Hypo, Hyperthyroidism & Hashimoto's Thyroiditis

Objectives:

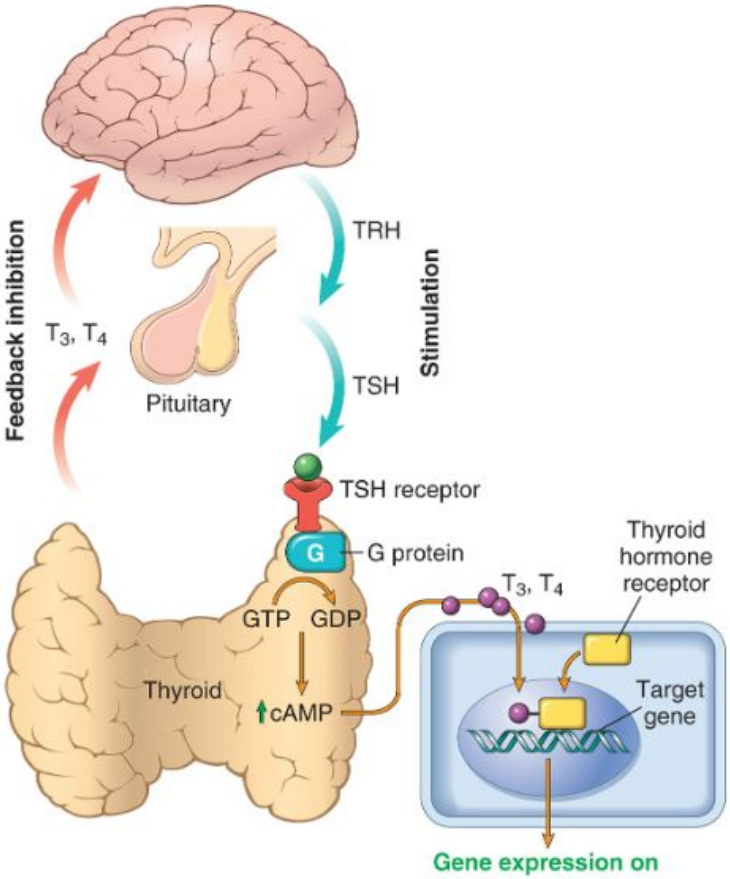
- Know the ways in which thyroid disorders present.
- Know the major causes and manifestations of hypo, hyperthyroidism and thyroiditis .
- Know the causes of a solitary nodule in the thyroid.
- Understand the classification, pathology and behavior of thyroid carcinoma.

Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit**

Red: Important
Grey: Extra notes

Introduction.

The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below & anterior to the larynx. It develops embryologically from developing pharyngeal epithelium (tongue develops from the same structure). The thyroid gland contains the largest store of hormones of any endocrine gland.



Normal physiology of thyroid gland:

TRH (from hypothalamus) → stimulates **TSH** release (from anterior pituitary) → goes by blood to TSH receptors in thyroid gland → stimulates G protein → increase intracellular cAMP → secretion of **T3** (triiodothyronine) & **T4** (thyroxine) from the thyroid to blood → they go to body cells & inside the nucleus they target genes to initiates transcription of certain proteins that produces many effects, such as: Upregulation of proteins, carbohydrates and lipids breakdown (catabolism).

* Negative feedback loop between thyroid & pituitary, hypothalamus.

Disorders of thyroid hormones are divided into:

1. **Hyperthyroidism** = Thyrotoxicosis (Hypersecretion of T3 & T4).
2. **Hypothyroidism** (Hypo Secretion of T3 & T4).

Each type could be caused by various factors, as discussed later.

- They are common in our region, especially in **women**.

Thyrotoxicosis

Hypermetabolic state caused by elevated circulating levels of free T3 and T4.

