Pathology of Thyroid gland

Hypo, Hyperthyroidism and Hashimoto's Thyroiditis

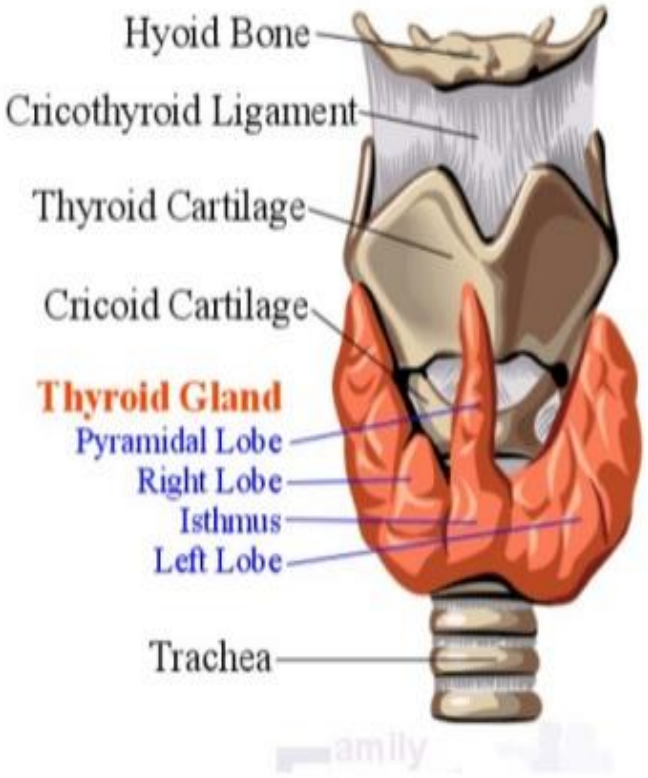
Objectives

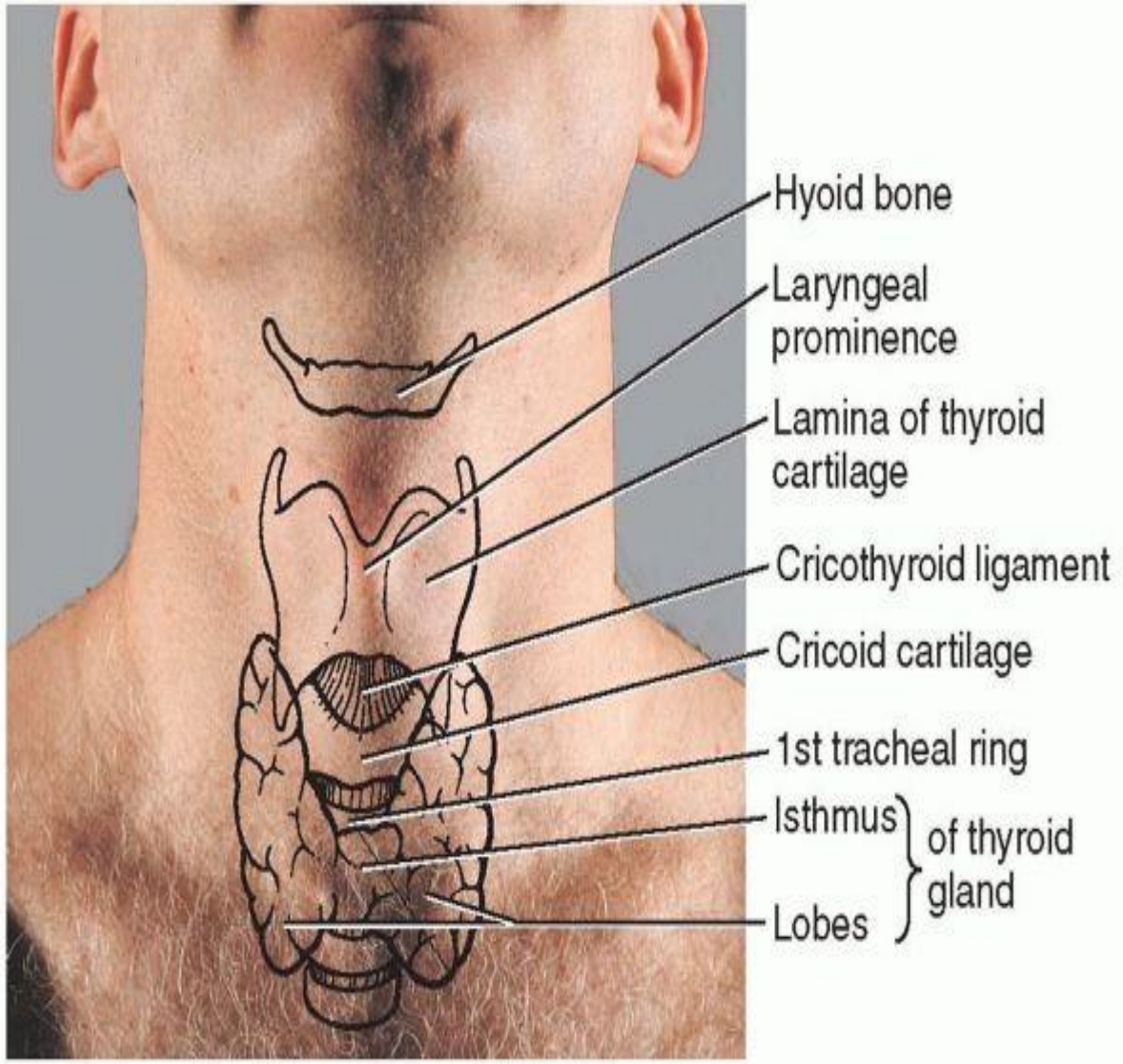
- Know the ways in which thyroid disorders present.
- Know the major causes and manifestations of hypo, hyperthyroidism and thyroiditis .
- Know the causes of the thyroid endemic goiter and its pathology.

Thyroid anatomy

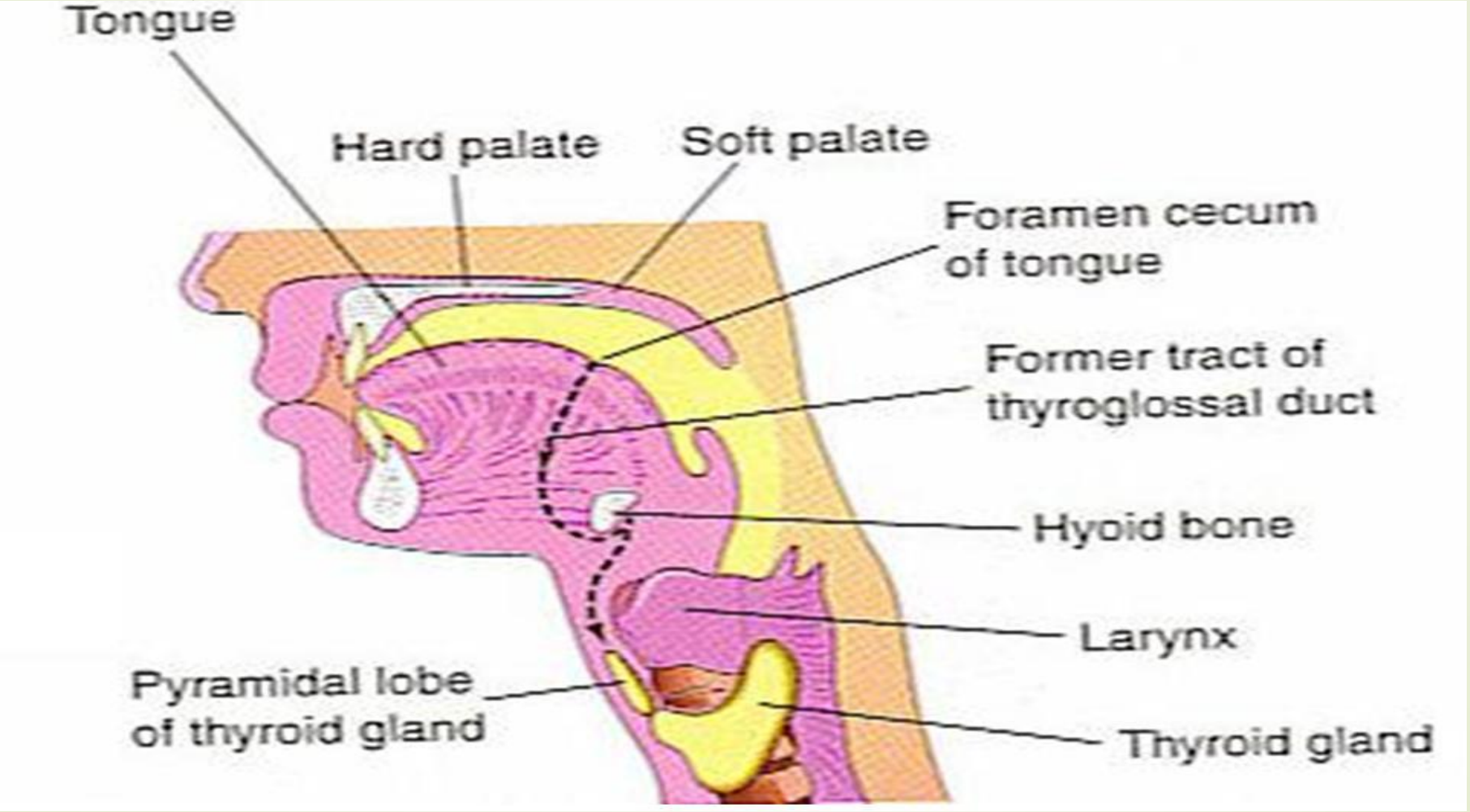
- The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx.
- The thyroid gland develops embryologically from an invagination of the developing pharyngeal epithelium that descends from the foramen cecum at the base of the tongue to its normal position in the anterior neck

