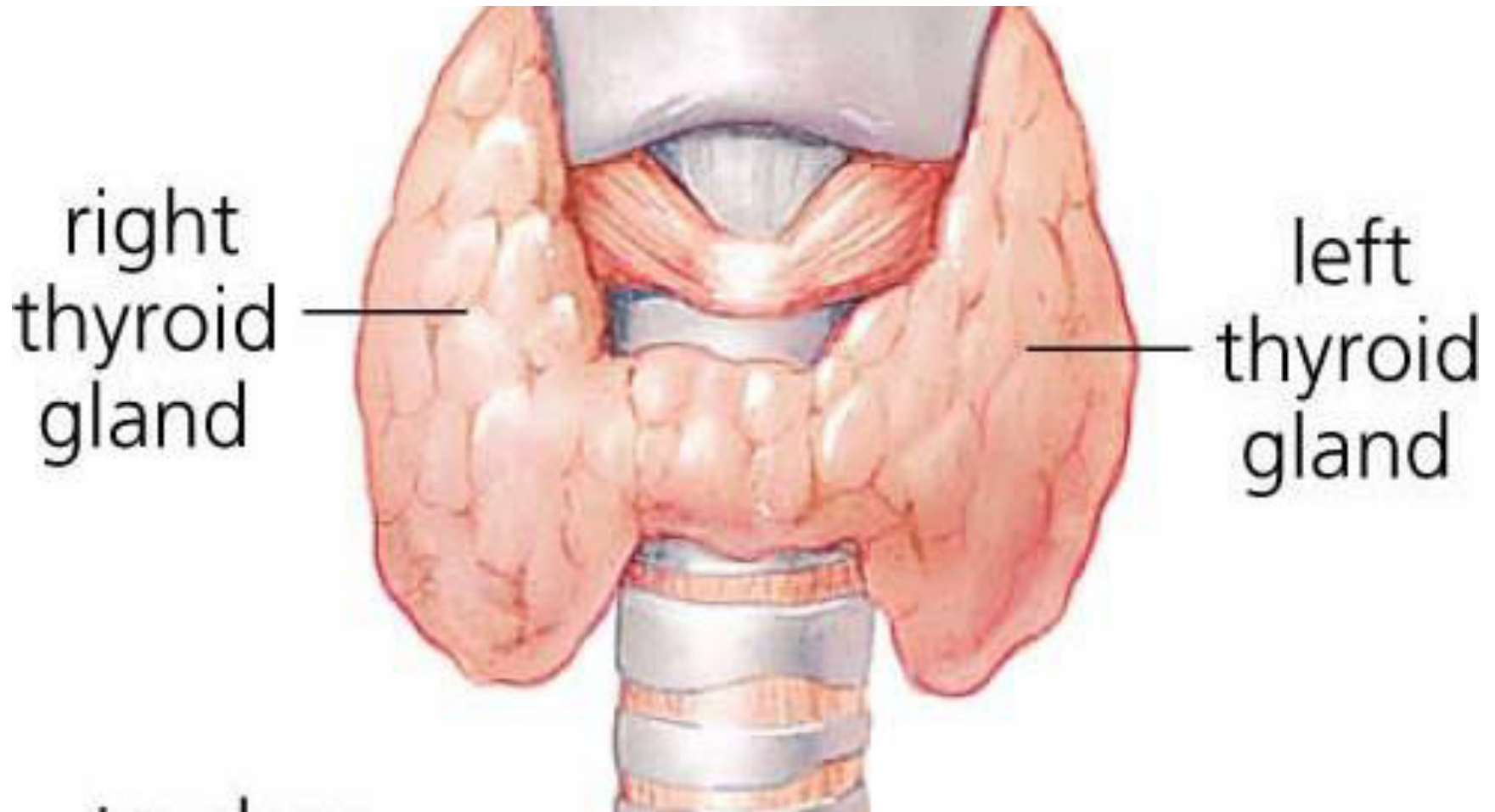


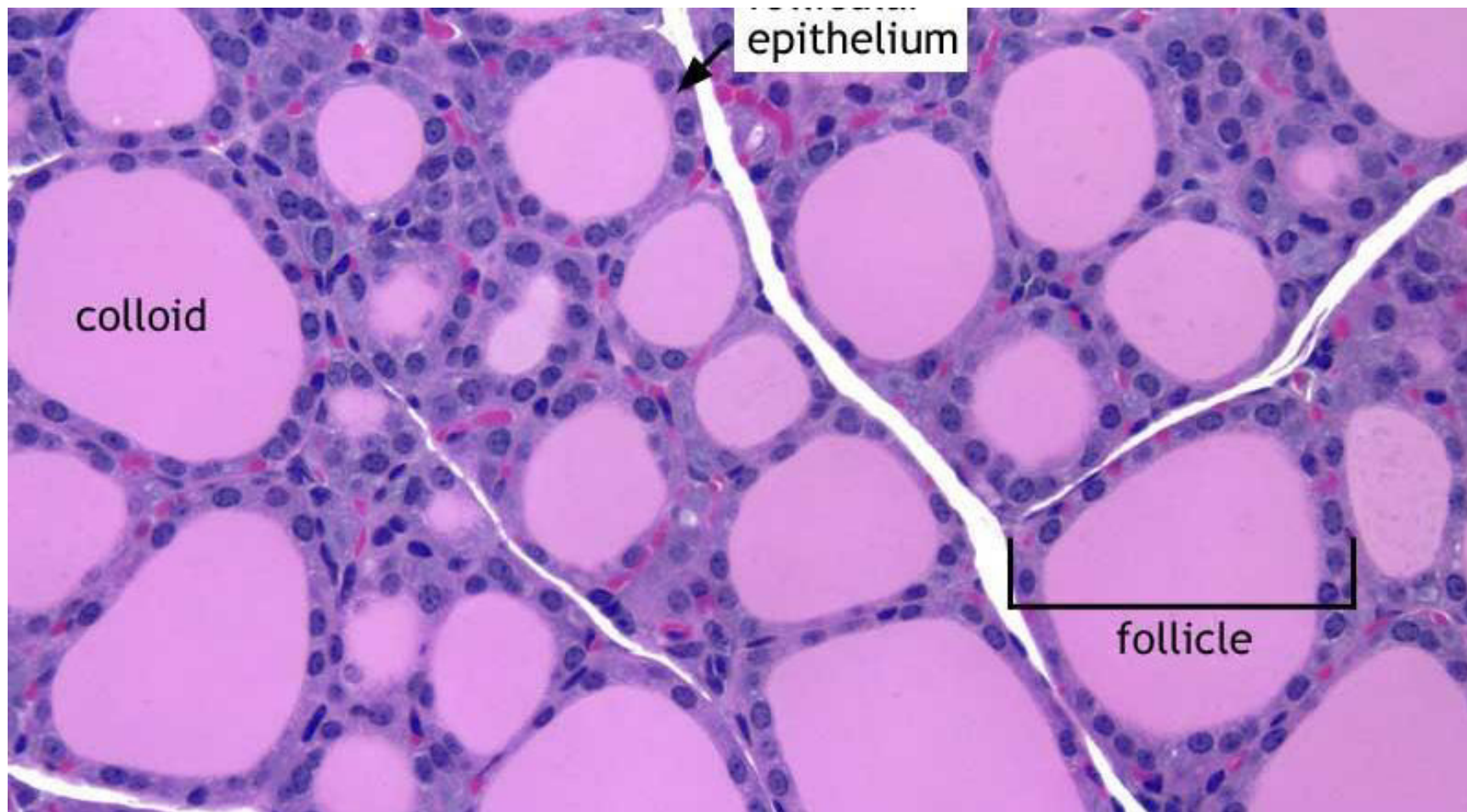
Thyroid gland 1 & 2

Dr Heyam Awad

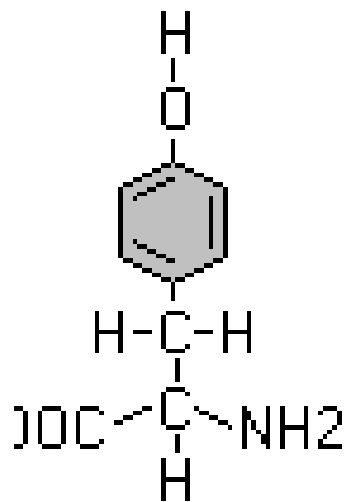
FRCPath

Thyroid gland

