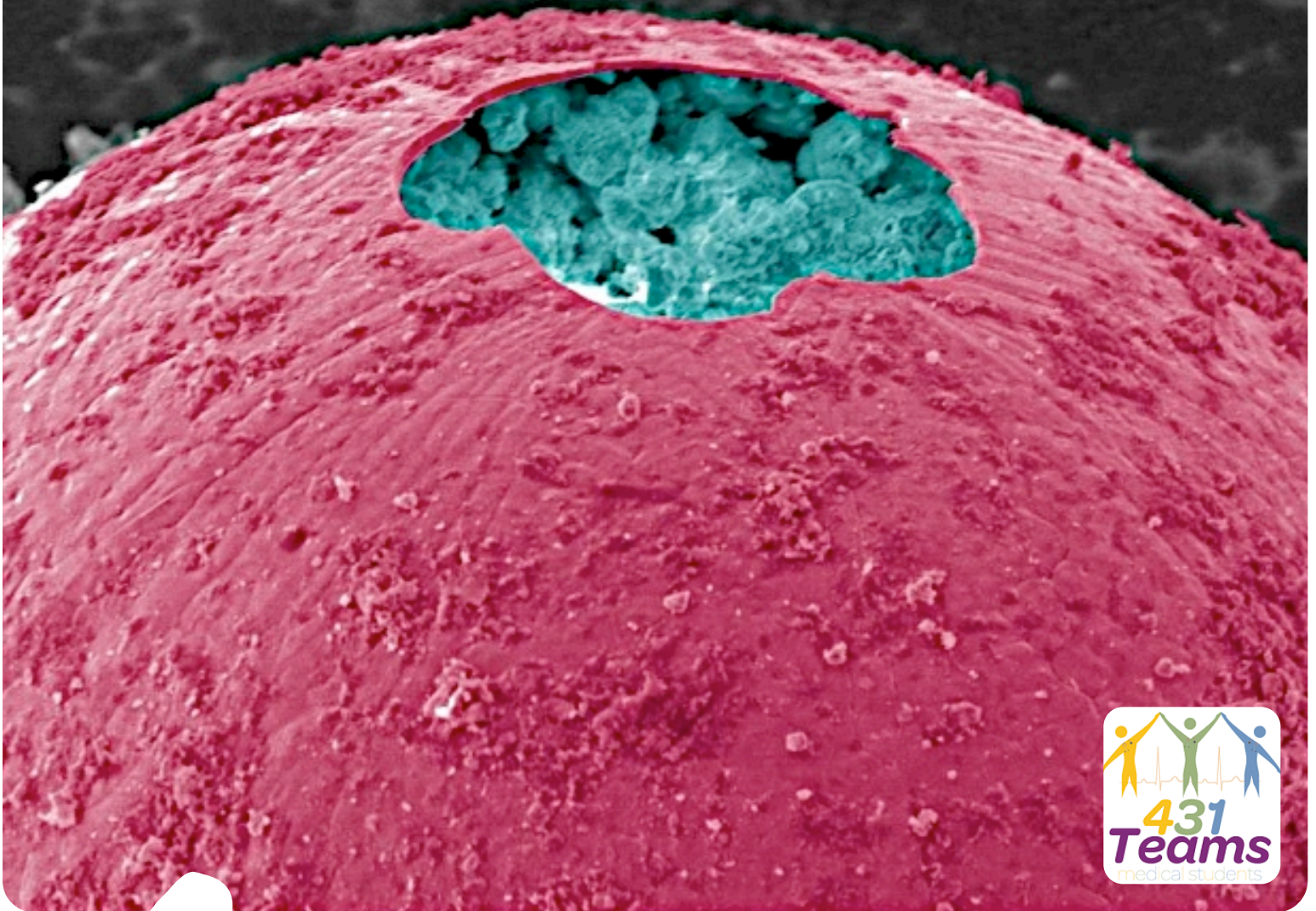


PATHOLOGY

TEAM



Leaders

Hazim Jokhadar & Sadeem Al-dawas

Done By

Mamdoh Al-enezi & Sarah Al-saif

Revised By

Abdullah Al-khwaiter

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**. Normal variations in the structure of the thyroid gland include the presence of a pyramidal lobe, a remnant of the thyroglossal duct above the isthmus.
- The thyroid gland is one of the most **responsive** organs in the body and contains the **largest store** of hormones of any endocrine gland.
- Each thyroid lobe is divided into **lobules**, each composed of about 20 to 40 evenly dispersed **follicles**.
- It is **important** to recognize diseases of the thyroid, because most are **amenable** to medical or surgical management.

How does it work ... ?

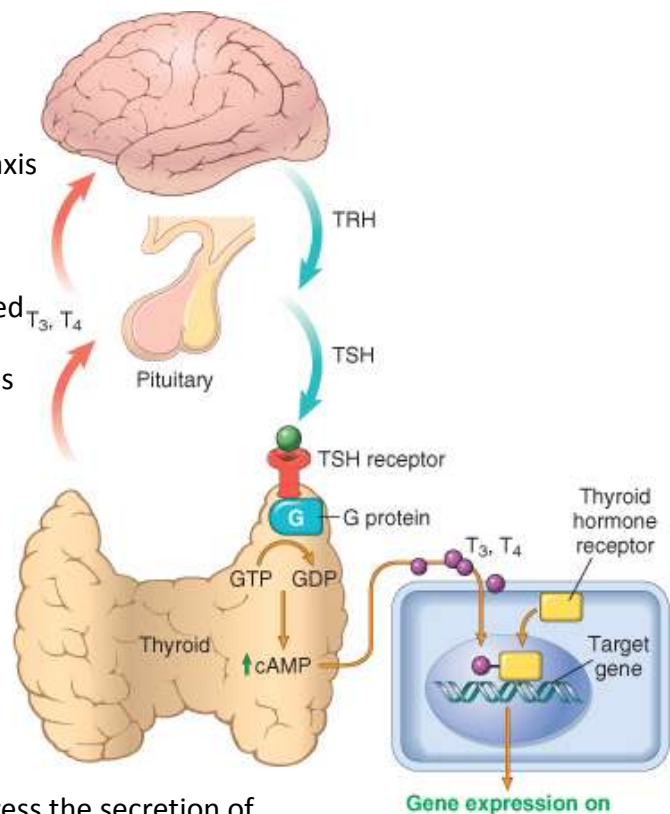
Homeostasis in the hypothalamus-pituitary-thyroid axis and mechanism of action of thyroid hormones.

Secretion of thyroid hormones (T_3 and T_4) is controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary.

Decreased levels of T_3 and T_4 stimulate the 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. This relationship is termed a negative-feedback loop.

TSH binds to the TSH receptor on the thyroid follicular epithelium, which causes activation of G proteins, and cyclic AMP (cAMP)-mediated synthesis and release of thyroid hormones (T_3 and T_4). In the periphery, T_3 and T_4 interact with the thyroid hormone receptor (TR) to form a hormone-receptor complex that translocates to the nucleus and binds to so-called thyroid response elements (TREs) on target genes initiating transcription.



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Hypothyroidism ..



Important
Information

All thyroid diseases are more common in **females** than in **males**, regardless of "neoplastic or non neoplastic"

Hypothyroidism is a very **common** disease, and it is classified into:

- **Primary** (problem in the thyroid)
- **Secondary** (problem not in the thyroid – usually pituitary>hypothalamus)