Anatomy of Thyroid gland

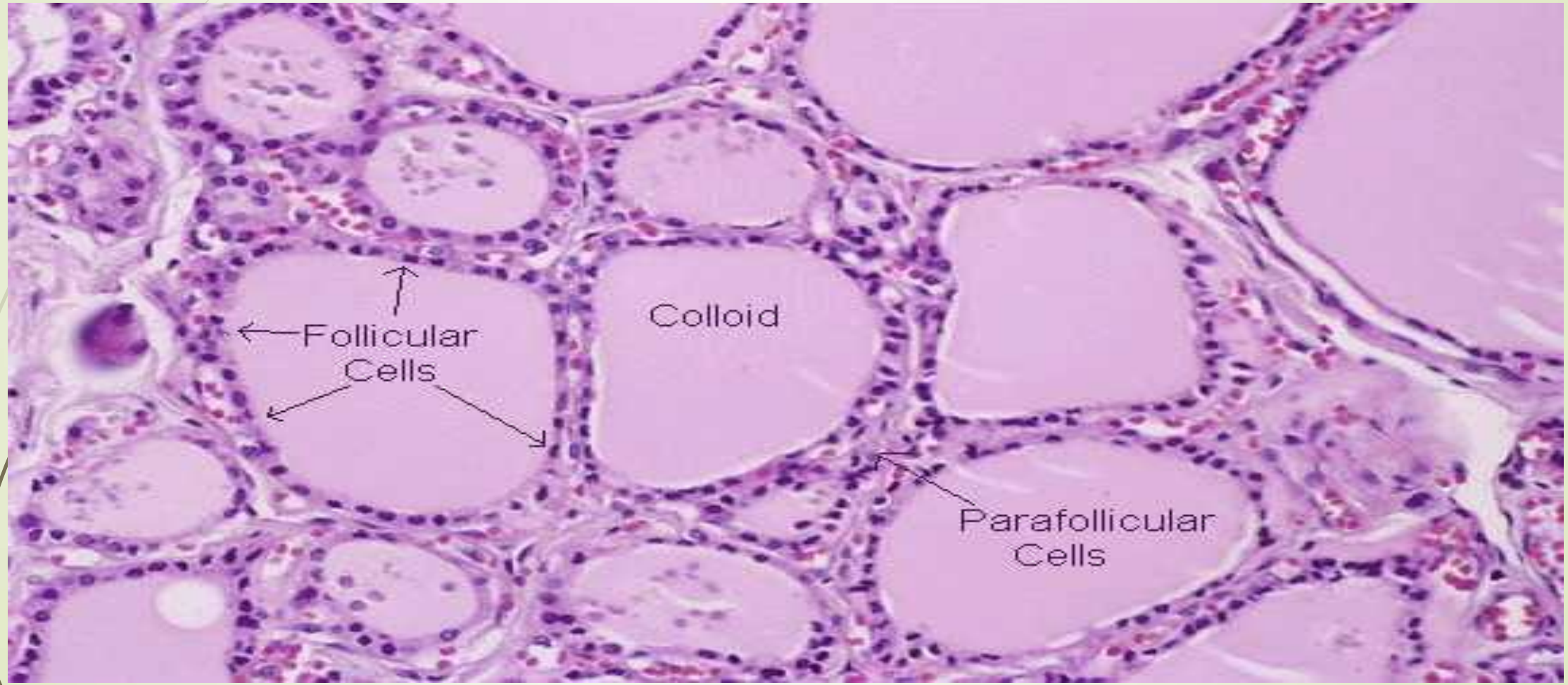




Ectopic thyroid tissue



Histology



Thyroid Diseases

- Clinical recognition of diseases of the thyroid is important, because most are amenable to medical or surgical management.
- **Diseases include:**
- Excessive release of thyroid hormones (hyperthyroidism).
- Thyroid hormone deficiency (hypothyroidism).
- Mass lesions .

Hyperthyroidism

- **Thyrotoxicosis is a hypermetabolic state due to elevated circulating levels of free T_3 and T_4.**

- **Because it is caused most commonly by hyperfunction of the thyroid gland, thyrotoxicosis often is referred to as hyperthyroidism.**

- In certain conditions, however, the oversupply either is related to excessive release of pre-formed thyroid hormone (e.g., in thyroiditis) or comes from an extrathyroidal source, rather than a hyperfunctioning gland

Hyperthyroidism

The three most common causes of thyrotoxicosis:

- **Primary:**

- Diffuse hyperplasia of the thyroid associated with Graves disease (accounts for 85% of cases)
- Hyperfunctional multinodular goiter
- Hyperfunctional adenoma of the thyroid

Causes of Thyrotoxicosis

- **ASSOCIATED WITH HYPERTHYROIDISM**
- Primary

Diffuse toxic hyperplasia (Graves disease)

Hyperfunctioning ("toxic") multinodular goiter

Hyperfunctioning ("toxic") adenoma

Iodine-induced hyperthyroidism

Neonatal thyrotoxicosis associated with maternal Graves disease

- Secondary

TSH-secreting pituitary adenoma (rare)[*]

- **NOT ASSOCIATED WITH HYPERTHYROIDISM**
- Granulomatous (de Quervain) thyroiditis (painful)
- Subacute lymphocytic thyroiditis (painless)
- Struma ovarii (ovarian teratoma with ectopic thyroid)
- Factitious thyrotoxicosis (exogenous thyroxine intake)

Clinical manifestation of thyrotoxicosis:

- Hypermetabolic state induced by excessive amounts of thyroid hormone ,over activity of the sympathetic nervous system:
  - *Constitutional symptoms (weight loss, fever, sweating…)*
  - *Gastrointestinal*
  - *Cardiac*
  - *Neuromuscular*
  - *Ocular*
  - *Thyroid storm (medical emergency)*
  - *Apathetic hyperthyroidism*

Diagnosis of hyperthyroidism:

- **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***
- **Free thyroid hormone assays**
- **Measurement of radioactive iodine uptake by the thyroid gland**

Hypothyroidism

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

- Worldwide, the most common cause of hypothyroidism is dietary deficiency of iodine , while in most developed nations, autoimmune causes predominate

