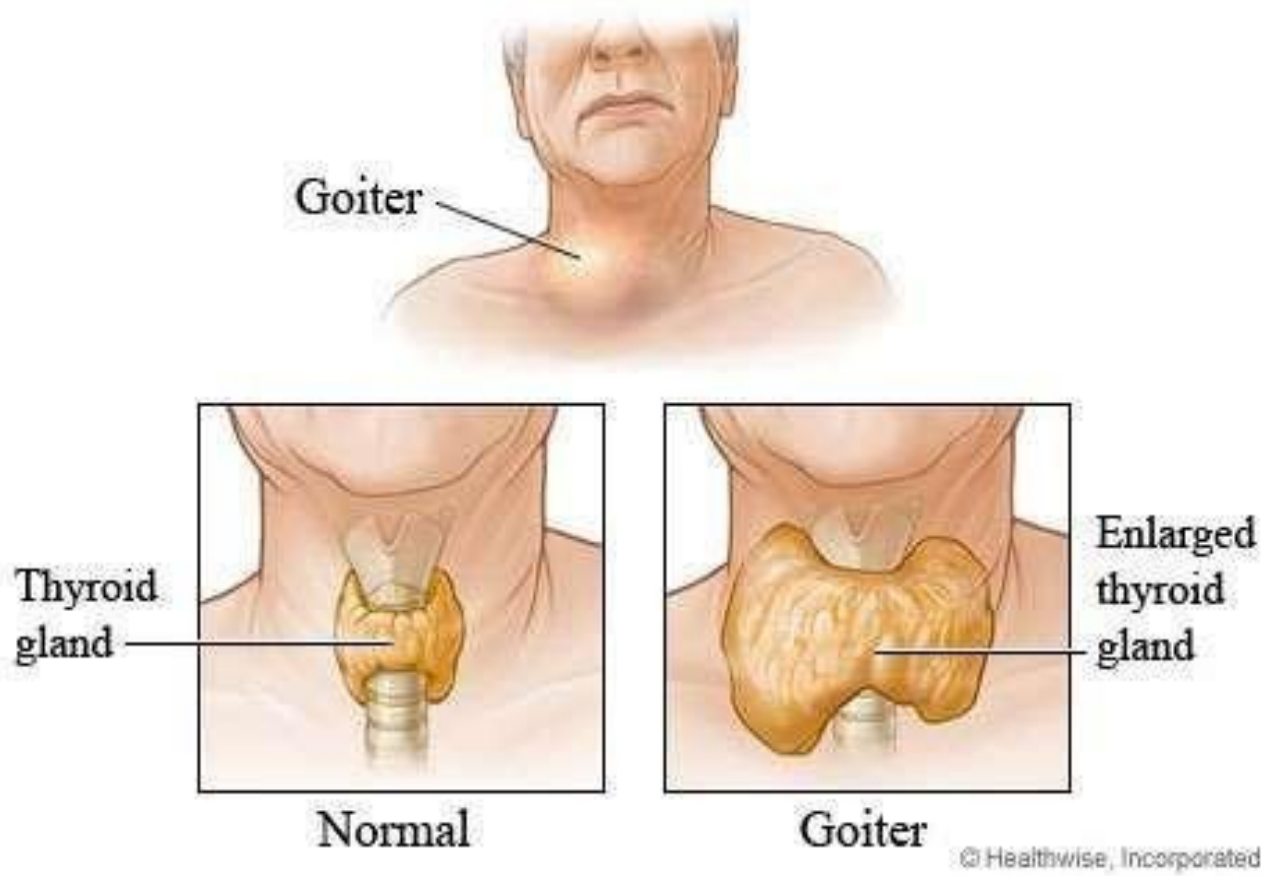
Riedel thyroiditis: fibrosis



Goiter

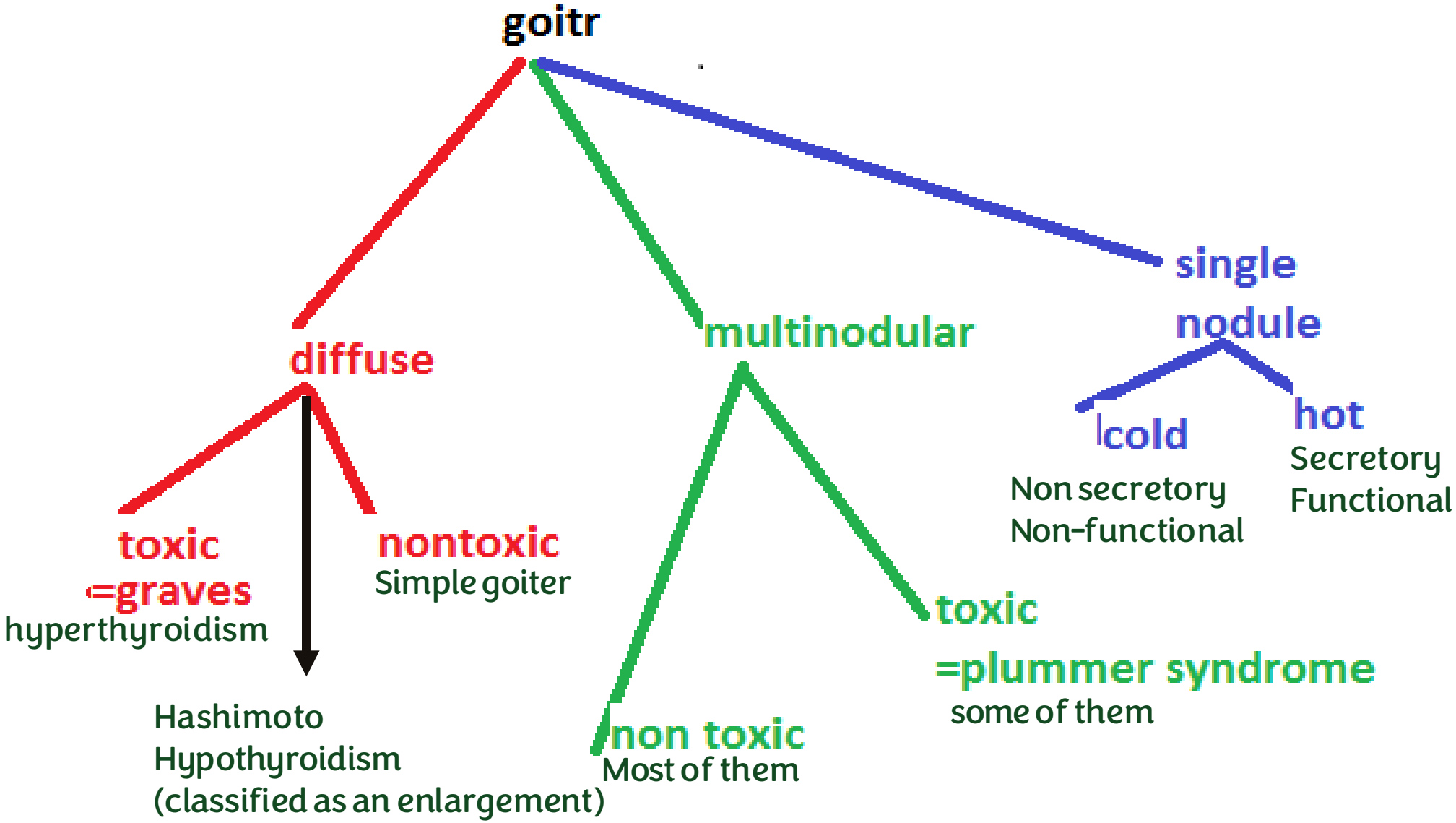
- **Goiters**
- General term: means enlargement of the thyroid gland.
- **But here we mean endocrine diseases called goiters.**

- Remember:
- Toxic = Secretory = hot
- Non-toxic = non-secretory = cold.



Goiter

All can be functional or non-functional



Goiter Diseases (Summary)

- **Diffuse + toxic → Graves**
- **Diffuse + non-toxic → Hashimoto**
- **Multinodular + non-toxic → Multinodular goiter**
- **Multinodular + toxic → Plummer syndrome**

Graves disease

1. 100% of patients present with hyperthyroidism (necessary).

- Symptoms that may appear but if they appear they are specific for Graves disease:
- **Exophthalmos →** eyes getting out of their socket partially. There is a difference between wide staring gaze and exophthalmos.
- Wide staring gaze → contraction of extraocular muscles.
- Exophthalmos → getting out of socket.