- ✓ *Hypothyroidism* is caused by any **structural** or **functional** derangement that interferes with the production of **adequate** levels of thyroid hormone.
- ✓ Hypothyroidism is a fairly common disorder, and by some estimates the population prevalence of **overt** hypothyroidism is 0.3%, while **subclinical** hypothyroidism can be found in **greater** than 4%. (Subclinical hypothyroidism usually presents with obesity with no improvement with diet and exercise)
- ✓ The prevalence of hypothyroidism **increases** with **age**, and it is nearly **tenfold** more common in women than in men.
- ✓ It can result from a defect anywhere in the **hypothalamic-pituitary-thyroid axis**.
- ✓ As in the case of hyperthyroidism, this disorder is divided into
 - **Primary (majority)** hypothyroidism arises from an **intrinsic abnormality in the thyroid itself**
 - **Secondary** hypothyroidism occurs as a result of **pituitary and hypothalamic disease**.
- ✓ **Congenital** hypothyroidism
 - Most often the result of **endemic iodine deficiency** in the diet
 - **Less** common causes include **inborn errors of thyroid metabolism** (dysmorphonogenetic goiter)
- ✓ **Acquired** hypothyroidism can be caused by **surgical** or **radiation**-induced ablation of thyroid parenchyma (usually with patients with previous radiation therapy in or near the head and neck region; eg: breast cancer)
- ✓ **Autoimmune hypothyroidism** (Hashimoto's) is the **most common cause of hypothyroidism** in **iodine-sufficient** areas of the world.
- ✓ **Secondary** (or central) hypothyroidism is caused by deficiency of TSH, and far more uncommon, TRH deficiency.

Primary

Secondary (central)

Developmental
thyroiddysgenesis:
(*PAX8*, *FOXE1*, TSH receptor mutations)

Pituitary failure

Post-ablative,
Iodine deficiency

Hypothalamic failure (rare)

Surgery, radioiodine therapy, or
external irradiation
Drugs (lithium, iodides, p-
aminosalicylic acid, iodides, p-
aminosalicylic acid

Autoimmune hypothyroidism

Hashimoto thyroiditis
(**Autoimmune, Number 1 cause of
hypothyroidism**)

Congenital biosynthetic defect
(dysmorphogenetic goiter)*

Classic Clinical Manifestations:

Classic clinical manifestations of hypothyroidism include **cretinism** and **myxedema**.

Cretinism:

Cretinism: in children

Myxedema :in Adult

- **Severe mental retardation**, **short stature**, **coarse facial features**, a protruding tongue, and umbilical hernia.

Myxedema:

- **Slowing of physical** and mental activity, **mental sluggishness**, **being overweight**.
- Glycosaminoglycans and hyaluronic acid (**matrix substances**) accumulate in skin, subcutaneous tissue, and visceral sites, this results in non-pitting edema (**in the front of legs and shins**), a broadening and **coarsening of facial features**, enlargement of the tongue, deepening of the voice.

Investigations:

❖ **Laboratory evaluation** has a **vital role** in the diagnosis of suspected hypothyroidism because of the nonspecific nature of symptoms.

1. *Measurement of the serum **TSH***

- **The most sensitive** screening test for this disorder.
- TSH is **increased** in **primary hypothyroidism**

Due to a loss of feedback inhibition of thyrotropin-releasing hormone (TRH) and TSH production by the hypothalamus and pituitary, respectively.

- TSH is **not increased** in persons with hypothyroidism caused by **primary hypothalamic or pituitary disease (secondary)**.

❖ **≠ Serum T₄** is **decreased** in individuals with hypothyroidism of any origin



Thyrotoxicosis:

- ❖ **Hyperthyroidism** is a type of **thyrotoxicosis**: (a hyper metabolic syndrome which occurs when there are elevated serum levels of T3 and/or T4)
- ❖ Graves disease is the **most common** form of

Graves reported in 1835 his observations of a disease characterized by "**violent** and long **continued palpitations in females**" associated with **enlargement of the thyroid gland**.

Graves disease is the **most common** cause of endogenous **hyperthyroidism**.

A triad of clinical findings characterizes it:

- ✓ **Diffuse enlargement** of the thyroid (*diffuse: non-nodular*)
- ✓ Thyroid **hyperfunction**
- ✓ Resultant **exophthalmos**. →
- ✓ Localized, infiltrative **dermopathy**, sometimes called (*pretibialmyxedema*), which is present in a minority of patients.