Causes of hypothyroidism

PRIMARY

- Developmental (thyroid dysgenesis: PAX8, FOXE1, TSH receptor mutations)
- Thyroid hormone resistance syndrome (THRB mutations)
- Postablative Surgery, radioiodine therapy, or external irradiation
- Autoimmune hypothyroidism Hashimoto thyroiditis[*]
- Iodine deficiency[*]
- Drugs (lithium, iodides, p-aminosalicylic acid)[*]
- Congenital biosynthetic defect (dyshormonogenetic goiter)[*]

SECONDARY (CENTRAL)

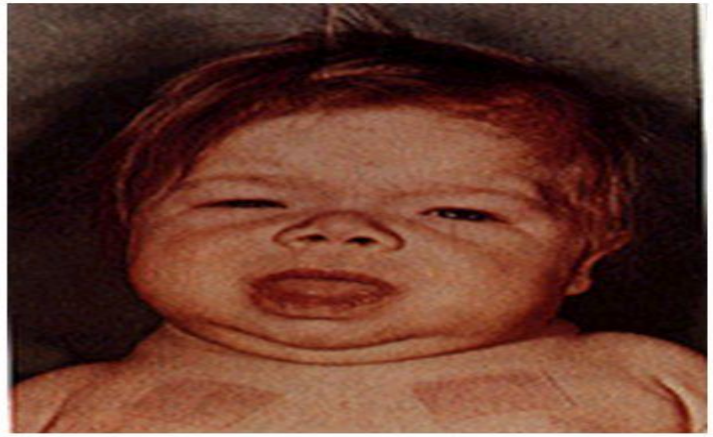
- Pituitary failure
- Hypothalamic failure (rare)

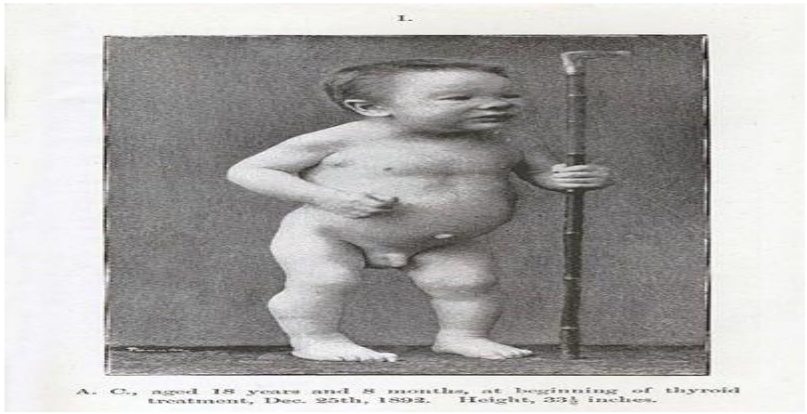
Clinical manifestations of hypothyroidism

- **Cretinism** refers to hypothyroidism developing in infancy or early childhood: Endemic cretinism, sporadic cretinism

Clinical features of cretinism include impaired development of the skeletal system and central nervous system, with severe mental retardation, short stature, coarse facial features, a protruding tongue, and umbilical hernia.

CRETINISM





A. C., aged 18 years and 8 months, at beginning of thyroid treatment, Dec. 25th, 1893. Height, 33½ inches.

Clinical manifestations of hypothyroidism

- Hypothyroidism developing in older children and adults results in a condition known as *myxedema*
- Manifestations of myxedema include
- generalized apathy and mental sluggishness that in the early stages of disease may mimic depression.
- Cold intolerance, obesity.
- Broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice. Constipation. Pericardial effusions are common
- In later stages, the heart is enlarged, and heart failure may supervene.

Laboratory evaluation

- **Measurement of serum TSH is the most sensitive screening test for this disorder**
- The serum TSH is increased in primary hypothyroidism
- Serum T_4 is decreased in patients with hypothyroidism of any origin.

Thyroiditis

Clinically significant types of thyroiditis:

(1)Hashimoto thyroiditis (or chronic lymphocytic thyroiditis)

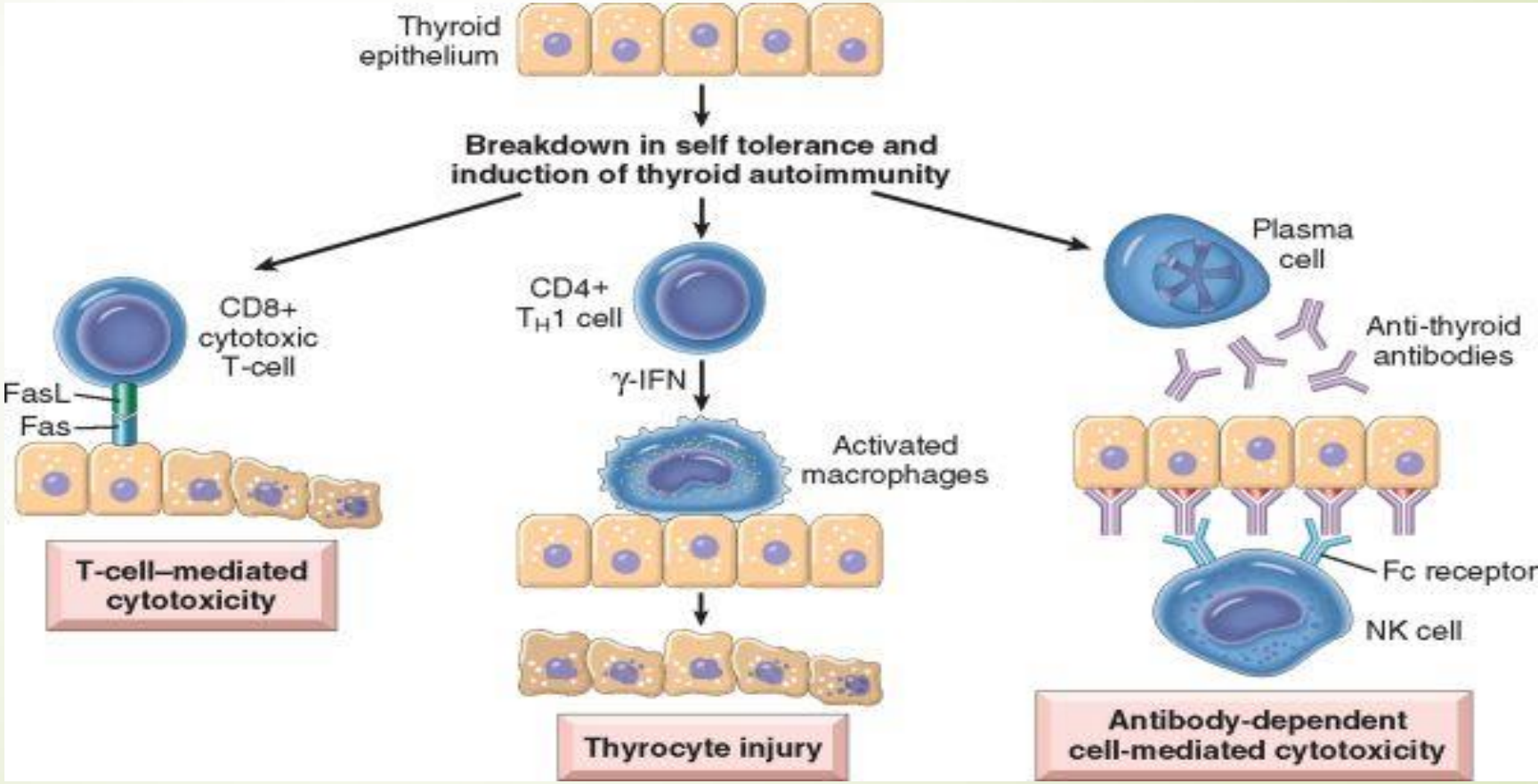
(2) Subacute (granulomatous) thyroiditis, (de Quervain).

Chronic Lymphocytic (Hashimoto) Thyroiditis

- *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, with female predominance in a ratio of 10:1 to 20:1.