Characterized by:

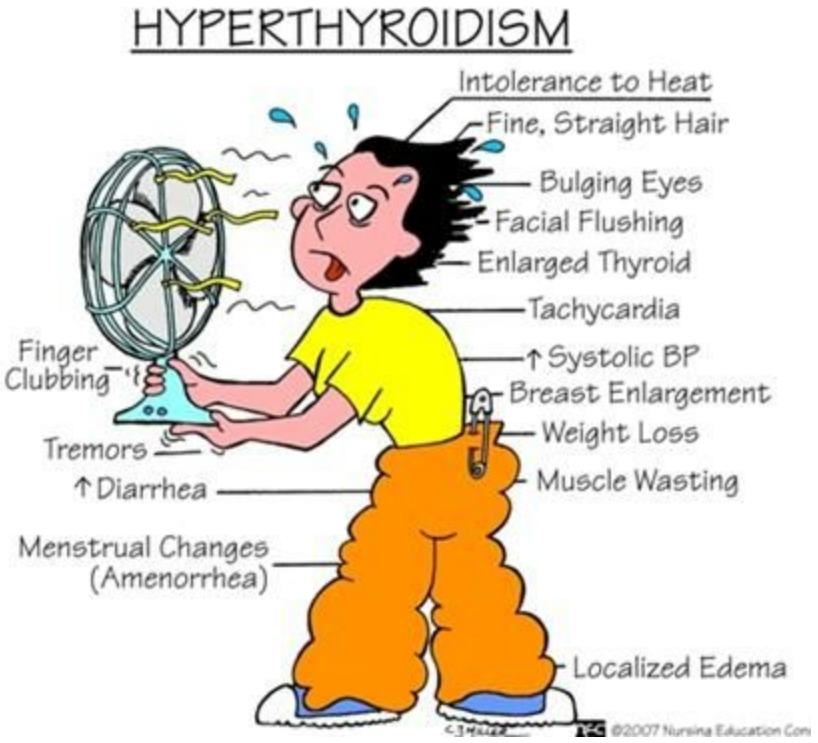
1. Increases in basal metabolic rate due to increased in synthesis of Na+-K+ ATPase.
2. Increases in sympathetic nervous system activity due to increase in expression of B1 adrenergic receptors.

Symptoms:

Increases in basal metabolic rate	Increases in sympathetic nervous system activity
Heat intolerance، sweating، anxiety Redness of face, **Weight loss despite the increase appetite,** Diarrhea with malabsorption. - hyperfunctional & diffuse enlargement (Goiter) - hypercalcemia, hypo-cholesterolemia and hyperglycemia	● Anxiety ● **Tremors** ● Insomnia ● **Tachycardia** ● Cardiac manifestation (palpitations in normal cases, heart failure in advanced cases) ● Arrhythmia (ex: fibrillation especially in elderly)

Symptoms seen in Graves Disease ONLY:

- Exophthalmos.
- Pretibial myxedema.



Thyrotoxicosis means the elevation of serum thyroid hormones. It can be caused by two factors:

1. **Associated with hyperthyroidism.**
2. **Not associated with hyperthyroidism.**

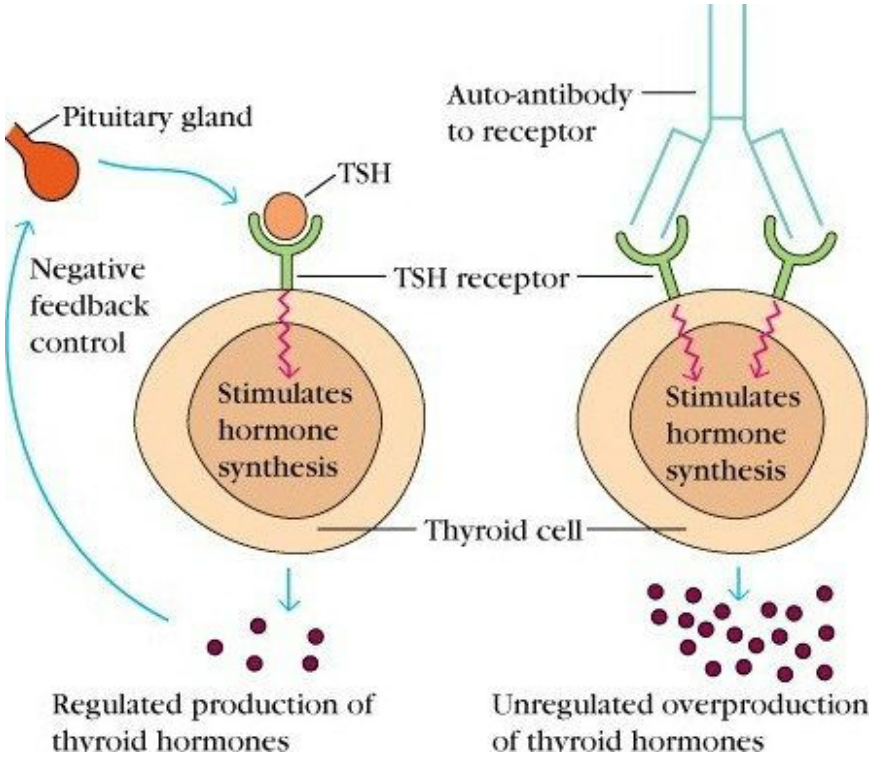
For better understanding: Hyperthyroidism is caused by extrathyroidal source (e.g. antibodies, ↑ TSH) that stimulates the gland to produce more hormones, so it's not a problem from the gland itself!
In the other hand, other causes that aren't associated with hyperthyroidism (e.g. thyroiditis) are caused by the excessive release of *preformed* - already stored in gland - thyroid hormones.