Graves disease has a peak incidence between the ages of 20 and 40,

Women are affected up to seven times more frequently than men. This disorder is said to be present in 1.5% to 2.0% of women in the United States. Genetic factors are important in the etiology of Graves disease.

An increased incidence of Graves disease occurs among family members of affected patients, and the concordance rate in monozygotic twins is as high as 60%.

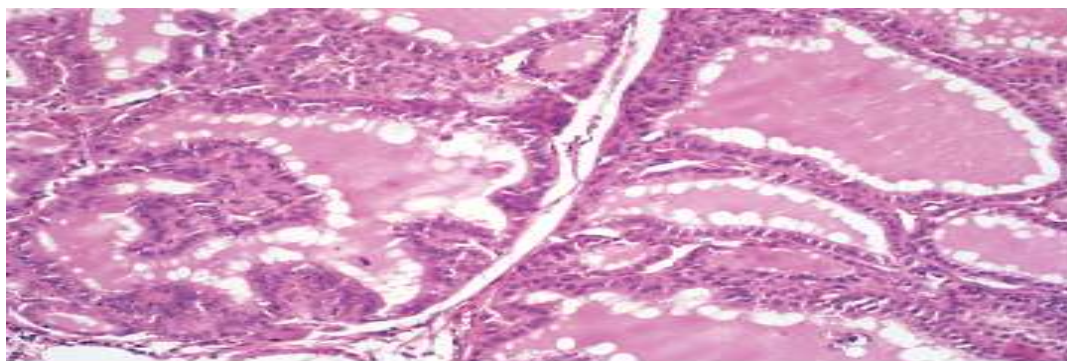


Hyperthyroidism:

- Hypermetabolic state caused by elevated circulating levels of **free T3 and T4**
- Caused most commonly by hyperfunction of the thyroid gland
- The common practice is to use the terms **thyrotoxicosis** and **hyperthyroidism** interchangeably

Causes of Thyrotoxicosis:

A-Associated with Hyperthyroidism	B- Not Associated with Hyperthyroidism
<p><u>Primary:</u></p> <p>1-Diffuse hyperplasia of the thyroid associated with Graves disease (<u>accounts for 85% of cases</u>)</p> <p>2- Hyperfunctional multinodular goiter</p> <p>3- Hyperfunctional adenoma of the thyroid</p> <p><u>Secondary:</u></p> <ul style="list-style-type: none"> • TSH-secreting pituitary adenoma (rare) 	<p>1-Subacute granulomatous thyroiditis (<i>painful</i>)</p> <p>2-Subacute lymphocytic thyroiditis (<i>painless</i>)</p> <p>3-Factitious thyrotoxicosis (exogenous thyroxine intake)</p> <p>4-Struma ovarii (ovarian teratoma with thyroid)(rare)</p>



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Histopathology findings:

Diffusely hyperplastic thyroid in a case of Graves disease. The follicles are lined by **tall, columnar epithelium**. The crowded, **enlarged epithelial cells** project into the lumens of the follicles. These cells actively **resorb** the **colloid in the centers** of the follicles, resulting in the **scalloped appearance** of the edges of the colloid

Graves disease:

- **Graves disease** is an **autoimmune** disorder: (**autoantibodies** to the **TSH receptor** are central to disease pathogenesis)
- Thyroid-stimulating immunoglobulin (**TSI**), Thyroid growth-stimulating immunoglobulins (**TGI**), and TSH-binding inhibitor immunoglobulins (**TBII**).
- **Coexistence** of **stimulating** and **inhibiting** immunoglobulins in the serum of the **same** patient, a finding that could explain why some patients with Graves disease spontaneously develop episodes of **hypothyroidism** (**Rare**)



Thyroiditis:

- **Thyroiditis**: inflammation of the thyroid gland, include diverse group of diseases
- **Acute** illness with severe **thyroid pain** (e.g., infectious thyroiditis, subacute granulomatous thyroiditis)
- Disorders with **little** inflammation, manifested by thyroid dysfunction (**subacute lymphocytic thyroiditis** and **fibrous** [Reidel] **thyroiditis**).