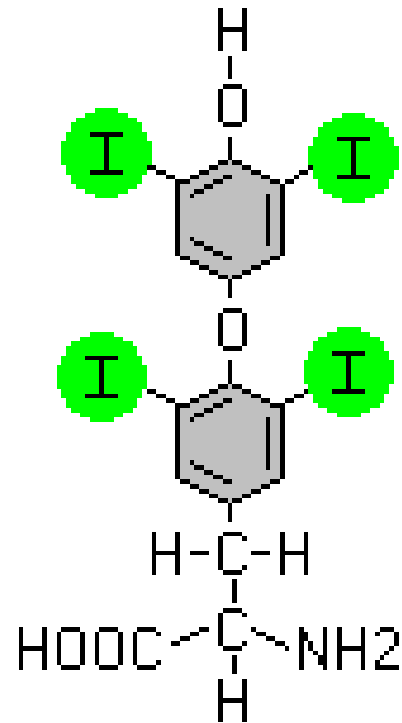




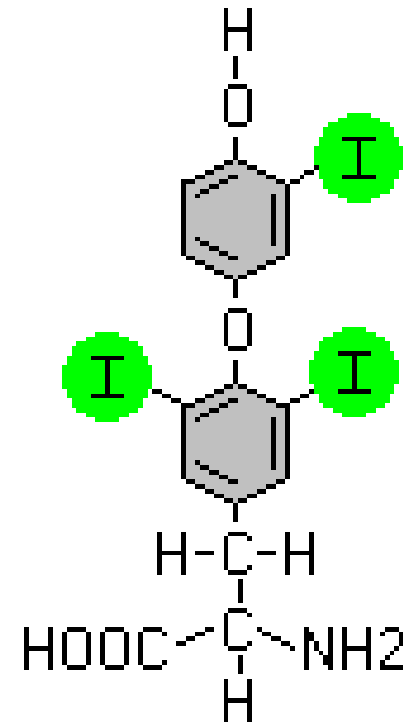
Thyroid hormones



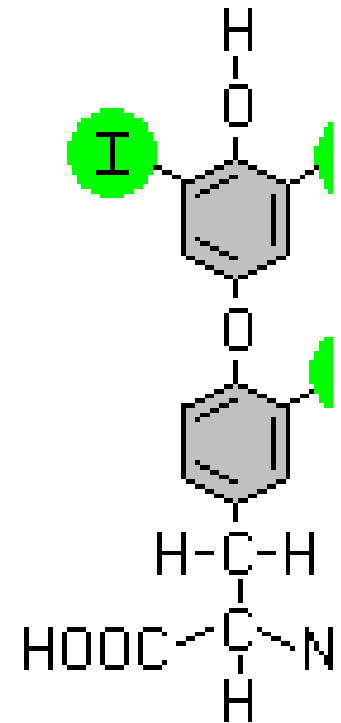
Tyrosine



Thyroxine (T4)

