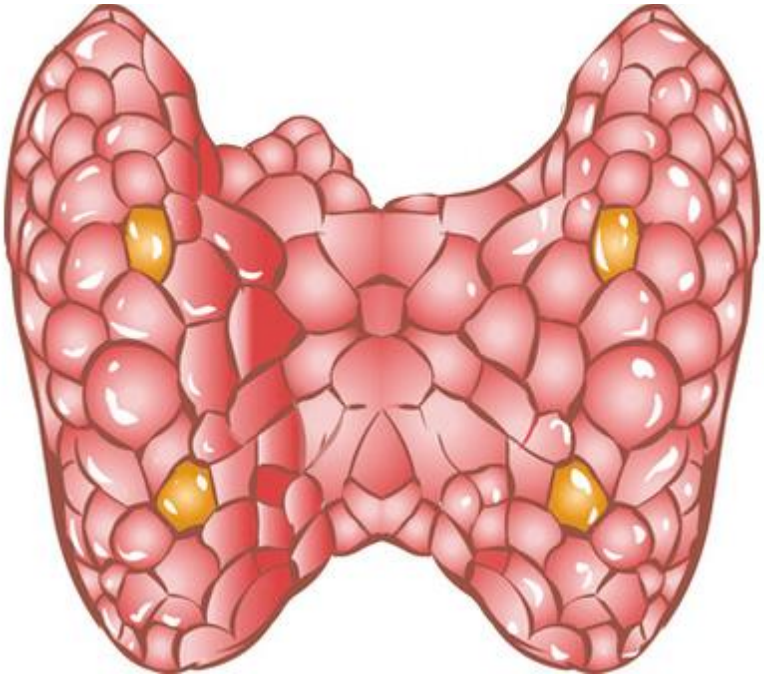
Lecture 1
Thyroid

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by
هشام الغفيلي & خولة العماري

Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

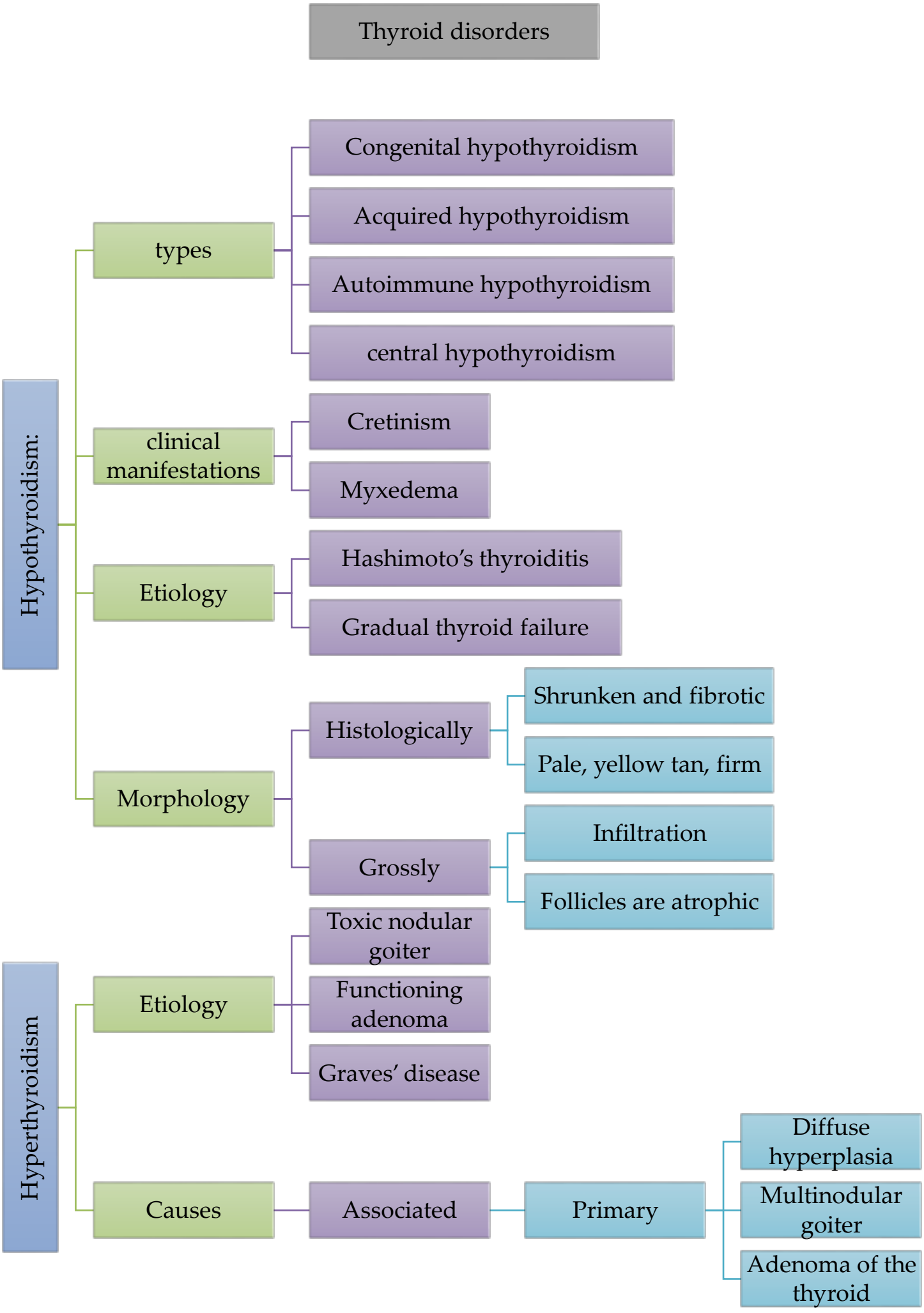


Objectives:

You should

- Know the structure and function of the thyroid gland
- Know the ways in which thyroid disorders present
- Know the major causes & manifestations of hypo and hyperthyroidism
- Know the causes of goiter

References: Lecture Slides, Robbins, Dr. Rikabbi & Dr. Hala's Notes.


Thyroid disorders
Hypothyroidism:
types
Congenital hypothyroidism
Acquired hypothyroidism
Autoimmune hypothyroidism
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Cretinism
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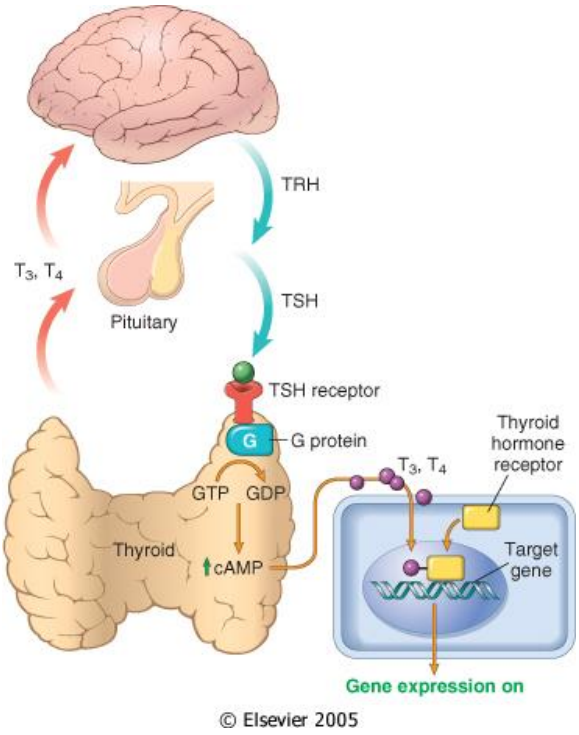
Follicles are atrophic
Hyperthyroidism
Etiology
Toxic nodular goiter
Functioning adenoma
Graves' disease
Causes
Associated
Primary
Diffuse hyperplasia
Multinodular goiter
Adenoma of the thyroid

Common in KSA, and it's very common in females.

Structure and function of The Thyroid Gland:

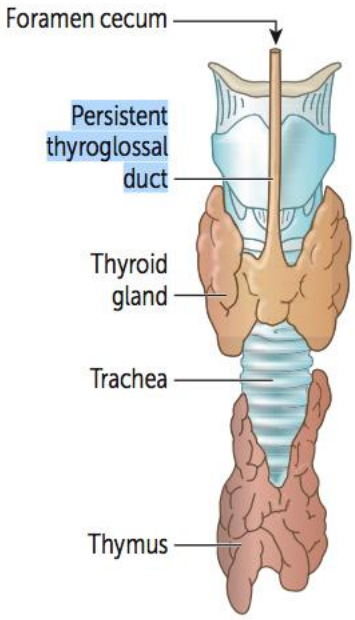
- The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx.
- The thyroid gland is one of the most responsive organs in the body and contains the largest store of hormones of any endocrine gland.
- The main function of Thyroid is to Synthesize and secrete T_3 and T_4.
- T_3 and T_4 are regulated by TRH from hypothalamus and TSH from the Pituitary:

Decreased levels of T_3 and T_4 → ↑ release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary, causing T_3 and T_4 levels to rise. Elevated T_3 and T_4 levels, in turn, suppress the secretion of both TRH and TSH.



Congenital abnormalities:

The thyroid gland develops embryologically from an evagination of the developing pharyngeal epithelium that descends from the foramen cecum at the base of the tongue to its normal position in the anterior neck.



Connected to tongue by hypoglossal duct, which normally disappears but may persist as pyramidal lobe of thyroid.

Lingual thyroid:

Ectopic thyroid tissue, most commonly located at the base of the tongue, caused by failure of descending of the gland.

Thyroglossal cyst:

A fibrous cyst that forms from a persistent thyroglossal duct. Presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue.