Causes:

Associated with hyperthyroidism
Primary (↑ free T3, T4 & ↓ TSH) [most common cause of thyrotoxicosis]
Diffuse hyperplasia of the thyroid associated with **Graves** disease (accounts for **85%** of cases)
Hyperfunctional multinodular goiter (or plummer disease)
Hyperfunctional (toxic) adenoma of the thyroid
Iodine induced hyperthyroidism
Early Hashimoto's Thyroiditis (in the beginning of the inflammation the gland starts to secrete a huge amount of hormones -that was already formed-, after that it turns to be hypo secreting after depletion of stored hormones)
Drugs: levothyroxine.
Secondary (↑ free T3, T4 & ↑ TSH)
TSH-secreting pituitary adenoma (rare)
May not be associated with hyperthyroidism
Granulomatous (de Quervain) thyroiditis (painful)
Subacute lymphocytic thyroiditis (painless)
Struma ovarii (ovarian teratoma with ectopic thyroid)
Factitious thyrotoxicosis (exogenous thyroxine intake) as female taking it to lose weight.

Graves disease.

Graves disease is autoimmune disorder characterized by autoantibodies that mimic the action of TSH. It increases the production & release of thyroid hormones by occupying the receptors in thyroid gland for TSH and keeping them stimulated → Hyperthyroidism, or sometimes inhibited → Hypothyroidism.



Pathogenesis: Autoantibodies that work in TSH receptor. These antibodies are of **3** types:

1. **Thyroid-stimulating immunoglobulin: LATS** (long acting thyroid stimulator) **IgG Ab** bind to TSH receptor & mimic the action of TSH → stimulate adenyl cyclase → ↑ thyroid hormone.
2. **Thyroid growth-stimulating immunoglobulin:** also directed against **TSH receptor →** leads to **proliferation** of thyroid follicular epithelium.
3. **TSH-binding inhibitor immunoglobulin:** anti-TSH receptor Ab → prevent TSH from binding to its receptor on thyroid epithelial cells → inhibit thyroid cell function → ↓ thyroid hormone.

Coexistence of stimulating and inhibiting immunoglobulins in the serum of the same patient, explains why some patients with Graves disease spontaneously develop episodes of hypothyroidism.

Clinical manifestation:

- Thyrotoxicosis manifestation (mentioned earlier).
- **Diffuse goiter** → hyperplasia and hypertrophy of thyroid gland.
- Increase flow to the thyroid → **audible bruit** (enlargement of thyroid will make it hearable by the stethoscope because of the increased blood flow to the gland)
- **Ophthalmopathy** → exophthalmos.
- **Dermopathy** → pretibial myxedema.

Exophthalmos

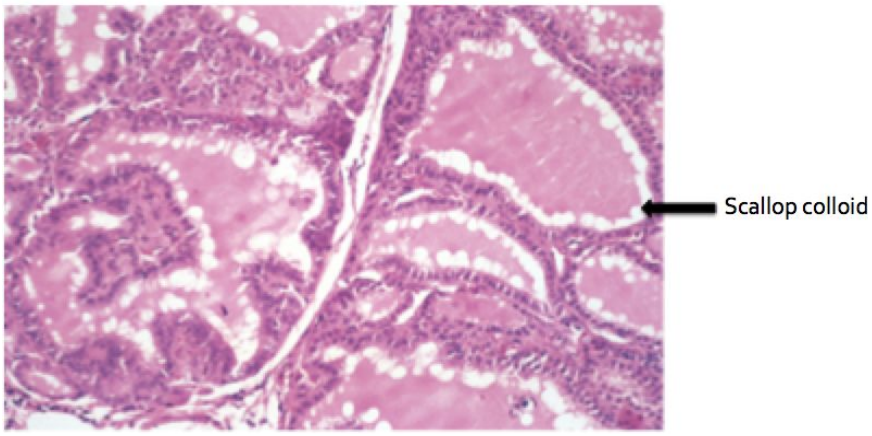
Cause of exophthalmos: Activation of T-lymphocytes (T8 & T4) causes:→ edema & swelling of extraocular muscles, accumulation of extracellular matrix components, specifically hydrophilic glycosaminoglycan, inflammation in retroorbital space & accumulation of fat → protrusion of eyes (only 40% of patients).