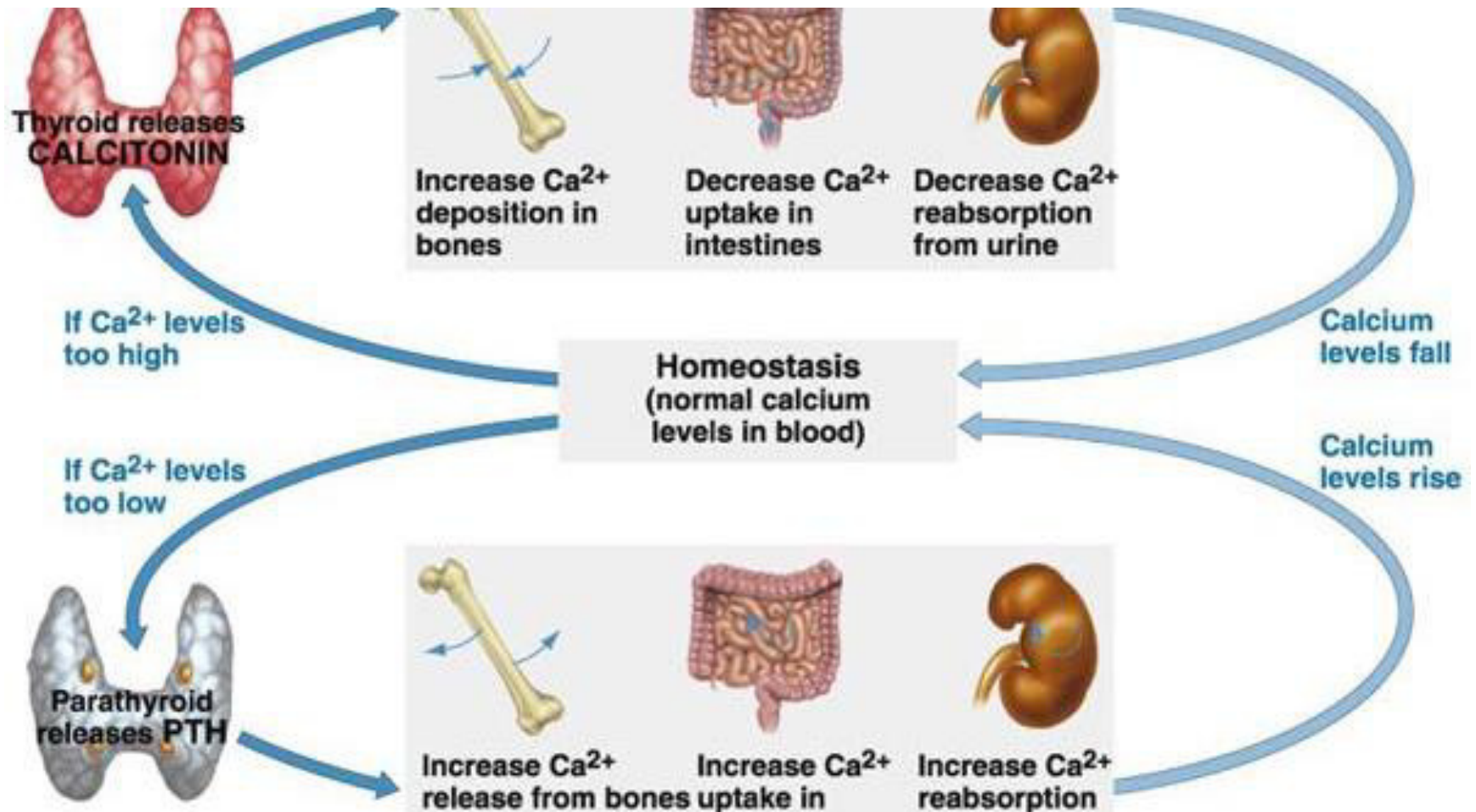


**Triiodothyronine
(T3)**



**"Reverse T3"
(inactive)**

Parafollicular cells



Thyroid diseases

- Hyperthyroidism
- Hypothyroidism
- Thyroiditis
- Graves disease
- Diffuse nontoxic goiter and multinodular goiter
- neoplasms

THYROTOXICOSIS

Associated with hyperthyroidism (Thyroid hyperfunction):

1. **Primary**
 - a. Diffuse toxic hyperplasia (Graves disease)
 - b. Hyperfunctioning (Toxic) multinodular goiter)
 - c. Hyperfunctioning (toxic) adenoma
2. **Secondary** -- TSH-secreting pituitary adenoma (rare)

Thyrotoxicosis not associated with hyperthyroidism is less common