2. Infiltrative ophthalmopathy (results in exophthalmus):

Tissue, fat cells infiltrative (behind the eye) and pushes it outward.
Exophthalmos persists even if you treat hyperthyroidism.
Not all patients experience exophthalmos.
It affects the vision indirectly.
If it results in prevention of eye closure → dryness.

- **Bilateral exophthalmos:** Both eyes.
- **Unilateral exophthalmos:** associated with tumor behind the eye.

3. Localized infiltrative dermopathy

usually in the shin → **pretibial myxedema**
Pretibial myxedema & Myxedema (Gull syndrome) are completely different.

Graves disease

- **Pretibial Myxedema** → No edema, infiltrative dermopathy.
  Myxedema (Gull syndrome) → edema. Infiltration happens also in **clubbing syndrome**.

<u>Pathogenesis of Graves disease:</u>

- **Autoimmune disease**
  - 3 Immunoglobulins:

1. Thyroid stimulating immunoglobulin → hyperthyroidism.
2. Thyroid growth stimulating immunoglobulin → proliferation → goiter.
3. TSH binding inhibitor immunoglobulin → TSH antagonism.

Clinical presentation may have hypothyroidism rather than hyper because there is a alternation between hyper & hypothyroidism, transient hypothyroidism, so if you measure it again after a while you'll see hyperthyroidism.

Thyrotoxicosis / Hyperthyroidism are clinically used **interchangeably.**
But thyrotoxicosis means that hyperthyroidism is caused by the thyroid gland itself.

Graves disease

- Named after an Irish surgeon: Robert Graves.
- Robert Invented the seconds-hand on watches and he used the timing of the pulse using the watch.
- Introduced giving food and liquids to patients with fever instead of withholding nourishment.
- One of the first doctors to introduce bedside learning.

GRAVES DISEASE

The most common cause of endogenous hyperthyroidism with a peak incidence in women between the ages of 20 and 40.

Triad of manifestations:

A. Thyrotoxicosis, All patients
B. Localized, infiltrative dermopathy (pretibial myxedema), minority of cases and involves the skin overlying the shins, and manifests as scaly thickening
C. Infiltrative ophthalmopathy with resultant exophthalmos in 40% of patients

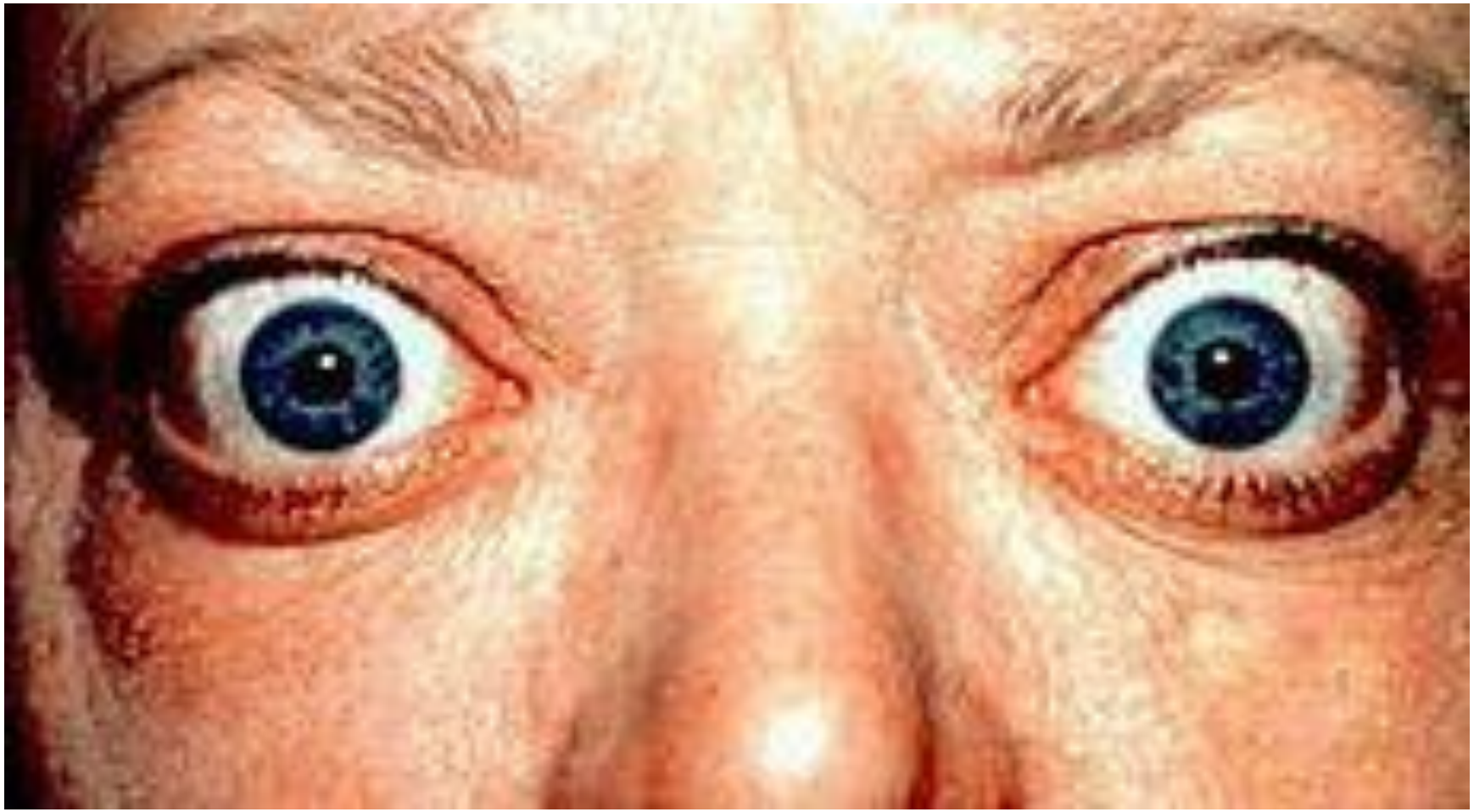
Exophthalmos is the result of increased volume of the retro-orbital connective tissues by