Hashimoto Thyroiditis :Pathogenesis

Hashimoto thyroiditis is caused by a breakdown in **self-tolerance** to thyroid autoantigens. Thus, circulating autoantibodies against thyroid antigens are present in the vast majority of patients



Chronic Lymphocytic (Hashimoto) Thyroiditis

- A significant genetic component.
- Increased susceptibility to Hashimoto thyroiditis is associated with polymorphisms in multiple immune regulation–associated genes, the most significant of which is the linkage to **cytotoxic T lymphocyte–associated antigen-4**gene (*CTLA4*)

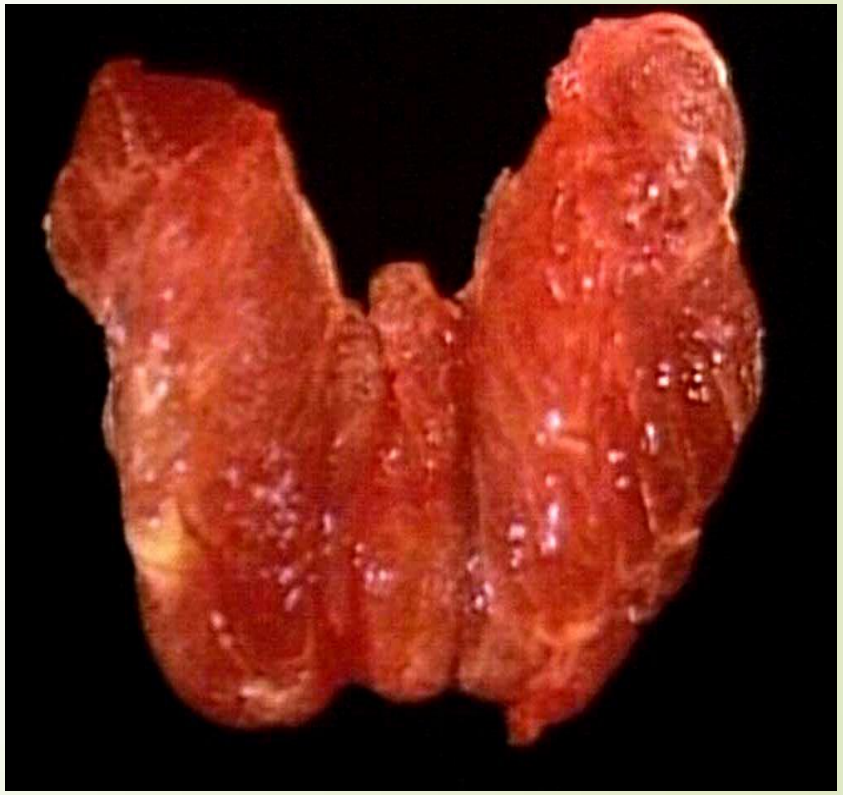
Hashimoto Thyroiditis: clinical features

- *Painless enlargement of the thyroid, usually associated with some degree of hypothyroidism*
- It *may be preceded by transient thyrotoxicosis* caused by disruption of thyroid follicles, with secondary release of thyroid hormones (*hashitoxicosis*).
- As hypothyroidism supervenes, T_4 and T_3 levels progressively fall, accompanied by a compensatory increase in TSH.
- Patients with Hashimoto thyroiditis often have *other autoimmune diseases* and are at *increased risk for the development of B cell non-Hodgkin lymphomas*

Hashimoto Thyroiditis Morphology

- Diffuse and symmetrical enlargement

- The cut surface is pale and gray-tan in appearance, and the tissue is firm and somewhat friable.



Hashimoto Thyroiditis :Morphology

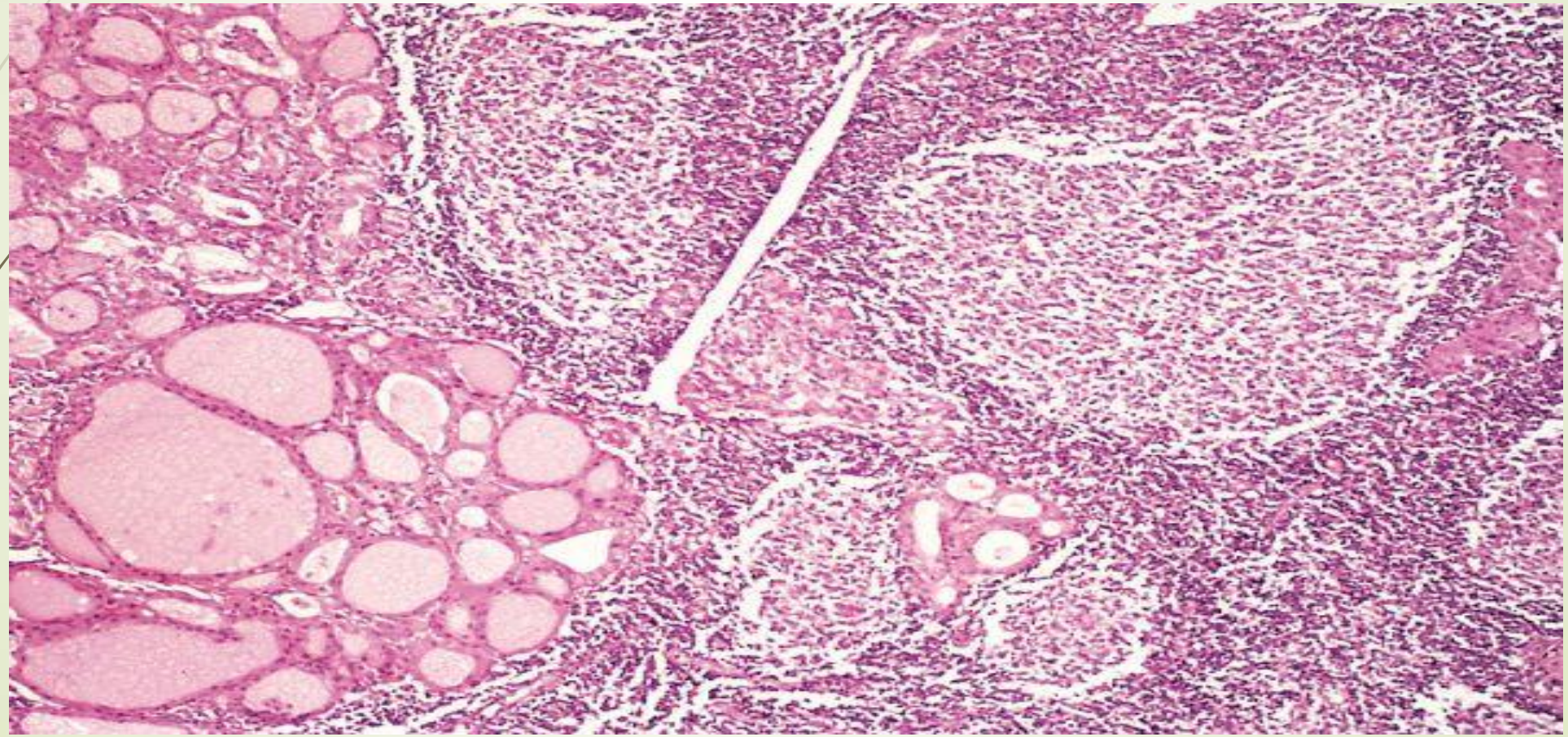
1)infiltration of the parenchyma by a **mononuclear inflammatory infiltrate** containing small lymphocytes, plasma cells, and well-developed **germinal centers.**

2) 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,** or **oxyphil, cells.**

3) Interstitial connective tissue is increased and may be abundant. Less commonly, the thyroid is small and atrophic as a result of more extensive fibrosis **(fibrosing variant)**

Unlike in Reidel thyroiditis, the fibrosis does not extend beyond the capsule of the gland.

Hashimoto Thyroiditis Morphology



Subacute Granulomatous (de Quervain) Thyroiditis

- Subacute thyroiditis is believed to be caused by a viral infection or an inflammatory process triggered by viral infections.
- A majority of patients have a history of an upper respiratory infection just before the onset of thyroiditis.
- The onset of this form of thyroiditis often is acute, characterized by *pain* in the neck (particularly with swallowing), fever, malaise, and variable enlargement of the thyroid.