- Lingual thyroid: interferes with swallowing and respiration. (rare)
- Thyroglossal cyst: may be confused with lipoma, lymph nodes disease…etc. To differentiate, ask the patient to swallow and the cyst will move up and down. (common)

Disorders of the thyroid manifest in four main ways:

The masses can be benign or malignant

- Hypofunction (hypothyroidism)
- Hyperfunction (hyperthyroidism)
- Enlargement of the gland (goiter)
- Solitary masses

Hyperthyroidism (thyrotoxicosis):

Hypermetabolic state due to **Elevated** circulating T_3 and T_4, the resulting clinical syndrome being known as **thyrotoxicosis**.

Hyperthyroidism is only one category of thyrotoxicosis, and it's the **most common** one.

Etiology: Causes of thyrotoxicosis based on **association with hyperthyroidism**:

Associated	**Primary**	▪ **Graves disease** (accounts for 85% of cases). ▪ **Hyperfunctioning ("toxic") multinodular goiter:** ⇒ Rarely, one or more nodules in a multinodular goiter may develop hypersecretory activity, resulting in thyrotoxicosis. ▪ **Hyperfunctioning ("toxic") adenoma of the thyroid:** ⇒ Rarely, functioning thyroid adenomas have enough secretory activity to induce thyrotoxicosis. Such adenomas may also present as solitary thyroid masses. ▪ Iodine-induced hyperthyroidism.
	Secondary	TSH-secreting pituitary adenoma (rare).
May not be associated		▪ Granulomatous (de Quervain) thyroiditis (painful). ▪ Subacute lymphocytic thyroiditis (painless). ▪ Struma ovarii (ovarian teratoma with ectopic thyroid). ▪ Factitious thyrotoxicosis (exogenous thyroxine intake).

Clinical features of thyrotoxicosis:

Weight loss, hair loss, diarrhea, menorrhagia

Exophthalmos and pretibial myxoedema (Only in Graves')

Cardiac manifestations (tachycardia, palpitations & atrial fibrillation)

Warm moist skin, proximal myopathy, osteoporosis

Eye changes (exophthalmos, lid lag, lid retraction).

Nervousness , tremor and muscle weakness

Heat intolerance and excessive sweating

Thyroid storm is the sudden hypersecretion of thyroid hormone, they have a sympathetic overload effect

- Sympathetic nervous system overstimulation is caused by excess thyroid hormones which act on Beta-adrenergic receptors leading to tachycardia, sweating …etc.
- Loss of weight despite increased appetite. 10% only have ocular symptoms

Diagnosis:

The diagnosis of hyperthyroidism is based on clinical features and **laboratory data**.

- The measurement of serum TSH is the most useful single screening test for hyperthyroidism. (TSH is decreased even at the earliest stages)
- Measurement of T3 and T4 (T3 is better)
- radioactive iodine uptake by the thyroid gland

T3 is more sensitive than T4

Graves' disease:

Most common. Graves': 80% of hyperthyroidism. It is rare in males.

Graves' thyroiditis is an 'organ- specific' autoimmune disease; autoantibodies bind to the TSH receptor on thyroid epithelial cells and **mimic the stimulatory action** of TSH.

- Has a peak incidence between the ages of 20 and 40.
- Women affected more commonly than men.
- Most common cause of endogenous hyperthyrodisim.

Genetic susceptibility to Graves disease is associated with the presence of **HLA-DR3**, polymorphisms in genes encoding the inhibitory T cell receptor **CTLA-4** and the tyrosine **phosphatase PTPN22.**

- **Characterized by a triad of clinical findings:**
  - Hyperfunctional, diffuse enlargement of the thyroid. (present in all cases)
  - Infiltrative ophthalmopathy (exophthalmos[1]). (40 % of patients)
  - Localized, infiltrative dermopathy (pretibial myxedema[2]).

If the patient develops proptosis[3] or pretibial myoxoedema, the diagnosis of Graves' disease is almost certain since these changes are not seen in the thyrotoxicosis due to other causes.

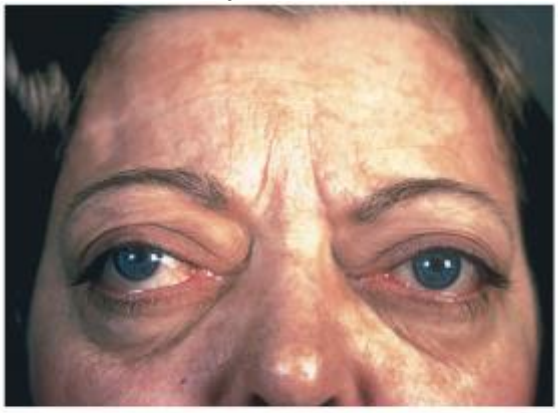


Figure 19–6 Patient with hyperthyroidism. A wide-eyed, staring gaze, caused by overactivity of the sympathetic nervous system, is one of the classic features of this disorder. In Graves disease, one of the most important causes of hyperthyroidism, accumulation of loose connective tissue behind the orbits also adds to the protuberant appearance of the eyes.