1. Marked infiltration of T cells with inflammatory edema
2. Accumulation of glycosaminoglycans
3. Increased numbers of adipocytes (fatty infiltration).

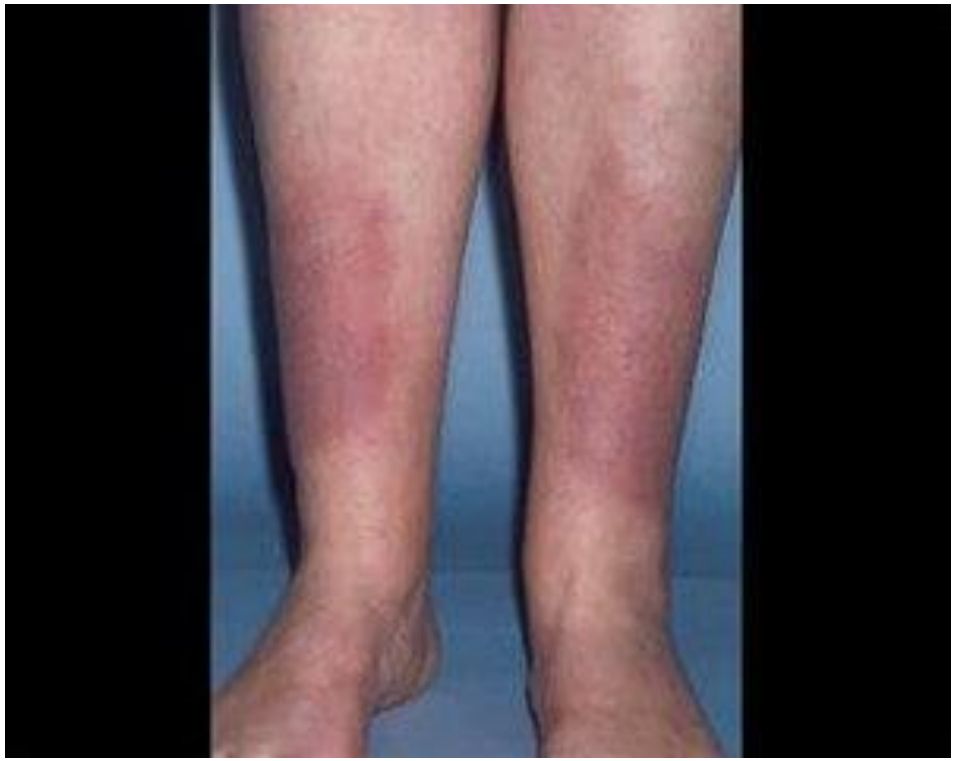
- These changes displace the eyeball forward, potentially interfering with the function of the extraocular muscles

- Exophthalmos may persist after successful treatment of the thyrotoxicosis, and may result in corneal injury.

exophthalmus



Pretibial myxedema



PATHOGENESIS

- Genetic factors are important in the causation of Graves disease, the incidence is increased in relatives of affected patients, and the concordance rate in monozygotic twins is 60%.