- Excessive release of pre-formed hormone in thyroiditis
- Ectopic secretion of thyroid hormones.

Clinical manifestations of thyrotoxicosis

- a. *Constitutional symptoms* : warm flushed skin, heat intolerance and excessive sweating
 - Weight loss despite increased appetite.
- b. Malabsorption, and diarrhea.
- c. Tachycardia and elderly patients may develop heart failure due to aggravation of pre-existing heart disease
- d. Nervousness, tremor, and irritability

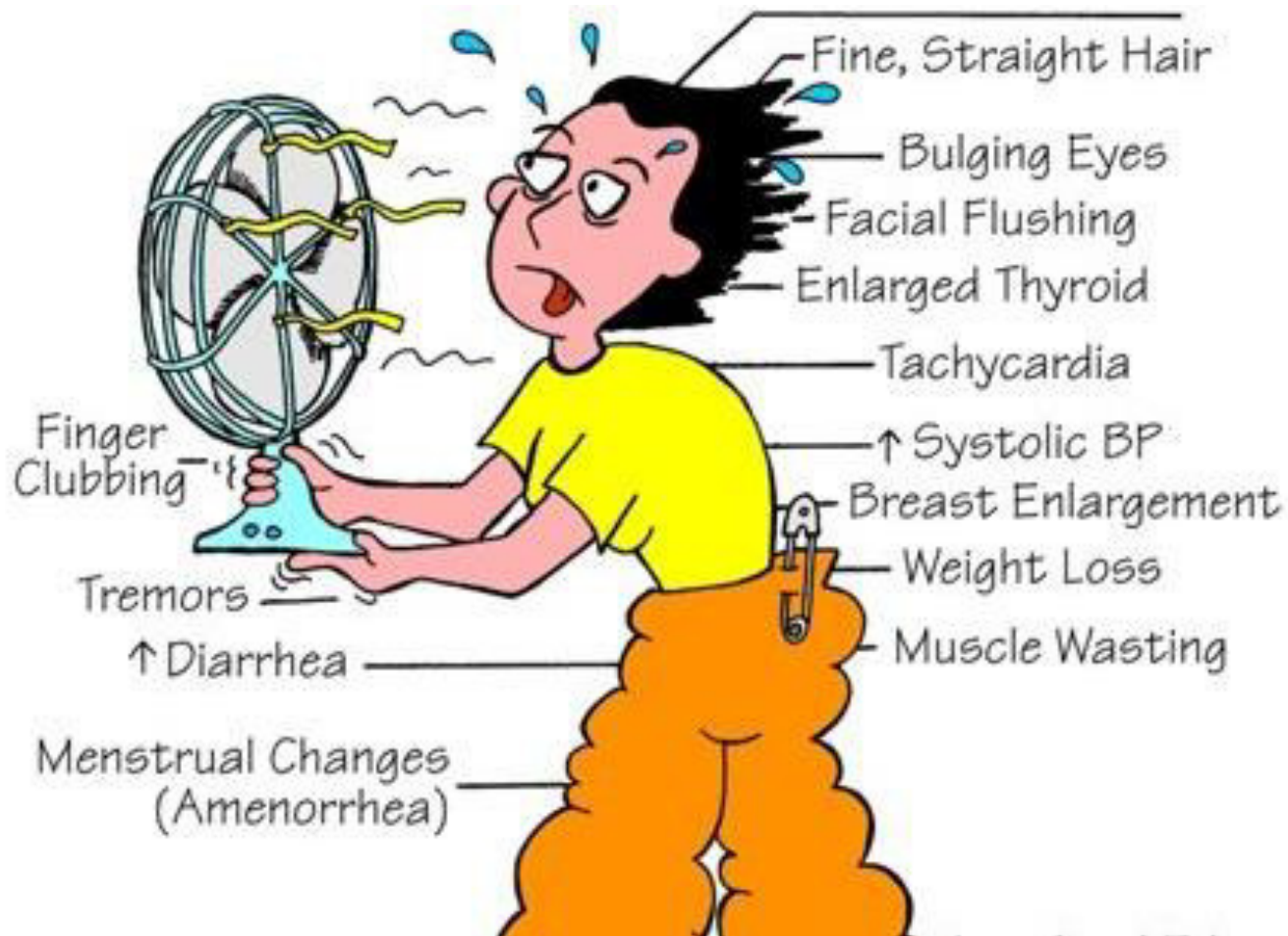
e. A wide, staring gaze and lid lag because of sympathetic overstimulation of the levator palpebrae superioris

Note: True *thyroid ophthalmopathy* associated with proptosis is a feature seen only in Graves disease.

f. 50% develop proximal muscle weakness (*thyroid myopathy*).

g. Thyroid storm : Designates the abrupt onset of severe hyperthyroidism, and this condition occurs most commonly in individuals with Graves disease and it is a medical emergency because significant numbers of untreated **patients die of cardiac arrhythmias**

hyperthyroidism



Lab tests

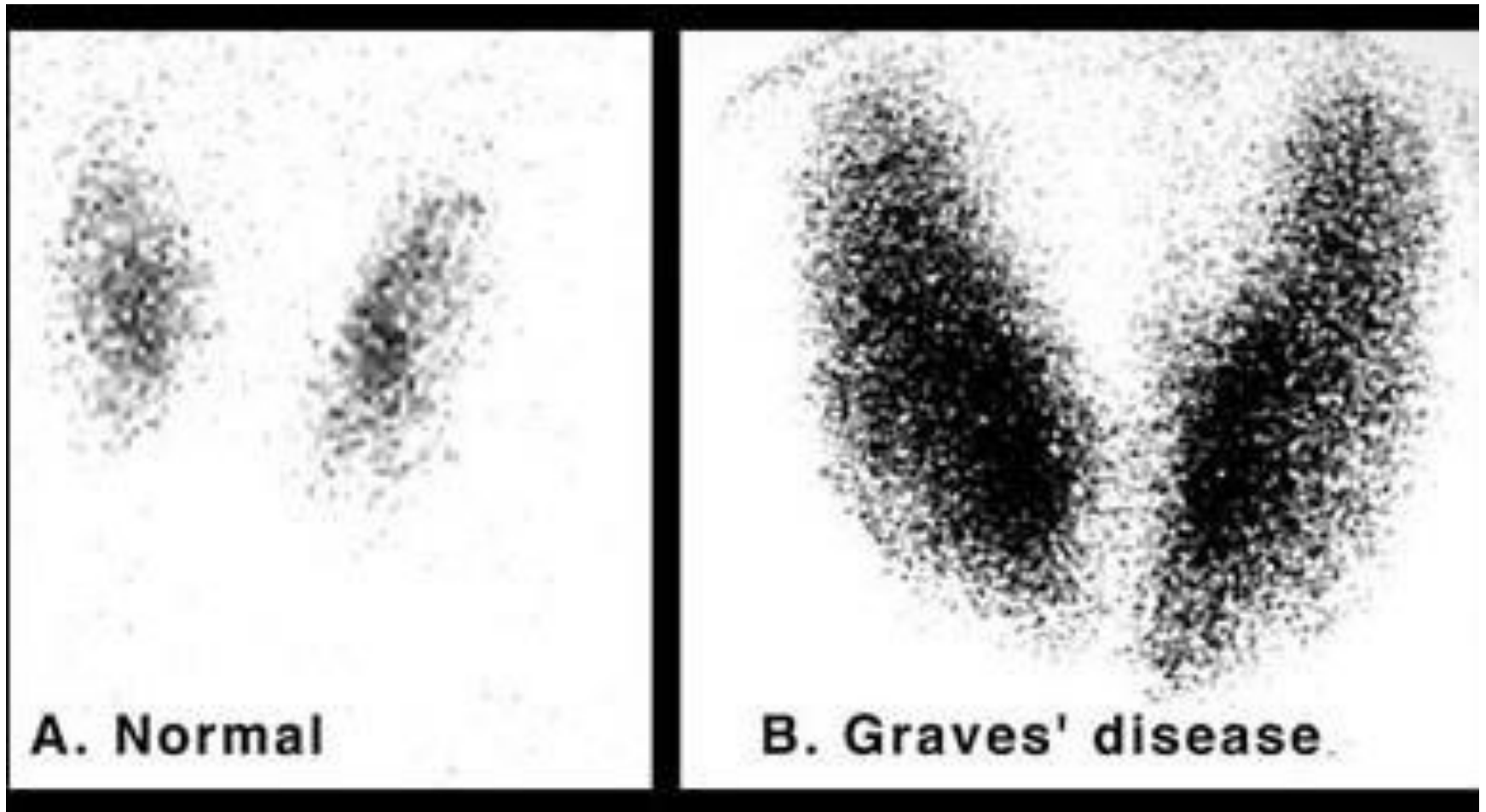
- *The measurement of serum TSH is the most useful single screening test for hyperthyroidism, because TSH levels are decreased even at the earliest stages, when the disease may still be subclinical*

- Once the diagnosis of thyrotoxicosis has been confirmed measurement of **radioactive iodine** uptake by the thyroid gland often is valuable in determining the etiology

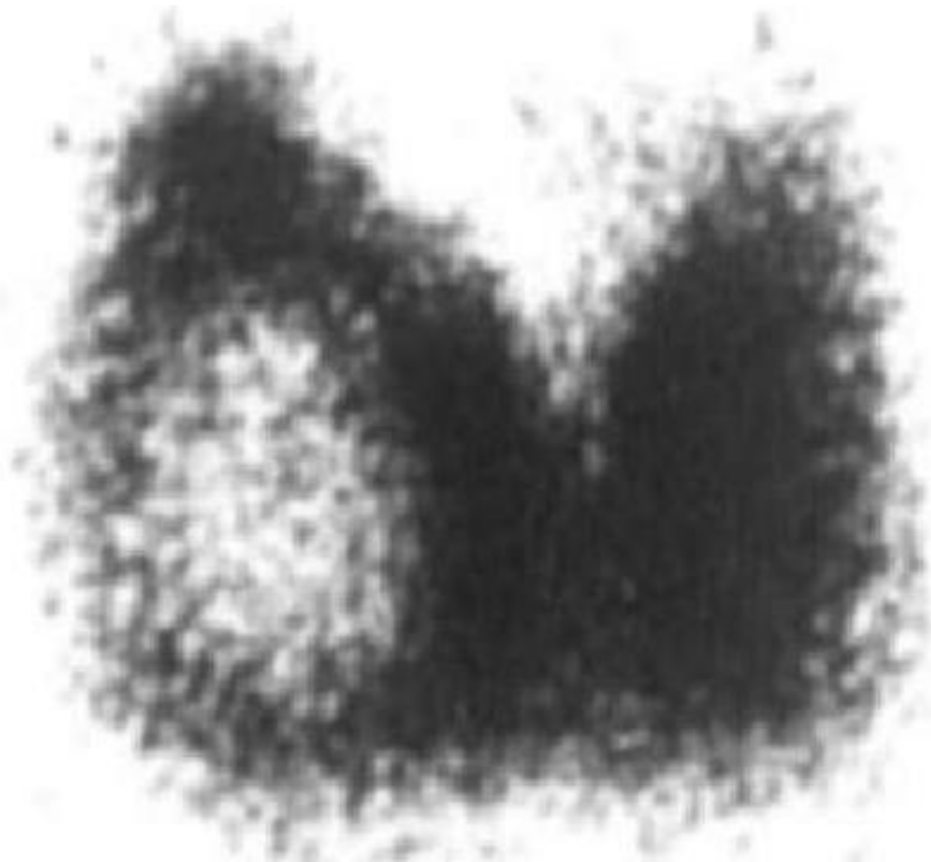
For example, such scans may show :

- a. Diffusely increased (whole-gland) uptake in Graves disease,
- b. Increased uptake in a solitary nodule in toxic adenoma
- c. Or decreased uptake in thyroiditis.