[1] Protrusion of the eyes
[2] An infiltrative dermopathy, resulting as a rare complication of Graves' disease
[3] Protrusion of the eyes

Pathogenesis:

Autoantibodies that work on TSH receptor and cause Graves' disease are of 3 types:

- **Thyroid-stimulating immunoglobulin:** LATS[4] IgG binds to TSH receptor & mimics the action of TSH → stimulate adenyl cyclase → ↑ thyroid hormone.
- **Thyroid growth-stimulating immunoglobulin:** Also directed against TSH receptor → leads to proliferation of thyroid follicular epithelium.
- **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.

Pathogenesis of the infiltrative ophthalmopathy[5]:

A T cell–mediated autoimmune phenomenon is involved → **an** increase of the retro-orbital space caused by:

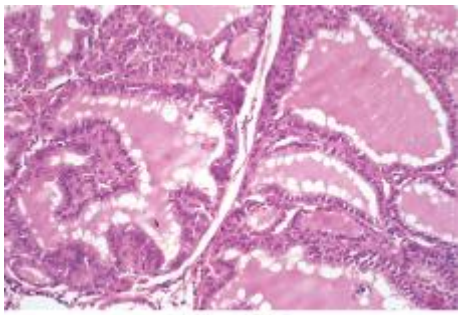
1. Infiltration of the retro-orbital space by **mononuclear cells** (Mostly T cells).
2. Inflammatory **edema.**
3. Accumulation of **glycosaminoglycans.**
4. Increased numbers of adipocytes.

Follicular cells become columnar due to the abundant cytoplasm and the lumen of the thyroid follicular cells becomes scalloped due to excess secretion.

Histopathology:

- **Scalloped colloid appearance.**
- Epithelial cells turn to be columnar & hyperplastic.
- Lymphocytosis.

Lymphocytic infiltration for both (eye and gland (even skin)).
Scalloped colloid appearance and epithelial cells become columnar in the gland.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Hypothyroidism:

Insufficient circulating T_4 and T_3 leads to a **hypometabolic** state resulting in the clinical syndrome known as hypothyroidism.

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

Incidence increases with age, more common in women.

The symptoms of hypothyroidism may be confused with depression

Etiology:

There are many causes of hypothyroidism and the commonest cause in adults in Hashimoto's thyroiditis. Most of the remaining cases of hypothyroidism are due to radiotherapy or surgery or are drug induced.

Worldwide, the most common cause of hypothyroidism is dietary deficiency of iodine (see further on), while in most developed nations, autoimmune causes predominate (also postablative استئصال) (Robbins)

[4] long acting thyroid stimulator
[5] A clinical feature of Graves'

Primary (majority) and secondary types:

Dyshormonogenetic goiter: congenital deficiency of enzymes required for hormone synthesis.

Primary(majority):
Most often the result is endemic **iodine deficiency** (in the diet)
Rare developmental abnormalities (thyroid dysgenesis): mutation in PAX8, FOXE
Congenital biosynthetic defect (dyshormonogenetic goiter)
Post ablative
Autoimmune hypothyroidism, e.g. Hashimoto's thyroiditis
Acquired hypothyroidism: surgery, radioiodine therapy, or external irradiation
Drugs (lithium, iodides, p-aminosalicyclic acid)

Lithium is used for mania and bipolar disorders

Secondary (central) hypothyroidism: Caused by deficiency of TSH, and far more uncommonly, that of TRH	
Pituitary failure	Hypothalamic failure (rare)

Clinical Features:

- **Cretinism:** If hypothyroidism occurs during infancy, it results in a condition known as **cretinism**, in which mental and physical development is impaired. This condition is now **rare**. It manifests with:
  - **Severe mental retardation**, **short stature**, coarse facial features, a **protruding tongue**, obesity and **umbilical hernia**.
- **Myxedema:** If hypothyroidism occurs in older children or adults it results in a condition known as **myxedema**, in which skin appears edematous due to the accumulation of mucopolysaccharides in the dermis. It manifests with:
  - Glycosaminoglycans and hyaluronic acid, in skin, subcutaneous tissue, visceral sites.
  - Non-pitting edema, a broadening and coarsening of facial features, enlargement of the tongue, deepening of the voice.

- Myxoedematous face.
- Dry hair.
- Hoarse voice.
- Psychosis.
- Cold intolerance.
- Slowed physical and mental activity, lethargy, weight gain.
- Constipation, muscle weakness, carpal tunnel syndrome, menstrual irregularities.

- Loss of hair from skull and eyebrows.
- Oligomenorrhoea
- Somnolence
- Bradycardia
- Slowness in memory, thinking and answering (eg, you the patient where are you living? And she'll need 10 minutes for answering)
- Fatigued

Diagnostic methods are the same as Hyperthyroidism.