- A genetic susceptibility is associated with the presence of HLA-DR3.

- it is characterized by a breakdown in self-tolerance to thyroid autoantigens, and is the production of multiple autoantibodies

Autoantibodies in GRAVES :

1. Thyroid-stimulating immunoglobulin:

- An IgG antibody binds to the TSH receptor and mimics the action of TSH, with resultant increased hormones.

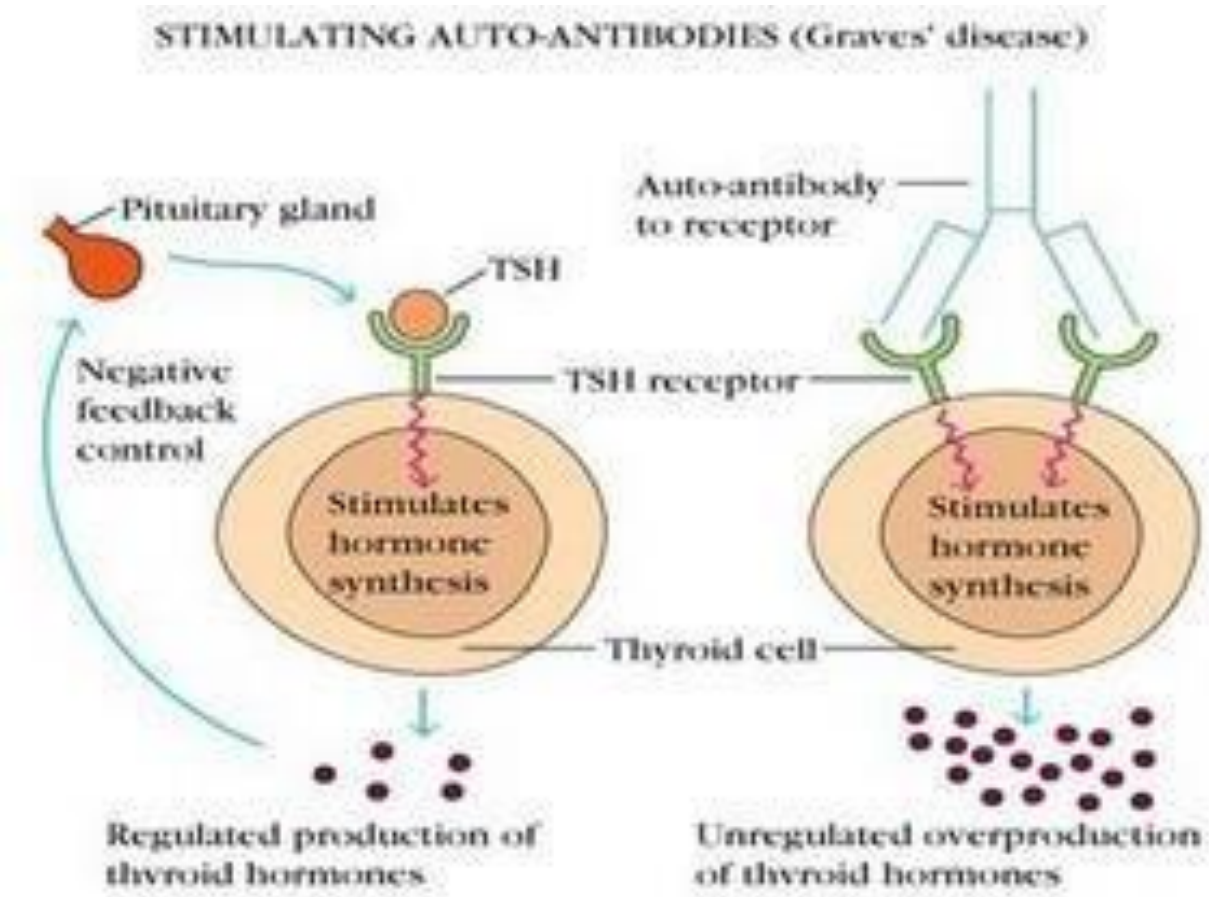
2. Thyroid growth-stimulating immunoglobulins:

- Directed against the TSH receptor, and have been implicated in the proliferation of follicular epithelium.