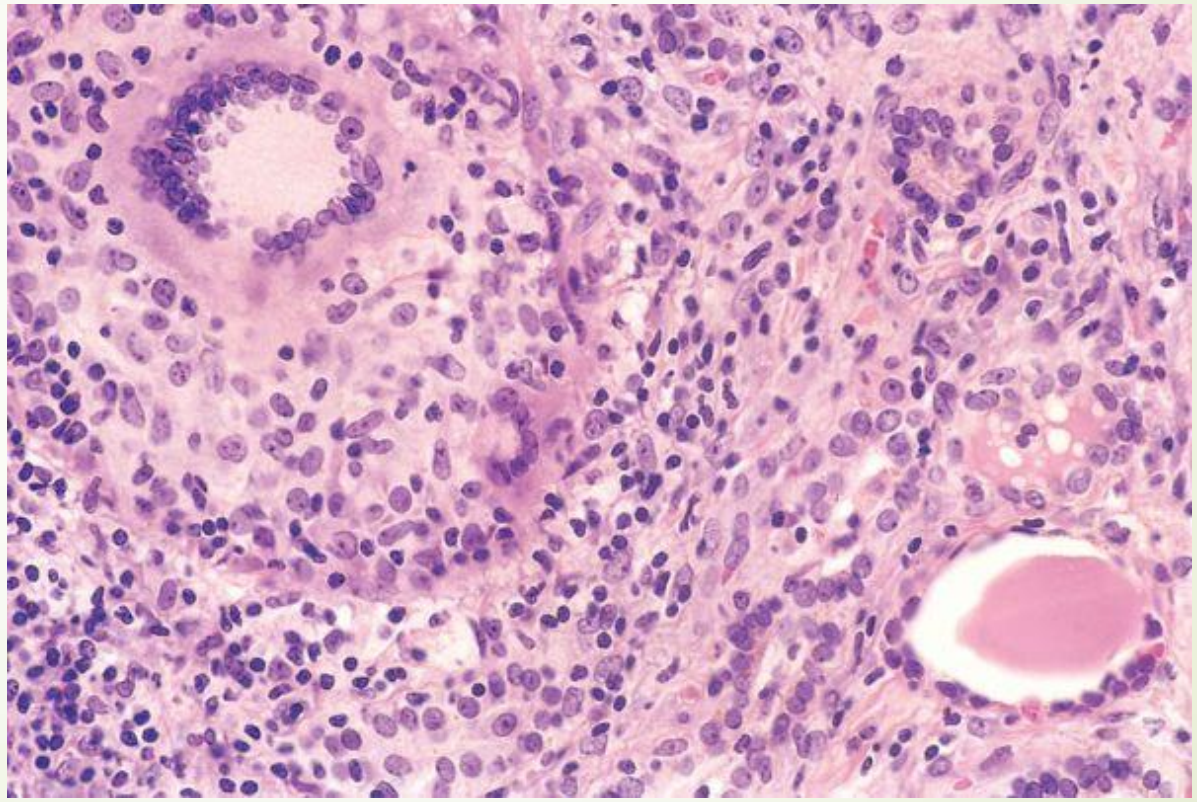
Subacute Granulomatous (de Quervain) Thyroiditis

- Transient hyperthyroidism may occur, as in other cases of thyroiditis, as a result of disruption of thyroid follicles .
- The leukocyte count and erythrocyte sedimentation rates are 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.

Subacute Granulomatous (de Quervain) Thyroiditis: Morphology

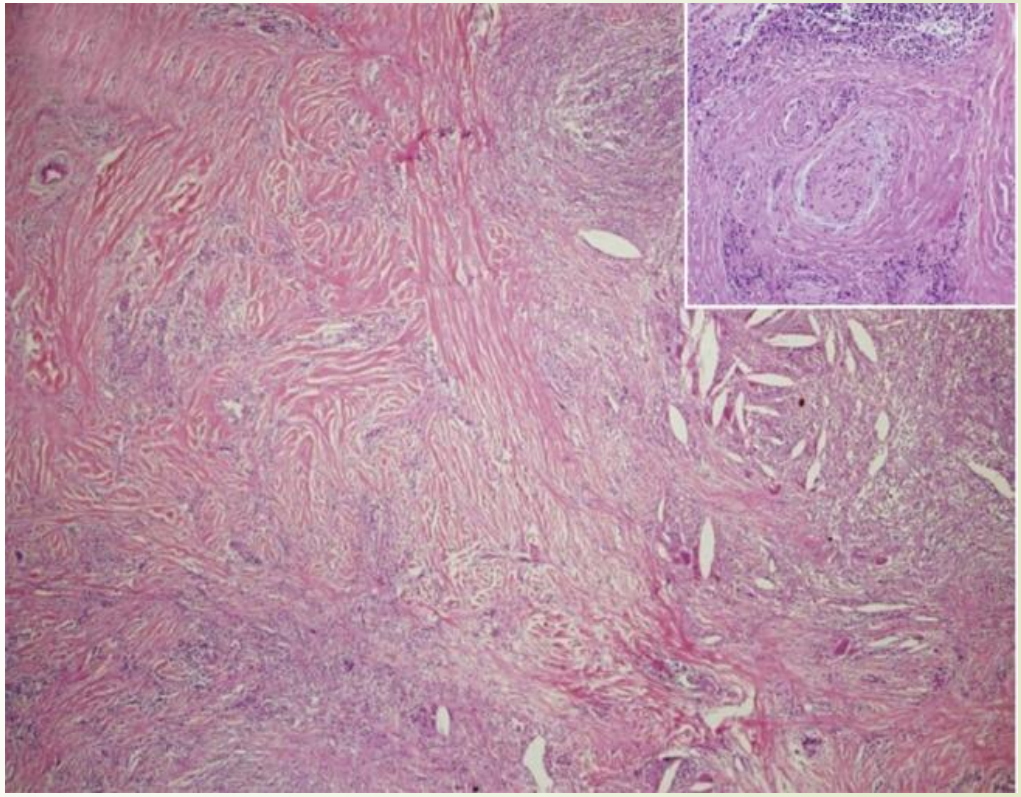
- The gland is firm, with an intact capsule, and may be unilaterally or bilaterally enlarged.
- Histologic examination reveals disruption of thyroid follicles, with extravasation of colloid leading to a polymorphonuclear infiltrate, which is replaced over time by lymphocytes, plasma cells, and macrophages.
- The extravasated colloid provokes an exuberant granulomatous reaction with giant cells.
- Healing occurs by resolution of inflammation and fibrosis

Subacute Granulomatous (de Quervain) Thyroiditis: Morphology



Riedel thyroiditis

- Rare disorder of unknown etiology, is characterized by extensive fibrosis involving the thyroid and contiguous neck structures.
- Clinical evaluation demonstrates a hard and fixed thyroid mass, simulating a thyroid neoplasm.



Graves disease

- *Graves disease is the most common cause of endogenous hyperthyroidism*. It is characterized by a triad of manifestations:

1-Thyrotoxicosis, caused by a diffusely enlarged, hyperfunctional thyroid, is present in all cases.

2-An infiltrative *ophthalmopathy* with resultant exophthalmos is noted in as many as 40% of patients.

3-A localized, infiltrative *dermopathy* (sometimes designated *pretibial myxedema*) is seen in a minority of cases.

Graves disease

- Graves disease has a peak incidence between the ages of 20 and 40, with *women being affected up to seven times more commonly than men*.
- Genetic factors are important in the causation of Graves disease

Graves disease: Pathogenesis

- **Graves disease is characterized by a breakdown in self-tolerance to thyroid autoantigens, of which the most important is the TSH receptor.**The result is the production of multiple autoantibodies, including:
- **Thyroid-stimulating immunoglobulin:** An IgG antibody that binds to the TSH receptor and mimics the action of TSH, relatively specific for Graves disease.
- **Thyroid growth-stimulating immunoglobulins:** Also directed against the TSH receptor.
- **TSH-binding inhibitor immunoglobulins:** These anti-TSH receptor antibodies prevent TSH from binding to its receptor on thyroid epithelial cells and in so doing may actually **inhibit** thyroid cell function.
- The coexistence of stimulating *and* inhibiting immunoglobulins in the serum of the same patient is not unusual—a finding that may explain why some patients with Graves disease spontaneously develop episodes of hypothyroidism.

- In Graves ophthalmopathy, a result of several causes

(1) marked infiltration of the retroorbital space by mononuclear cells

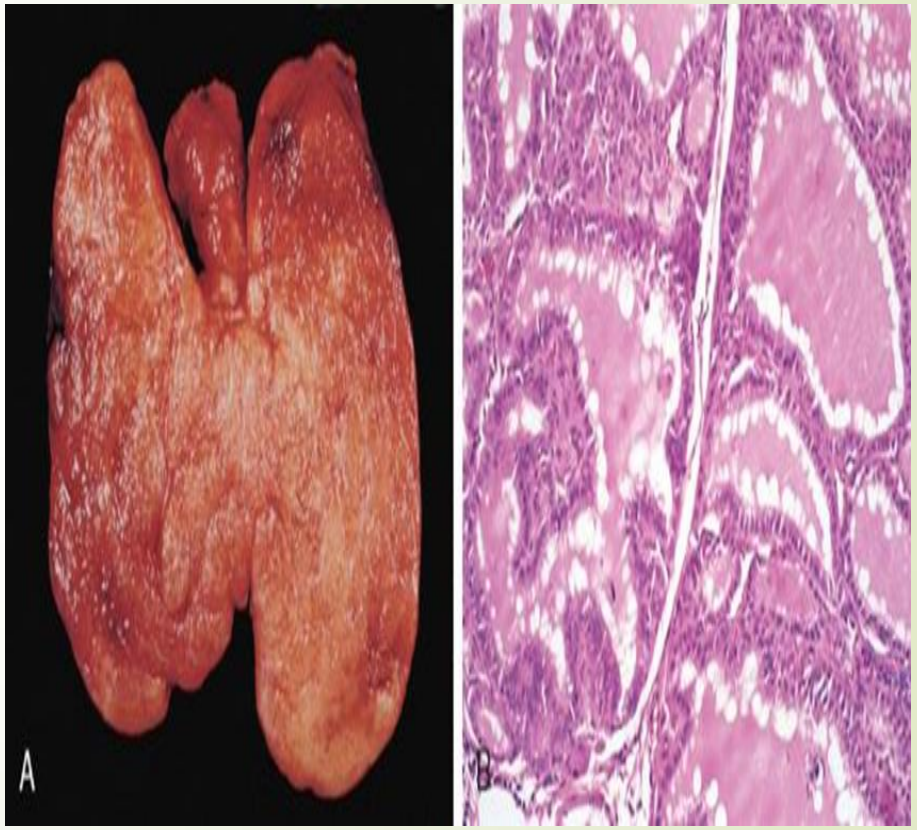
(2) inflammatory edema and swelling of extraocular muscles

(3) accumulation of extracellular matrix components

(4) increased numbers of adipocytes

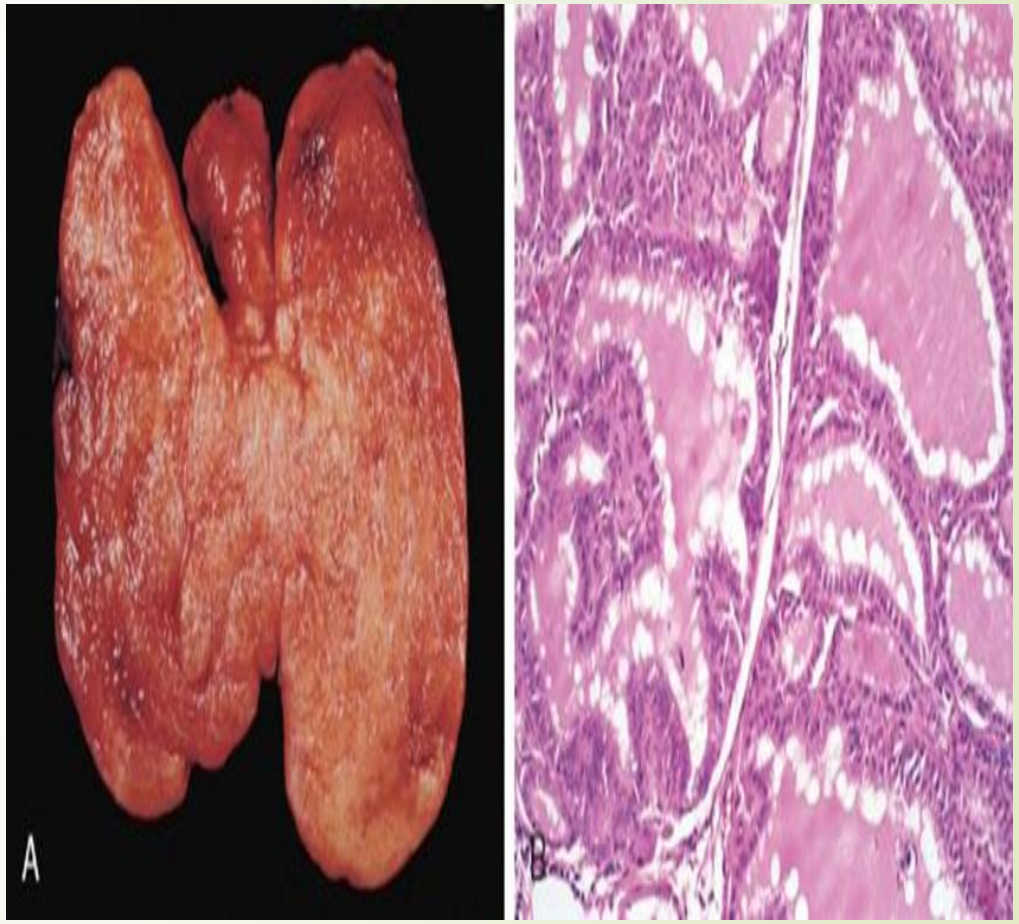
Graves disease: morphology

- The thyroid gland is enlarged (usually symmetrically) due to **diffuse hypertrophy and hyperplasia** of thyroid follicular epithelial cells. The gland is usually smooth and soft, and its capsule is intact.