Now we'll talk about some of the diseases that could cause hypothyroidism:

Thyroiditis:

Inflammation of the thyroid gland, include diverse group of diseases:

1. **Hashimoto's thyroiditis** which is very common.
2. Subacute granulomatous (giant cell or **de Quervain thyroiditis**).
3. **Riedel's thyroiditis**.

These diseases include conditions that result in **acute illness** with **severe thyroid pain** (e.g., infectious thyroiditis, subacute granulomatous thyroiditis).

Or Disorders with **little inflammation**, manifested by thyroid dysfunction (subacute lymphocytic (**painless**) thyroiditis and fibrous [Reidel] thyroiditis).

Subacute lymphocytic thyroiditis follows pregnancy it is painless and the diagnosis is done clinically

Thyroiditis is a rare cause of goiter.

Hashimoto's thyroiditis:

An organ specific autoimmune disease in which the immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase).

Antibodies directed **against** thyroid tissue and thyroglobulin have been detected in patients with this condition.

- Hashimoto thyroiditis is the **most common** cause of hypothyroidism in areas of the world where **iodine** levels are sufficient.
- Hashimoto thyroiditis and Graves' disease are the two **most common** immunologically mediated disorders of the thyroid.
- 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**.

Increased susceptibility to Hashimoto thyroiditis is associated with polymorphisms in **CTLA4 Gene.**

Pathogenesis:

Hashimoto thyroiditis is caused by a breakdown in self-tolerance to thyroid autoantigens.

The feature of Hashimoto's thyroiditis is progressive **depletion of thyroid epithelial cells** (thyrocytes), replaced by mononuclear cell infiltration and **fibrosis**.

Multiple **immunologic mechanisms** that may contribute to thyrocyte damage:

- **CD8+ cytotoxic T cell–mediated cell death** (T killer) → thyrocyte destruction.
- **Cytokine-mediated cell death:** Excessive T helper cell activation → production of inflammatory cytokines **(interferon-γ)** → recruitment and activation of macrophages and damage to follicles.
- **Binding of antithyroid antibodies** (antithyroglobulin, and antithyroid peroxidase antibodies).

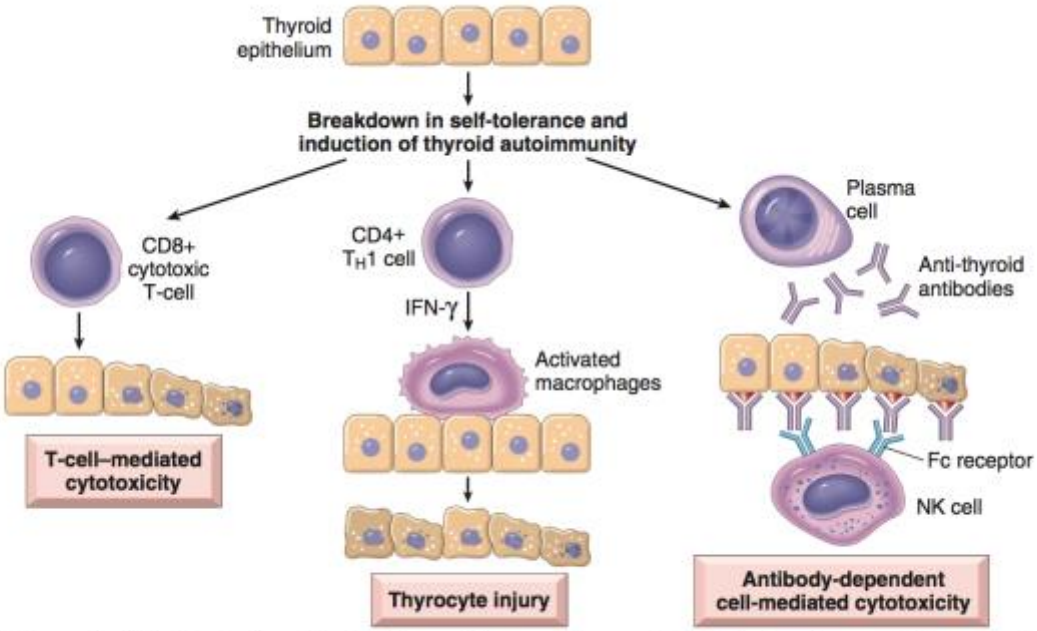


Figure 19–7 Pathogenesis of Hashimoto thyroiditis. Breakdown of immune tolerance to thyroid autoantigens results in progressive autoimmune destruction of thyrocytes by infiltrating cytotoxic T cells, locally released cytokines, or antibody-dependent cytotoxicity.

The doctor read this slide and said that they all lead to follicular damage

Clinical Features, may present in a number of ways:

- Comes to clinical attention as **painless enlargement** of the thyroid.
- With **goiter**, which recedes after time due to **atrophy and fibrosis** of the gland as a result of autoimmune destruction.
- With **hypothyroidism**.
- With **thyrotoxicosis** in the early stages of the disease, damage to the thyroid follicles may lead to a transient rise in thyroid hormone levels
- Increased risk for the development of **B cell non-Hodgkin lymphomas** and predisposition to **papillary carcinomas**.
- There might be **gradual thyroid failure** by autoimmune destruction of the thyroid gland.