Diagnosis:

- T3 and T4 is increased and TSH is low.
- Autoantibodies against thyroid epithelium (TSH receptor).
- Radioactive iodine uptake is increased.
- Sometimes patients need thyroidectomy in very severe cases.

Histopathology:

- Scalloped[1] colloid appearance (a white material separates colloid from epithelium of follicle) caused by the active pinocytosis of thyroglobulin by the epithelial cells → Thin colloid (pale color, vacuolated).
- Epithelial cells turn to be columnar & hyperplastic.
- Lymphocytosis.
- Convoluted follicles



[1] شكله يشبه الصدف.

Hypothyroidism.

Hypothyroidism is caused by any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone.

- Prevalence of overt hypothyroidism is 0.3%, while subclinical hypothyroidism can be found in **greater than 4%.**
- Increases with age.
- Ten fold more common in women than in men

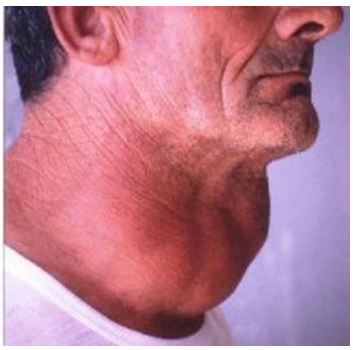
Causes:

Primary (majority**)**
Developmental (thyroid dysgenesis: mutations in ***PAX8***, ***FOXE1***, ***TSH*** **receptors**)
Postablative[2], Iodine deficiency (occurs mostly in cities far from sea, e.g in Riyadh more than Jeddah)
Acquired hypothyroidism: Surgery, **radioiodine therapy** (ablation[3] of thyroid parenchyma), or external irradiation.
Autoimmune hypothyroidism, e.g **Hashimoto's thyroiditis** (most common cause in iodine sufficient Pt's)
Congenital hypothyroidism: Less common (dyshormonogenetic goiter[4]), Most often the result of endemic (iodine deficiency in the diet.)
Drugs: Antipsychotic (**lithium**) - used for psychosis - , b aminosalicylic, iodate containing drugs.
Secondary (Central) Hypothyroidism: Caused by deficiency of TSH, and far more uncommonly, that of TRH.
Pituitary failure
Hypothalamic failure (rare)

[2] after Removal or excision
[3] surgical removal
[4] Dyshormonogenetic goiter is a rare cause of congenital hypothyroidism occurring due to a lack of enzymes necessary for the synthesis of thyroid hormones.

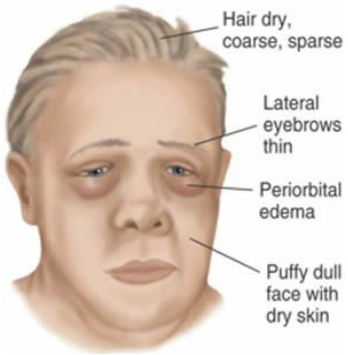
Clinical manifestations.

Manifestation	Age group	Causes	Features
Cretinism latin word means = حماقة/بلاهة	Infants & early childhood	1- maternal hypothyroidism during pregnancy. 2- thyroid agenesis. (abnormally formed) 3- Dyshormonogenetic goiter (unable to produce thyroid hormone because of enzyme deficiency) most common peroxidase. 4- iodine deficiency	● Mental retardation ● Short stature. (skeletal abnormality) ● coarse facial features. ● protruding tongue (enlarged). ● umbilical hernia. Cretinism is checked by neonatal screening and if found early it can be treated (should be treated in the first 6 months).
Myxedema (myx: mucus) - Usually occurs in the legs and behind the eye (exophthalmos) -	Older children & adults	1-Iodine deficiency 2-Hashimoto thyroiditis. **(most common)** 3-Drugs (lithium) 4-Surgical removal or radioablation of thyroid.	● Slowing of physical and mental activity. ● overweight despite normal appetite ● Glycosaminoglycans & hyaluronic acid, in skin, subcutaneous tissue, visceral sites → causes **Non-pitting edema**. ● Broadening and coarsening of facial features, enlargement of the tongue, deepening of the voice. ● Amenorrhea (young females). ● Cold intolerance with decreased sweating. ● Bradycardia ● Constipation ● **hypercholesterolemia →** due to decrease breakdown of fat.