Hashimoto's Thyroiditis :

- **Hashimoto thyroiditis** (or chronic lymphocytic thyroiditis) is **the most common cause of hypothyroidism** in areas of the world where iodine levels are sufficient.
- The name Hashimoto thyroiditis 1912 report by Hashimoto describing patients with goiter and intense lymphocytic infiltration of the thyroid (strumalymphomatosa).

Hashimoto's Thyroiditis con't:

- ✓ **Hashimoto thyroiditis** and **Graves disease** are the two most common **immunologically mediated disorders** of the thyroid.
- ✓ Hashimoto thyroiditis is an **autoimmune disease** in which the immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase).
- ✓ Hashimoto thyroiditis is characterized by **gradual thyroid failure** because of **autoimmune destruction of the thyroid gland**.
- ✓ The main feature of Hashimoto's thyroiditis is progressive depletion of thyroid epithelial cells (thyrocytes), replaced by **mononuclear cell infiltration and fibrosis**. (Infiltration by T-cells, macrophages and plasma cells)
- ✓ This disorder is most prevalent between 45 and 65 years of age, with a **female predominance** of 10:1 to 20:1.

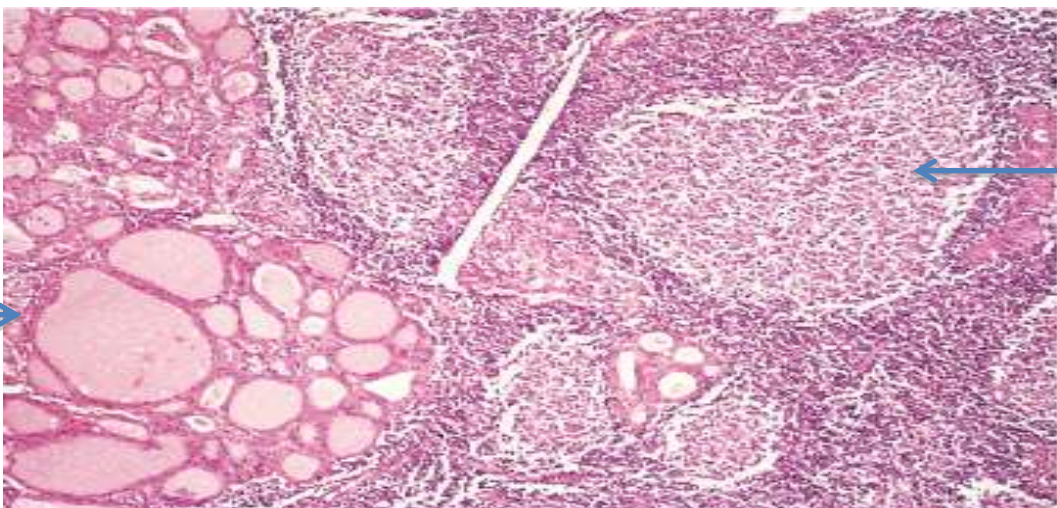
Although it is primarily a disease of older women, it can occur in children and is a major cause of nonendemic goiter in the pediatric population.

Epidemiologic studies have demonstrated a significant *genetic component to Hashimoto thyroiditis, although, as in most other autoimmune disorders, the pattern of inheritance is non-Mendelian and likely to be influenced by subtle variations in the functions of multiple genes. The concordance rate in monozygotic twins is 30% to 60%*, as well as the presence of circulating antithyroid antibodies in approximately 50% of asymptomatic siblings.