Morphology:

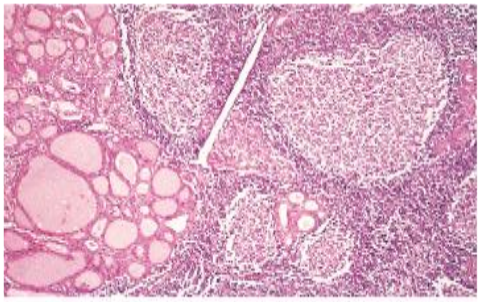
-It looks like a stone. (normally the gland is brown and highly vascular)
-salivary gland-like cut surface.

Gross

- The thyroid is often diffusely enlarged.
- The cut surface is pale, yellow tan, firm, and somewhat nodular.
- In advanced cases, the gland is shrunken and fibrotic.

Histologically

- Extensive infiltration of the parenchyma by lymphocytes and plasma cells.
- Lymphoid aggregates, often with well-developed **germinal centers**.
- The thyroid follicles are atrophic and are lined in many areas by epithelial cells.
- ↑ of the number of cells lining the follicles and ↓ in the amount of stored colloid.
- Those epithelial cells become eosinophilic and granular, at which time they are termed oncocytes or **Hürthle cells**.



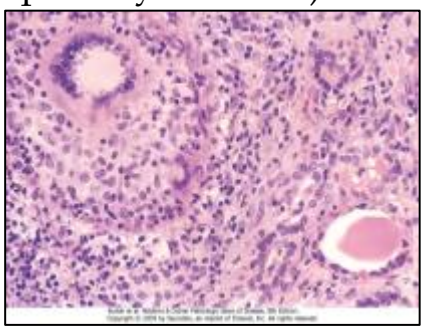
Diagnosis: cytology & histology
Antibodies: 1-anti-thyroglobulin antibodies.
2-anti-thyroid peroxidase antibodies

- Enlarged follicles since they are reactive.
- Hürthle cell change (very eosinophilic cytoplasm. On electron microscopy).

Subacute Granulomatous Thyroiditis: (de Quervain)

The thyroid is infiltrated by **multinucleated giant cells** admixed with other inflammatory cells (granulomatous). It's much less common than Hashimoto disease, most common between the ages of **30 and 50** and occurs in **women more than men**. It's a limited disease caused mostly by a viral infection or an inflammatory process triggered by viral infections (upper respiratory infection).

Histopathology:



- Disruption of thyroid follicles.
- Granulomatous reaction with **giant cells.**
- Polymorphonuclear infiltrate (lymphocytes, plasma cells, and macrophages).

Clinical findings:

The onset of this form of thyroiditis often is acute, characterized by **pain** in the neck (particularly with swallowing)

- Most common cause of painful thyroid gland. No cervical adenopathy.
- fever, malaise, tenderness on palpation and variable enlargement of the thyroid.
- Often preceded by an upper respiratory infection.
- The condition typically is self-limited.
- **Initial** thyrotoxicosis from gland destruction:
  - Increased serum T4, decreased serum TSH.
  - Permanent hypothyroidism is uncommon.

Multinodular Goiter:

There are two main causes of goiter: Simple and multinodular goiter & thyroiditis.

Enlargement of the thyroid, or goiter, is the **most common** manifestation of thyroid disease, it has two subtypes:

- ***Endemic goiter:***

  Endemic goiter occurs in geographic areas where the soil, water, and food supply contain little iodine.

- ***Sporadic Goiter:***

  It's less common than Endemic Goiter occurs in **Females more than males.** In individuals whose iodine uptake is suboptimal,ingestion of foodstuffs such as **cabbage and turnips** or inherited defects in thyroid hormone synthesis may cause sporadic goiter, however, they're rare.

It can also arise in the following settings:

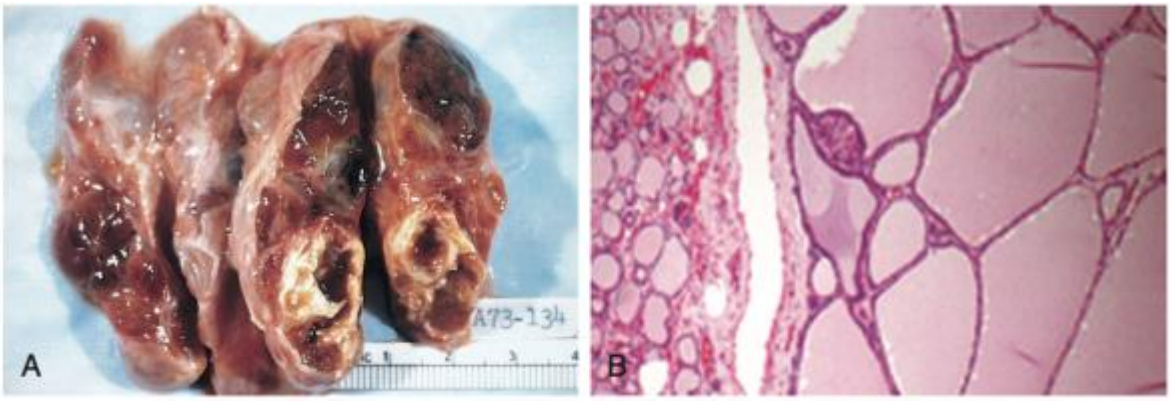
- Amiodarone, lithium could induce Goiter (drug-induced).
- Rare inherited defects in thyroid hormone synthesis.