Goiter

Cretinism



Myxedema

Goiter

Is the enlargement of thyroid gland. Goiter is the *most common* manifestation of thyroid diseases. It can be present in any thyroid disease such as:

- **Hypothyroidism** and **hyperthyroidism**, e.g: Iodine deficiency, Graves' disease, Hashimoto's disease, Solitary thyroid nodules, Inflammation.
- **Euthyroidism** (states of having normal thyroid function but has problem in thyroid itself).

When a patient comes to you with neck swelling you should make sure that it's goiter, because it could be lymphoma, soft tissue tumor or thyroglossal cyst... etc.

Types of neck masses:

1. Diffuse enlargement (swelling) → caused by hypothalamic disease.
2. Neck mass (uninodular or multinodular) → caused by other causes, e.g cyst, cancer, thyroiditis (multinodular).. etc.

Investigations:

1. TSH & **T4** (1st line in the investigation to know whether it's hyper or hypothyroidism). When it appears abnormal we perform the next test.
2. Next step is T3 (this test is hard to do).
3. **Radioactive studies (done for solitary nodule), nodules are divided into:**
    a. **Cold nodule** → non secreting mass. (Most of nodules).
    b. **Hot nodule (dark)** → secreting mass = takes up the iodine.
4. Fine needle aspiration → to check if its neoplasm.

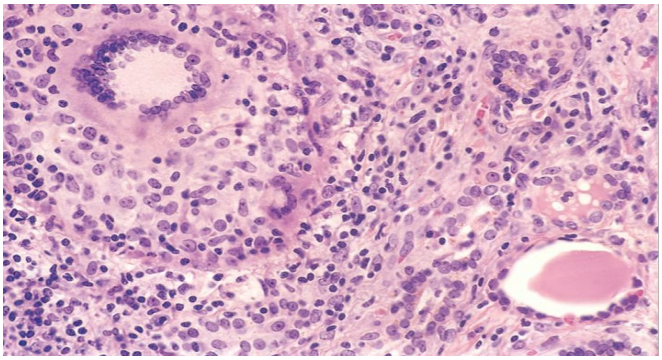
Thyroiditis.

It's inflammation of the thyroid gland, include diverse group of diseases.

Thyroiditis Types	
Acute illness with severe thyroid pain	**Little inflammation with thyroid dysfunction**
1. Infectious thyroiditis. 2. Subacute granulomatous (de Quervain) thyroiditis.	1. Subacute lymphocytic thyroiditis. 2. Fibrous [Riedel's] thyroiditis.

Subacute granulomatous thyroiditis. (only mentioned in female lecture)

- Subacute → after an acute illness.
- Granulomatous → Granulomatous inflammation with giant cells
- Viral infection (e.g., coxsackie virus, mumps).
- Occurs most often in women 40 to 50 years old.
- Presents as **Tender thyroid with transient hyperthyroidism.**



Clinical findings:

- Most common cause of **painful thyroid gland.**
- **Often preceded by an upper respiratory infection.**
- **Cervical adenopathy is *not* prominent.**
- **Initial thyrotoxicosis from gland destruction: Increased serum T4, decreased serum TSH.**
- **Self-limited; Does not progress to hypothyroidism.**
- **Permanent hypothyroidism is uncommon.**

Riedel fibrosing thyroiditis. (only mentioned in female lecture)

- Chronic inflammation with extensive fibrosis of thyroid.
- Fibrosis may extend to local structures (airway), may present with difficulty breathing.
- Presents as hypothyroidism with "hard as wood" nontender thyroid gland.

Note: Fibrosis that extend to local structures is also a feature of anaplastic carcinoma but usually it's present in old patients, while Reidel fibrosing present in young female. (differential diagnose)

Hashimoto's Thyroiditis.