- ✓ The thyroid is often **diffusely enlarged**
- ✓ The cut surface is pale, yellow, tan, firm, and somewhat nodular.
- ✓ Microscopic examination reveals extensive **infiltration of the parenchyma** by a mononuclear inflammatory **infiltrate containing small lymphocytes, plasma cells, and well-developed germinal centers**
- ✓ The thyroid follicles are atrophic and are lined in many areas by epithelial cells distinguished by **the presence of abundant eosinophilic, granular cytoplasm, termed Hürthle cells**.

Hürthle cells are dark and line the follicles

Can't be seen here, need higher magnification.



Germinal center of lymphoid follicles.

Summary:



HYPOTHYROIDISM:

-Cause: Any structural or functional derangement interfering with adequate hormone level production.

Primary: in thyroid, Secondary: pituitary>hypothalamus

-Most common cause: **Hashimoto Thyroiditis**

-10:1 female to male ratio, prevalence increases with age.

-Manifestations:

Children → Cretinism (severe mental retardation, short stature, protruding tongue, coarse facial features)

Adults → Myxedema (Slowing of mental activity, weight gain, coarsening of facial features, deepening of the voice).

-Investigations:

1. Serum TSH (most sensitive):

High in primary hypothyroidism

Low in secondary hypothyroidism

2. T4: decreased in all causes.

-Hashimoto's Thyroiditis:

-The most common cause of hypothyroidism in areas with sufficient iodine levels.

-Autoimmune → gradual thyroid failure

-**Prevalence:** at 45 -65 years of age. 10 to 20 times more common in women.

-**Characteristics:** The thyroid is diffusely enlarged,

-Microscopically:

Parenchyma: Extensive infiltration by mononuclear infiltrate containing small lymphocytes, plasma cells, and well developed **germinal centers**.

Thyroid follicles: Lined by **Hurthle cells** (epithelial cells with abundant eosinophilic granular cytoplasm).

HYPERTHYROIDISM:

Cause: Hyperfunctioning of the thyroid gland → Elevated free T4 and T3

Primary: Graves (most common cause of hyperthyroidism)

Secondary: TSH secreting pituitary adenoma.

More common in females than in males.

Thyrotoxicosis:

Triad of clinical finding:

Diffuse goiter enlargement

Hyper-functioning thyroid

Exophthalmos

Graves Disease:

The most common cause of endogenous hyperthyroidism.

Autoimmune; autoantibodies bind to TSH receptors

Females > males

Microscopic:

1. Diffusely hyperplastic thyroid
2. Follicles: lined by tall, columnar epithelium.
3. Enlarged epithelial cells → project into follicle lumen → **Scalloped appearance at the edges of the colloid**

Thyroiditis:

Inflammation of the thyroid gland

Causes:

Acute thyroiditis, subacute granulomatous thyroiditis → acute illness with severe pain.

Subacute lymphocytic thyroiditis and Reidel's thyroiditis → little inflammation, manifested by thyroid dysfunction.

Questions:

A 45-year-old woman with a known history of rheumatoid arthritis presents to her primary care physician with fatigue, weight gain and cold intolerance. Examination reveals an enlarged thyroid gland, coarse skin, and bradycardia. Her thyroid function test show elevated TSH and low levels of T3 and T4.

What is the most likely diagnosis?

- a) Primary hyperthyroidism
- b) Secondary hyperthyroidism
- c) Primary hypothyroidism
- d) Secondary hypothyroidism

Most likely caused by:

- a) Graves disease
- b) Hashimoto's thyroidism
- c) Pituitary adenoma

Which of the following histological findings is most consistent with a diagnosis with Hashimoto's thyroidism?

- a) Granulomatous inflammation
- b) Scalloping of colloid
- c) Lymphoid infiltrate with Hurthle cells.

Which of the following histological findings is more consistent with a diagnosis of Graves disease?

- a) Granulomatous inflammation
- b) Scalloping of colloid
- c) Lymphoid infiltrate with Hurthle cells.

Answers: c , b , c , b