Goiter can be:
a-Toxic: secreting hormones (hyperfunctioning).
b-nonfunctional: not secreting hormone, just swelling.(most)

Pathogenesis of Goiter:

Impairment of thyroid hormone synthesis → a compensatory rise in the serum TSH (usually renders the individual euthyroid) → **TSH-induced** hypertrophy and hyperplasia of thyroid follicular cells → diffuse and symmetric enlargement of the gland. With time, Recurrent episodes of hyperplasia → a more irregular enlargement of the thyroid termed **Multinodular goiter**

Note that the compensatory responses may be inadequate to overcome the impairment in hormone synthesis, resulting in **goitrous hypothyroidism**.



Grossly:

- Asymmetrically enlarged glands.
- Irregular nodules.
- Brown gelatinous colloid.

On Cut surface it shows:

- Fibrosis, hemorrhage.
- Cystic change.

Microscopically:

- Colloid-rich follicles
- Flattened follicular epithelium

Micro: nodules, fibrosis, enlarged follicles, areas of haemorrhage and abundant colloid.

Riedel's thyroiditis:

It's exceptionally rare. Characterized by replacement of the thyroid by fibrous tissue, often with **involvement of adjacent tissues** (retroperitoneum). **The etiology is unknown**. Patients present with an enlarged thyroid, which is hard and immobile on palpation thereby mimicking carcinoma. The condition may be associated with **retroperitoneal fibrosis**.

The fibrosis is unlimited here while in Hashimoto it is limited.
It is the destruction of all structures followed by fibrosis

Riedel:
- Very hard/fibrotic gland
- Not very painful
- Fibrosis: retroperitoneal or mediastinal

Further Reading:

Subacute Lymphocytic Thyroiditis (Read it just in case[6])

It's also known as **silent or painless thyroiditis**; in a subset of patients the onset of disease follows pregnancy (postpartum thyroiditis). This disease is most likely to be **autoimmune** in etiology. It mostly affects **middle-aged women**, who present with a **painless neck mass** or features of thyroid hormone excess. **The initial phase of thyrotoxicosis** (which is likely to be secondary to thyroid tissue damage) is followed by return to a euthyroid state within a few months. In a minority of affected persons the condition eventually progresses to hypothyroidism. Except for possible mild symmetric enlargement, the thyroid appears normal on gross inspection. The histologic features consist of lymphocytic infiltration and hyperplastic germinal centers within the thyroid parenchyma.