Is an autoimmune inflammation leading to destruction of thyroid gland leading to gradual thyroid failure. The immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase). The name Hashimoto thyroiditis 1912 report by Hashimoto describing patients with goiter and intense lymphocytic infiltration of the thyroid (struma lymphomatosa).

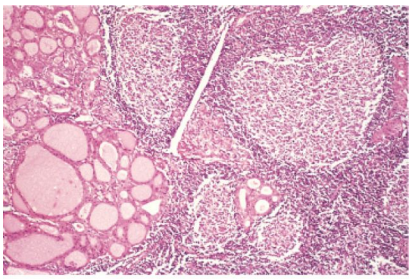
- Most common cause of hyperthyroidism where the levels of iodine is sufficient.

Hakaru Hashimoto

Clinical features:

- The TSH will be high and T4 is low
- Female predominance of (10:1) to (20:1), Age 45-65.
- The feature of Hashimoto's thyroiditis is progressive depletion of thyroid epithelial cells (**thyrocytes**), replaced by mononuclear cell infiltration and fibrosis.
- **Associated with HLA-B8.**
- Strong genetic component, 40% of monozygotic twins, as well as the presence of circulating antithyroid antibodies in approximately 50% of asymptomatic siblings.
- patients have an increased risk of getting B cell non-hodgkin lymphoma.
- It was the first disease to be recognized as autoimmune disease.

Note: hashimoto Thyroiditis is only start as hyperthyroidism because of the damage to the follicles, but then it is a hypothyroidism disorder.



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Gross: Cut surface is pale, yellow, firm, enlarged & it can be nodular also.

Histopathology:

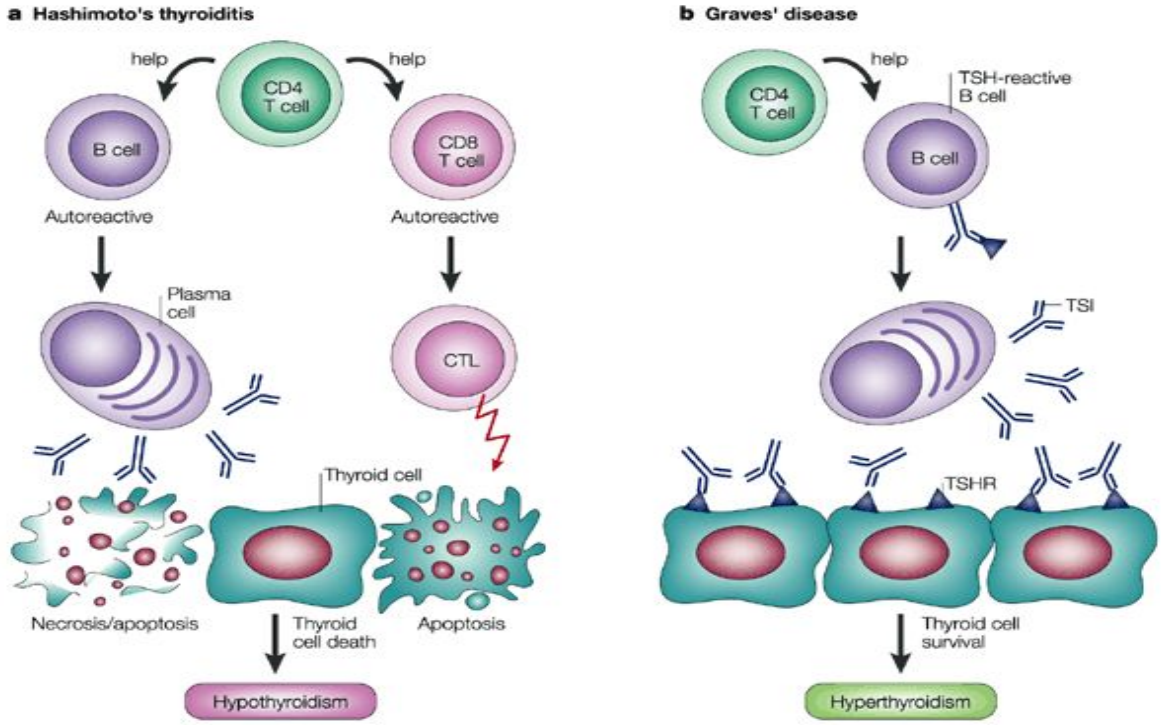
- **Mononuclear inflammatory infiltrate** containing→ small lymphocytes, *plasma cells,* and well-developed germinal centers (massively that it looks similar to a lymphoid tissue).
- The thyroid follicles are **atrophic** and are lined in many areas by epithelial cells distinguished by the presence of abundant **eosinophilic**, **granular** cytoplasm numerous prominent mitochondria, these new cells termed **Hürthle cells** or **oxyphil cells**.