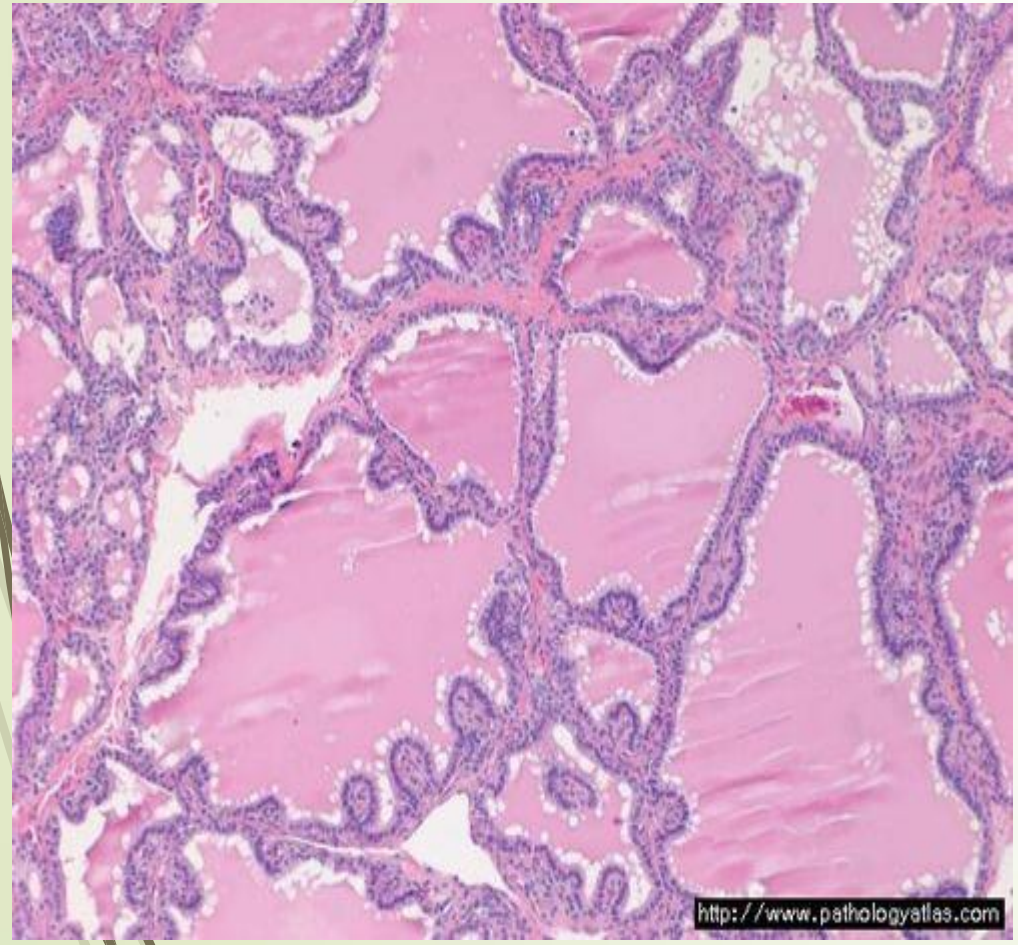


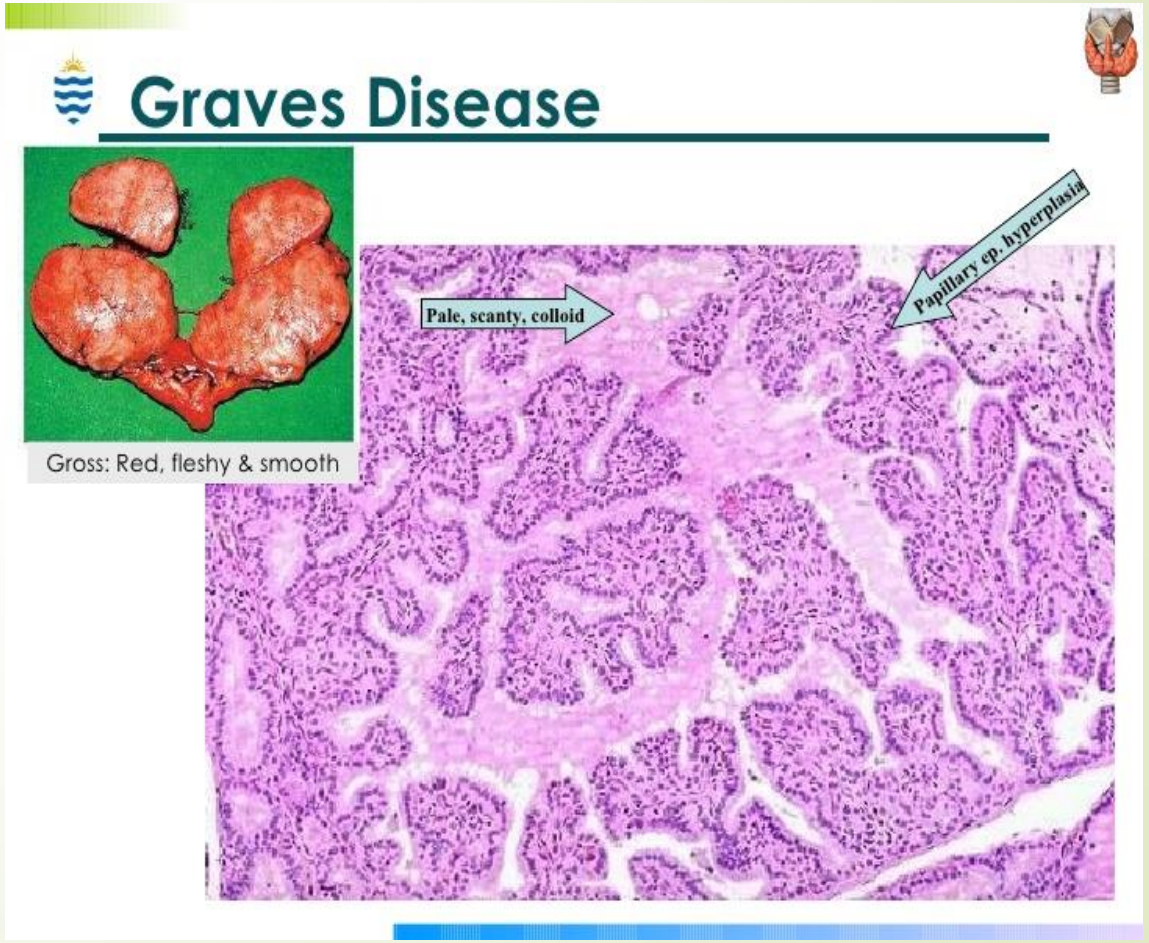
Graves disease: morphology

- On microscopic examination, the follicular epithelial cells in untreated cases are tall, columnar, and more crowded than usual. This crowding often results in the formation of small papillae. Such papillae lack fibrovascular cores, in contrast with those of papillary carcinoma.
- The colloid within the follicular lumen is pale, with scalloped margins.
- Lymphoid infiltrates, are present throughout the interstitium; germinal centers are common.



Graves disease: morphology





- Laboratory findings in Graves disease include elevated serum free T4 and T3 and depressed serum TSH.
- Because of ongoing stimulation of the thyroid follicles by TSIs, radioactive iodine uptake is increased, and radioiodine scans show a diffuse uptake of iodine