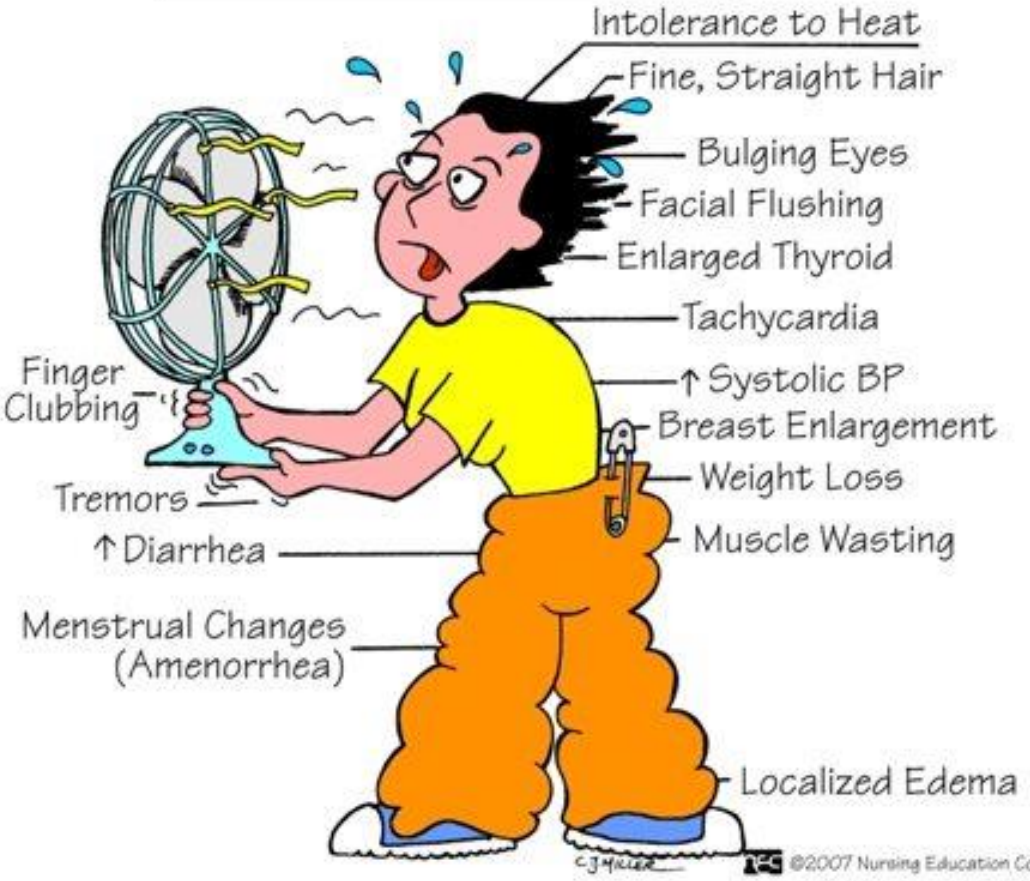
Acute bacterial thyroiditis

Acute inflammation of the thyroid can result from direct bacterial spread from adjacent tissues or by blood-borne spread. Patients present with thyroid pain, tenderness and enlargement. There may be systemic features of infection. The condition usually resolves with antibiotic treatment.

Hypothyroidism vs. hyperthyroidism

	Hypothyroidism	Hyperthyroidism
SIGNS/SYMPTOMS	Cold intolerance (↓ heat production)	Heat intolerance (↑ heat production)
	Weight gain, ↓ appetite	Weight loss, ↑ appetite
	Hypoactivity, lethargy, fatigue, weakness	Hyperactivity
	Constipation	Diarrhea
	↓ reflexes	↑ reflexes
	Myxedema (facial/periorbital)	Pretibial myxedema (Graves disease), periorbital edema
	Dry, cool skin; coarse, brittle hair	Warm, moist skin; fine hair
	Bradycardia, dyspnea on exertion	Chest pain, palpitations, arrhythmias, ↑ number and sensitivity of β-adrenergic receptors
LAB FINDINGS	↑ TSH (sensitive test for 1° hypothyroidism)	↓ TSH (if 1°)
	↓ free T_3 and T_4	↑ free or total T_3 and T_4
	Hypercholesterolemia (due to ↓ LDL receptor expression)	Hypocholesterolemia (due to ↑ LDL receptor expression)

HYPERTHYROIDISM



HYPOTHYROIDISM

Check Your Understanding

MCQs:

1. **Insufficient circulating T_4 and T_3 will lead to?**
   A. Hyperthyroidism
   B. Hypothyroidism
   C. Goiter
   D. Carcinoma

2. **A child presented to the clinic with impaired physical and mental development, umbilical hernia, coarse facial features and a protruding tongue; of the following, what is most likely the reason for his condition?**
   A. The child had hypothyroidism as an infant
   B. The child had hyperthyroidism as an infant
   C. The child had thyroiditis as an infant
   D. The child has myxedema

3. **Slow physical and mental activity, obesity, non-pitting edema, large tongue and deepening of the voice suggest that the patient has which of the following?**
   A. Cretinism
   B. Autoimmune hypothyroidism
   C. Myxedema
   D. Thyroiditis

4. **Most common cause of hypothyroidism in iodine-sufficient areas of the world is:**
   A. Cretinism
   B. Autoimmune hypothyroidism
   C. Acquired hypothyroidism
   D. Thyroiditis

5. **Which of the following is an autoimmune disease characterized by ophthalmopathy and infiltrative dermopathy?**
   A. Toxic nodular goiter
   B. Autoimmune hypothyroidism
   C. Thyroiditis
   D. Graves' disease

1:B 2:A 3:C 4:B 5:D

6. **Clinical features of thyrotoxicosis that only happened in graves?**
   A. Tachycardia, palpitations
   B. Nervousness
   C. Exophthalmos and pretibial myxedema

7. **The most useful single screening test for hyperthyroidism?**
   A. Serum TSH
   B. T4
   C. T3

8. **The most common cause of hypothyroidism in areas of the world where iodine levels are sufficient?**
   A. Congenital biosynthetic defect
   B. Hashimoto's thyroiditis
   C. Radioiodine therapy

9. **Skin appears edematous due to the accumulation of mucopolysaccharides in the dermis happens in?**
   A. Cretinism
   B. Myxedema

10. **The thyroid is infiltrated by multinucleated giant cells in?**
   A. Hashimoto's thyroiditis
   B. Quervain thyroiditis
   C. Riedel's thyroiditis

6:C 7:A 8:B 9:B 10:B

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق