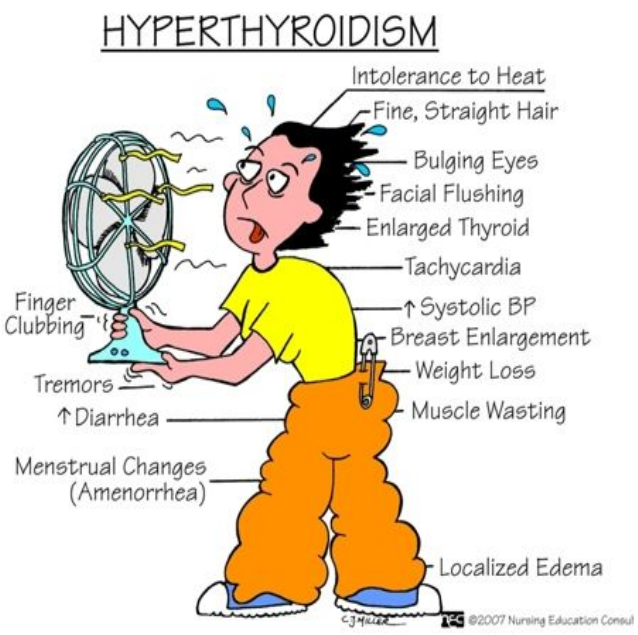
Investigations:

- TSH,T4 and T3 (thyroid function test). → The TSH will be high and T4 is low.
- Thyroid autoantibodies (anti-peroxidase thyroid antibodies, anti-thyroglobulin antibodies).

Summary.

- Hashimoto thyroiditis and Graves disease are the two most common immunologically mediated disorders of the thyroid.





MCQ's.

1. A 60-year-old woolen has been feeling tired and sluggish for more than a year. Her thyroid gland is not palpable on physical examination. She has a decreased serum level of T4. but her serum TSH concentration is greatly increased. Which of the following factors is important in the pathogenesis of this condition?
(A) irradiation to the neck during childhood
(B) Anti-microsomal and anti-thyroglobulin antibodies
(C) Prolonged iodine deficiency
(D) Mutations in the RET protooncogene
(E) Recent viral upper respiratory tract infection

2. A 68-year-old male has end-stage. renal disease as a consequence of dominant polycystic kidney disease (DPKD). He has undergone hemodialysis three time, per week for the past 6 years. Which of the following endocrine lesions is the most likely complication of his chronic renal failure?
(A) Multinodular goiter
(B) Islet cell hyperplasia
(C) Adrenal atrophy
(D) Parathyroid hyperplasia
(E) Pituitary microadenoma

3. A middle-aged man has experienced diarrhea, nervousness, palpitation & increased irritability for the past 5 months. Proptosis and lid lag are among physical examination findings. Which of the following laboratory findings is most likely?
(A) Increased plasma insulin level
(H) Increased serum T4 level
(C) Increased serum TSH Level
(D) Increased serum cortisol level
(E) Increased sennn corticotropin level

4. Exophthalmos with weak extraocular muscle movement occurs in a 20-year-old female and her identical twin sister. Their conditions develop within 3 years of each other, what is the most closely related laboratory finding?
(A) Decreased serum free T4 level
(B) decreased serum calcium level
(C) Decreased serum TSH level
(D) Increased serum cortisol level

5. A 45-year-old female has a feeling of fullness in her neck but no other complaints. Physical examination confirms diffuse enlargement of the thyroid gland without any apparent masses, this enlargement & painless for more than a year. test for thyroid function reveal a normal free thyroxine (free Ts) and a slightly increased level of TSB. The most likely cause for these findings is:
(A) Toxic multinodular goiter
(B) papillary carcinoma
(C) subacute granulomatous thyroiditis