Iodine scans



Cold nodule



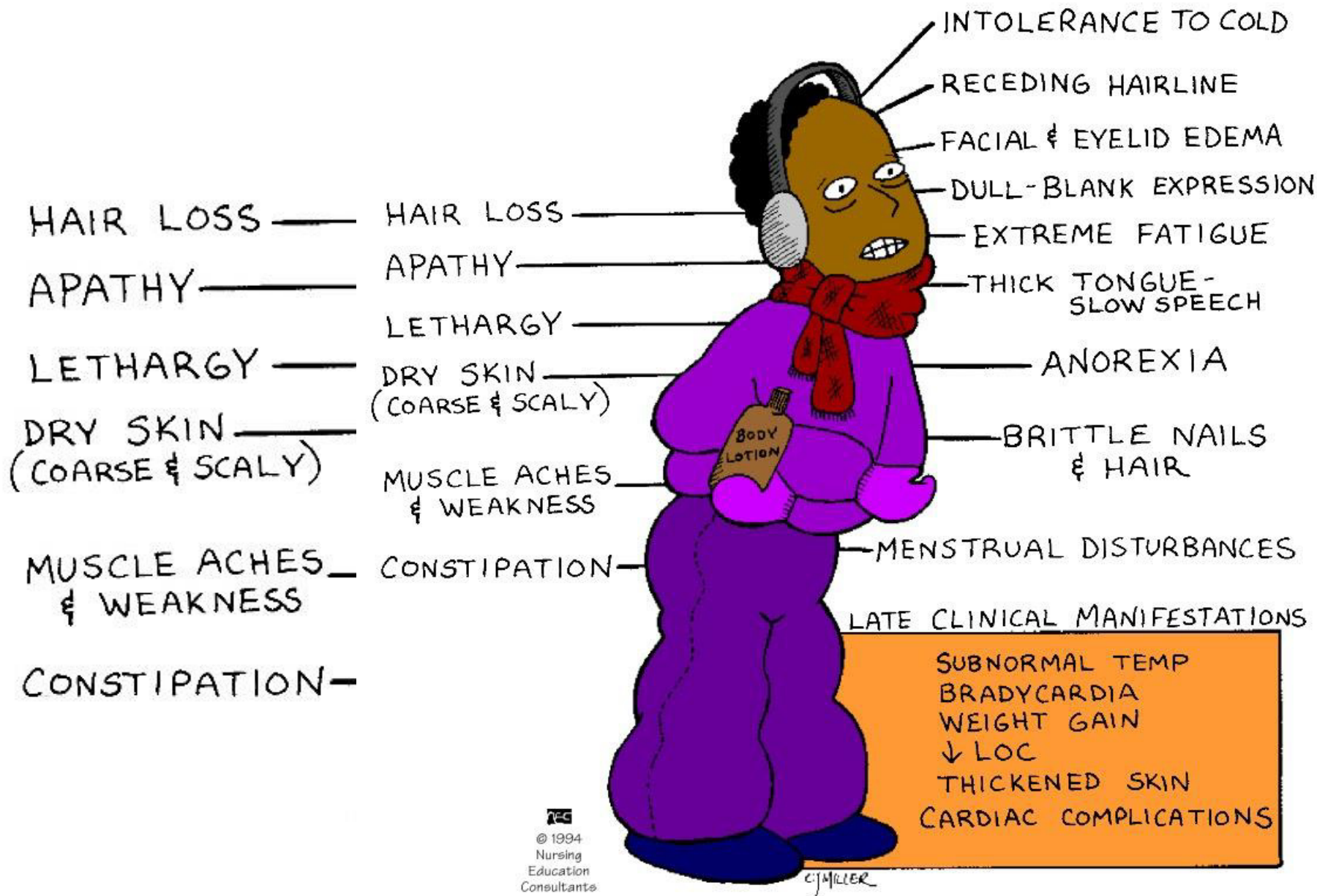
HYPOTHYROIDISM :

Primary causes

- a. - Worldwide, the most common cause of hypothyroidism is dietary deficiency of iodine.
- b. In most developed countries, autoimmune diseases predominate such as Hashimoto thyroiditis
- c. Genetic defects such as *Thyroid dysgenesis* or Congenital biosynthetic defect (dyshormogenic goiter).

Secondary causes: Pituitary or hypothalamic disorder

HYPOTHYROIDISM



hypothyroidism

- Cretinism
- myxedema

Cretinism :Refers to hypothyroidism developing in infancy or early childhood

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

Clinical features of cretinism include:

- Impaired development of skeletal system- short stature,
- Coarse facial features, protruding tongue, umbilical hernia.
- Central nervous system, with mental retardation

Myxedema. or Gull syndrome :

- Hypothyroidism in older children and adults and characterized by:
 - a. Patients are cold intolerant, and often obese.
 - 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.
- 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

Lab tests

Serum TSH is the most sensitive screening test .