3. TSH-binding inhibitor immunoglobulins:

- Prevent TSH from binding to its receptor on thyroid cells and in so doing may actually inhibit thyroid cell function, a finding explains why some patients with Graves spontaneously develop episodes of hypothyroidism.

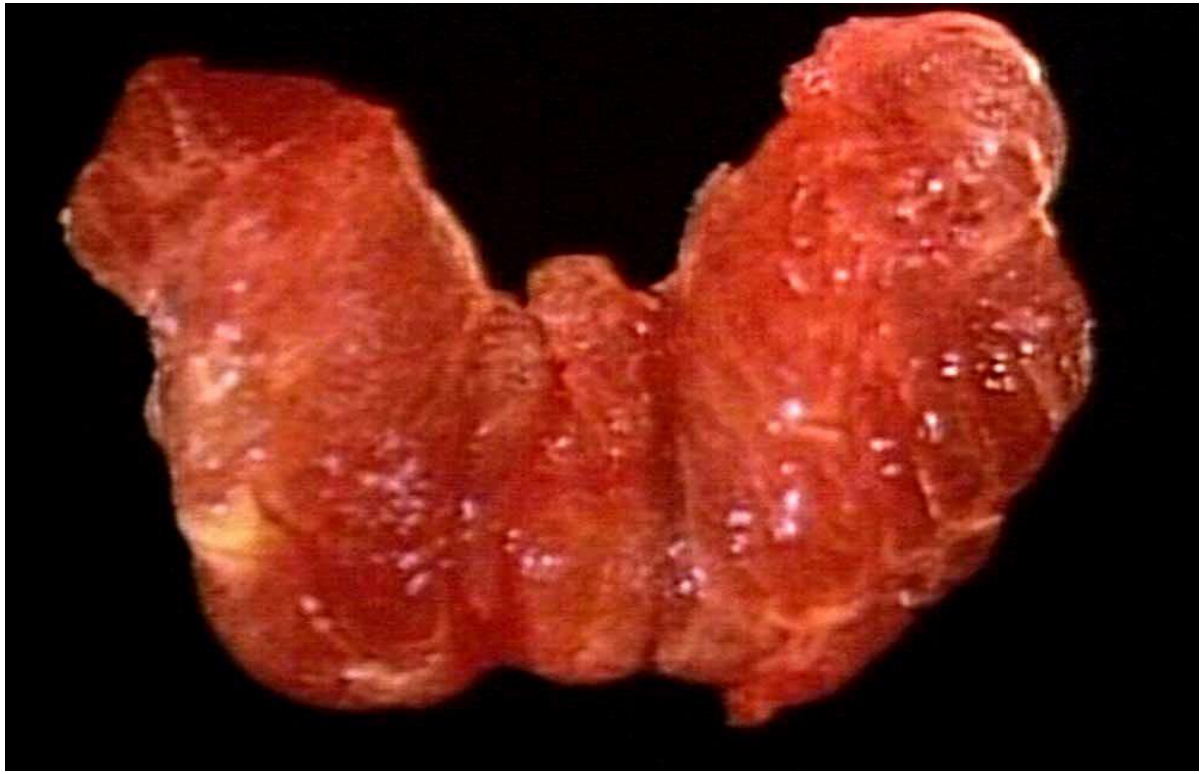
Note the autoantibodies in Grave's cause stimulation of hormone synthesis



Note:

The coexistence of stimulating ***and*** inhibiting immunoglobulins in the serum of the same patient may explain why some patients with Graves disease spontaneously develop episodes of hypothyroidism

Gross: Diffuse Symmetrical enlargement of the thyroid gland with intact capsule,



On microscopic examination,

a. The follicular cells in untreated cases are tall and crowded.

b. Lymphoid infiltrates, consisting predominantly of T cells, with few B cells and plasma cells are present throughout the interstitium; with formation of germinal centers.

رسالة من الفريق العلمي:

Whatever it takes…

- NST (2024 – Alive)

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			