(D) Hashimoto thyroiditis
(E) Diffuse nontoxic goiter

6. A 37-year-old woman complain, that she has had difficulty swallowing for about a week. accompanied by • feeling of fullness in the anterior neck. She has a slight fever. Palpation of the thyroid elicits pain. Her serum free T4 level is increased. When seen by an endocrinologist 2 months later. after waiting for an appointment, she no longer has these complaints, and the free T4 level is normal. The condition that best explains these findings is:
(A) Medullary carcinoma
(B) Subacute thyroiditis
(C) Toxic mullinodular goiter
(D) Toxic follicular adenoma
(E) Hashimoto thyroiditis

7. A 22-year-old female presents with a 7-kg weight loss without dieting over the last 4 months, She has experienced increasing anxiety and nervousness without apparent changes in her job or home life. Physical examination reveals a diffusely enlarged thyroid gland. Radioiodine uptake shows a diffuse increase in uptake. The microscopic appearance of the lesion leading to these findings is shown here at high power. This lesion is most likely caused by:
(A) Antibodies against TSH receptor
(B) Dietary deficiency of iodine
(C) Maternal deficiency in T4
(D) Irradiation to the neck

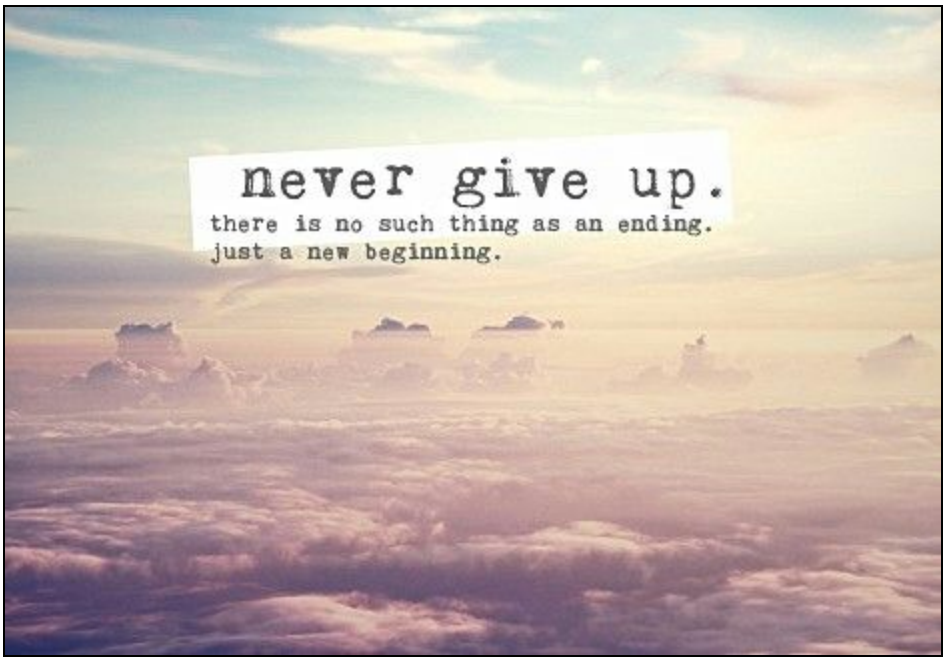
8. A 2-year-old child has had failure to thrive. The child is short, with coarse facial features, a protruding tongue, and an umbilical hernia. Profound mental retardation is apparent as the child matures. These findings are best explained by a lack of:
(A) Cortisol
(B) Norepinephrine
(C) Somatostatin
(D) Thyroxine
(E) Insulin

9. Which of the following tests should be done first when assessing the functional status of the thyroid gland?
(A) A total T4 level
(B) Total triiodothyruninc T3 level
(C) Thyroid-stimulating hormone (TSH) level
(D) Fine-needle aspiration
(E) Radioiodine scan

10. A 28-year-old woman has had difficulty concentrating at work for the past month. She is constantly getting up and walking around to visit co-workers. She complains that the work area is too hot. She seems nervous and often spills her coffee. She has been eating more but has lost 5 kg in the past 2 months. On physical examination her temperature is 37.5°C, pulse 101/minute, respiratory rate 22/minute, and blood pressure 145/85 mm Hg. Which of the following laboratory findings is most likely to be present in this woman?

(A) Decreased catecholamines
(B) Decreased iodine uptake
(C) Decreased plasma insulin
(D) Decreased TSH
(E) Increased ACTH
(F) Increased calcitonin

ANSWERS: 1-b 2-d 3-b 4-c 5-e 6-b 7-a 8-d 9-c 10-d



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