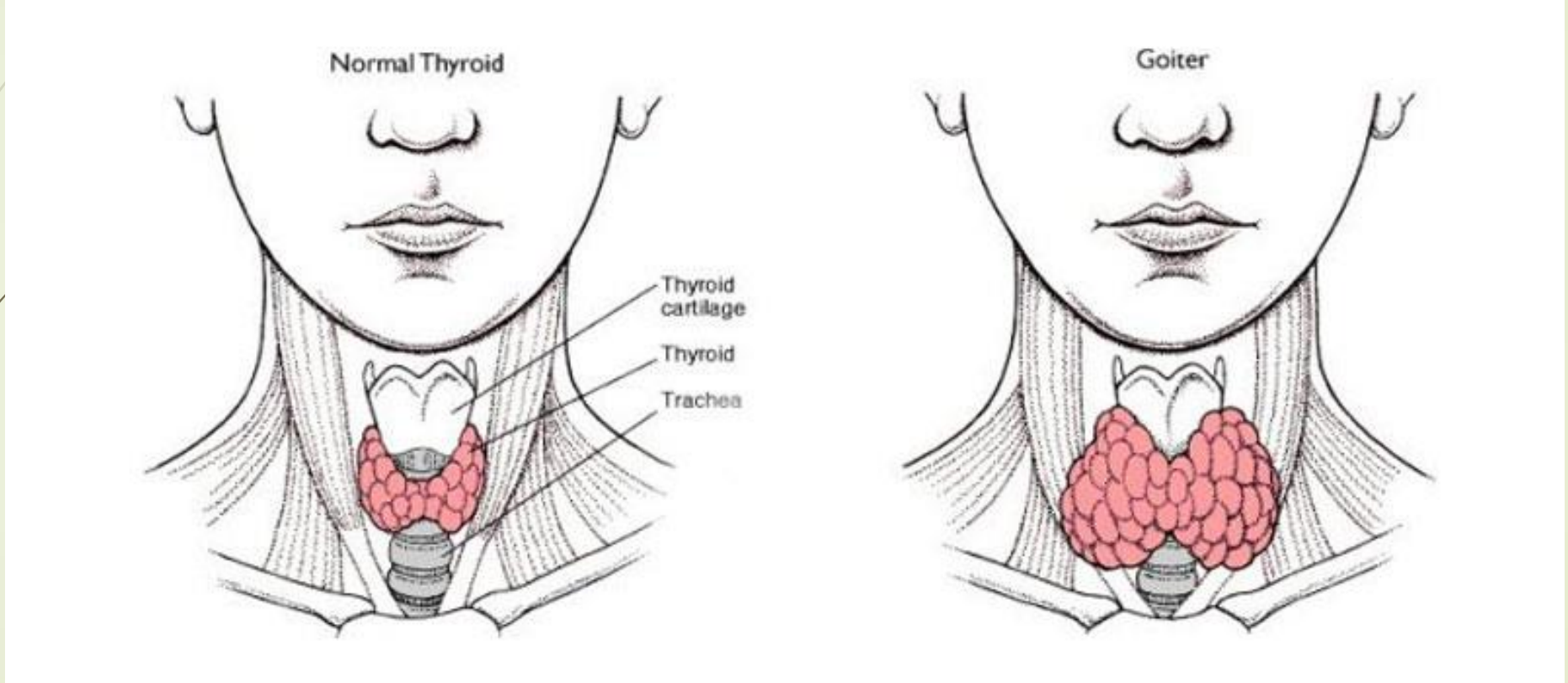
DIFFUSE AND MULTINODULAR GOITER

- Goiter: Enlargement of the thyroid, is the most common manifestation of thyroid disease.
- *They reflect impaired synthesis of thyroid hormone,* most often caused by dietary iodine deficiency
- Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH, causes hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, gross enlargement of the thyroid gland.
- The compensatory increase in functional mass of the gland is enough to overcome the hormone deficiency, ensuring a *euthyroid* metabolic state in the vast majority of affected persons.
- If the underlying disorder is sufficiently the compensatory responses may be inadequate to overcome the impairment in hormone synthesis, resulting in *goitrous hypothyroidism*

- Goiters can be endemic or sporadic.
- diffuse, symmetric enlargement of the gland **(diffuse goiter):** The follicles are lined by crowded columnar cells, which may pile up and form projections
- colloid-rich gland **(colloid goiter)**
- All long-standing diffuse goiters convert into **multinodular goiters**.
- Multinodular goiters typically are hormonally silent, although a minority (approximately 10% over 10 years) can manifest with thyrotoxicosis secondary to the development of **autonomous** nodules that produce thyroid hormone independent of TSH stimulation. This condition, known as toxic multinodular goiter or **Plummer syndrome.**

Goiter can arise in the following settings:

- 1-Endemic goiter due to iodine deficiency
- 2-ingestion of certain food e.g. cabbage
- 3-Rare inherited defect in thyroid hormone synthesis
- 4-Drug induced


Normal Thyroid
Thyroid cartilage
Thyroid
Trachea
Goiter

Multinodular goiter

- Multinodular goiters are multilobulate, asymmetrically enlarged glands, which may attain massive size.
- On cut surface, irregular nodules containing variable amounts of brown, gelatinous colloid are evident . Older lesions often show areas of fibrosis, hemorrhage, calcification, and cystic change.
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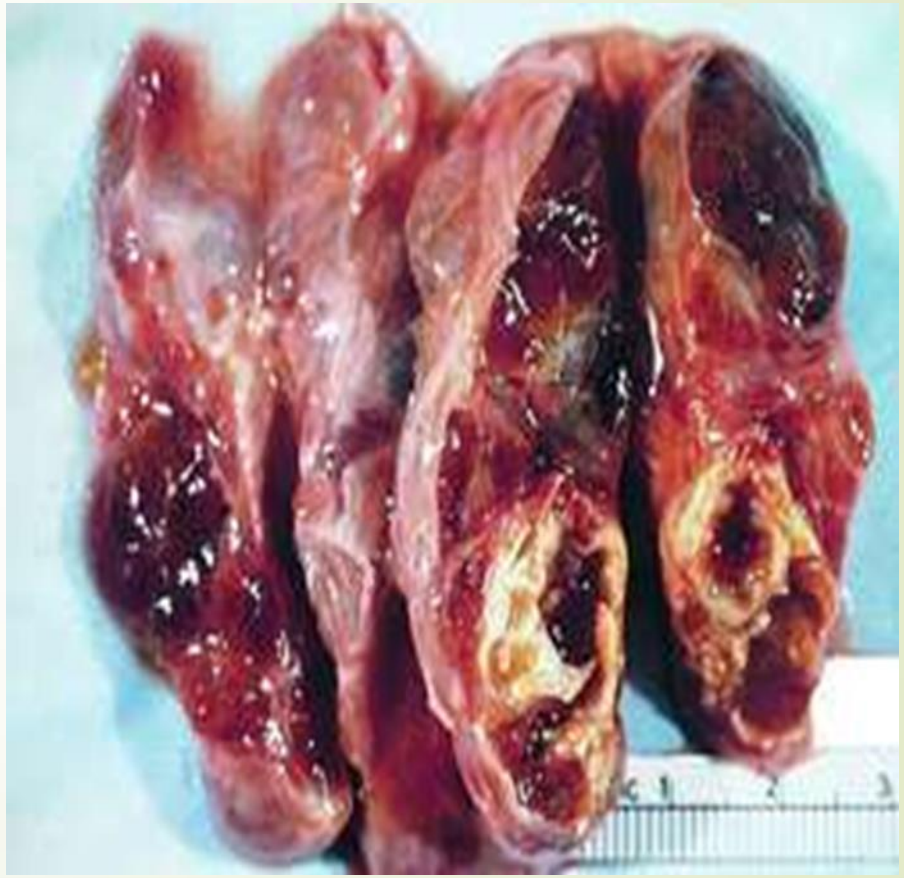
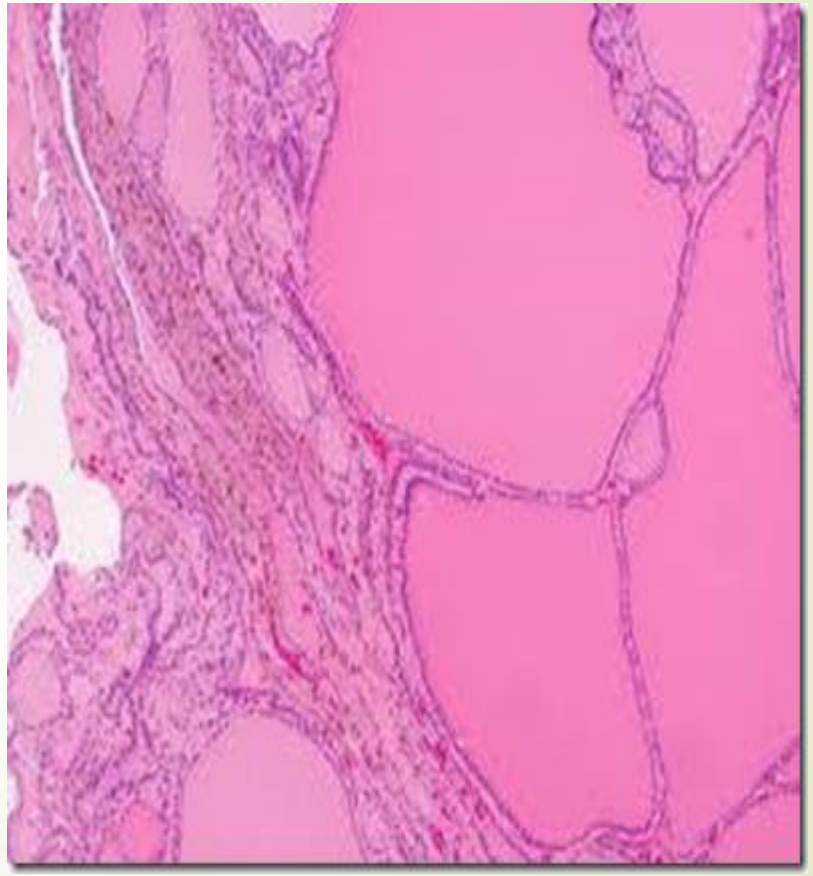


Multinodular Goiter

- The microscopic appearance includes colloid-rich follicles lined by flattened, inactive epithelium and areas of follicular epithelial hypertrophy and hyperplasia



Clinical features

- The dominant clinical features of goiter are those caused by the mass effects of the enlarged gland.
- In addition to the obvious cosmetic problem of a large neck mass, goiters also may cause airway obstruction, dysphagia, and compression of large vessels in the neck
- a hyperfunctioning (toxic) nodule may develop within a long-standing goiter, resulting in hyperthyroidism.
- The incidence of malignancy in long-standing multinodular goiters is low (less than 5%) but not zero, and concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (e.g., hoarseness).