- a. The serum TSH is increased in primary hypothyroidism
- b. The TSH is not increased in persons with hypothyroidism caused by primary hypothalamic or pituitary disease.
- c. Serum T_4 is decreased hypothyroidism of any origin.

Thyroiditis

Chronic Lymphocytic (Hashimoto) Thyroiditis

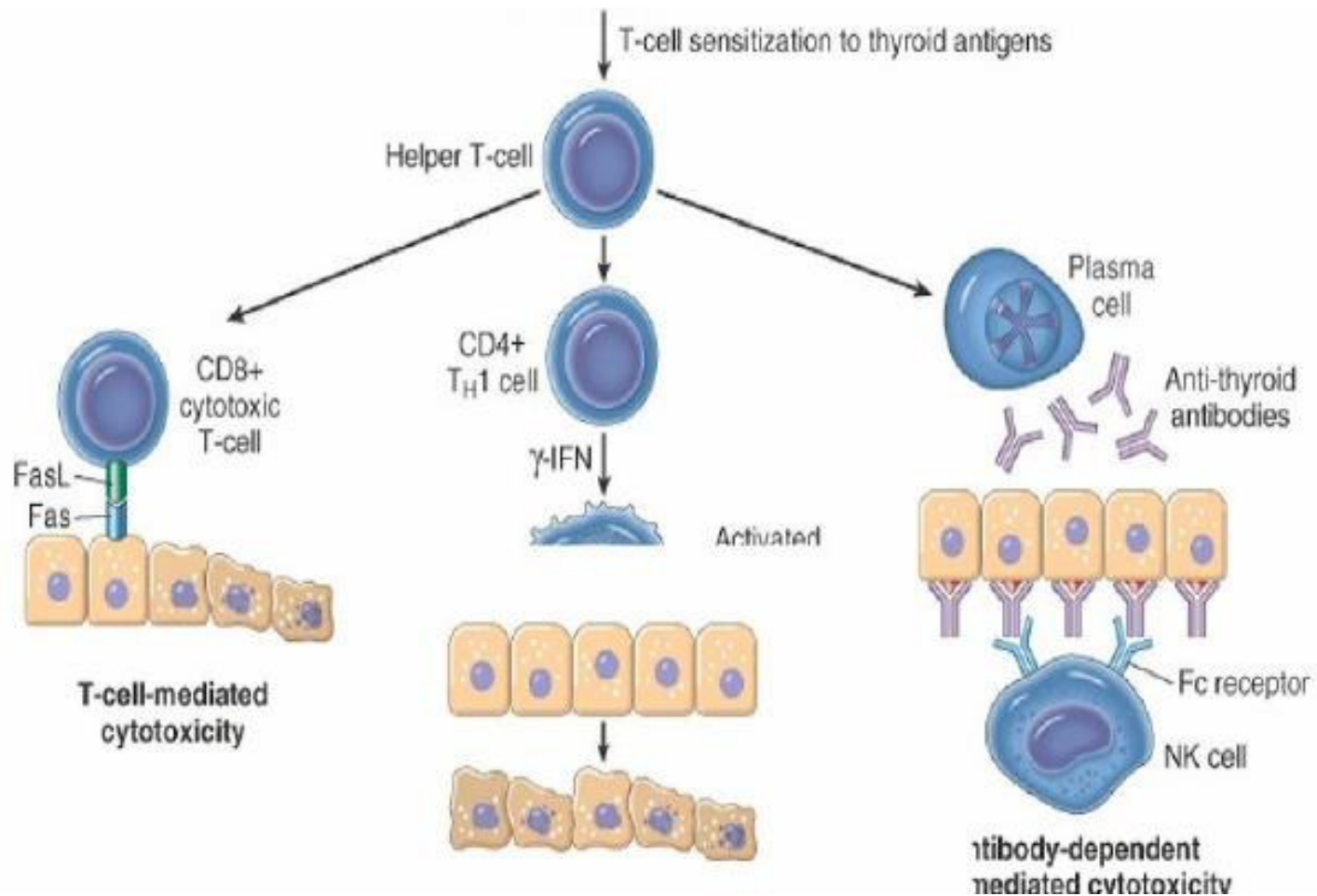
- *Is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient.*
- It is characterized by gradual thyroid failure secondary to autoimmune destruction of the thyroid gland
- It is most prevalent between the ages of 45 and 65 years and is more common in women than in men
- It can occur in children and is a major cause of non-endemic goiter in children

PATHOGENESIS :-

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.**

HASHIMOTO



▪

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 .

- Gross :
 - Diffuse and symmetric enlargement of the thyroid but localized enlargement may be seen in some cases to raise suspicion for neoplasm

Microscopic examination reveals

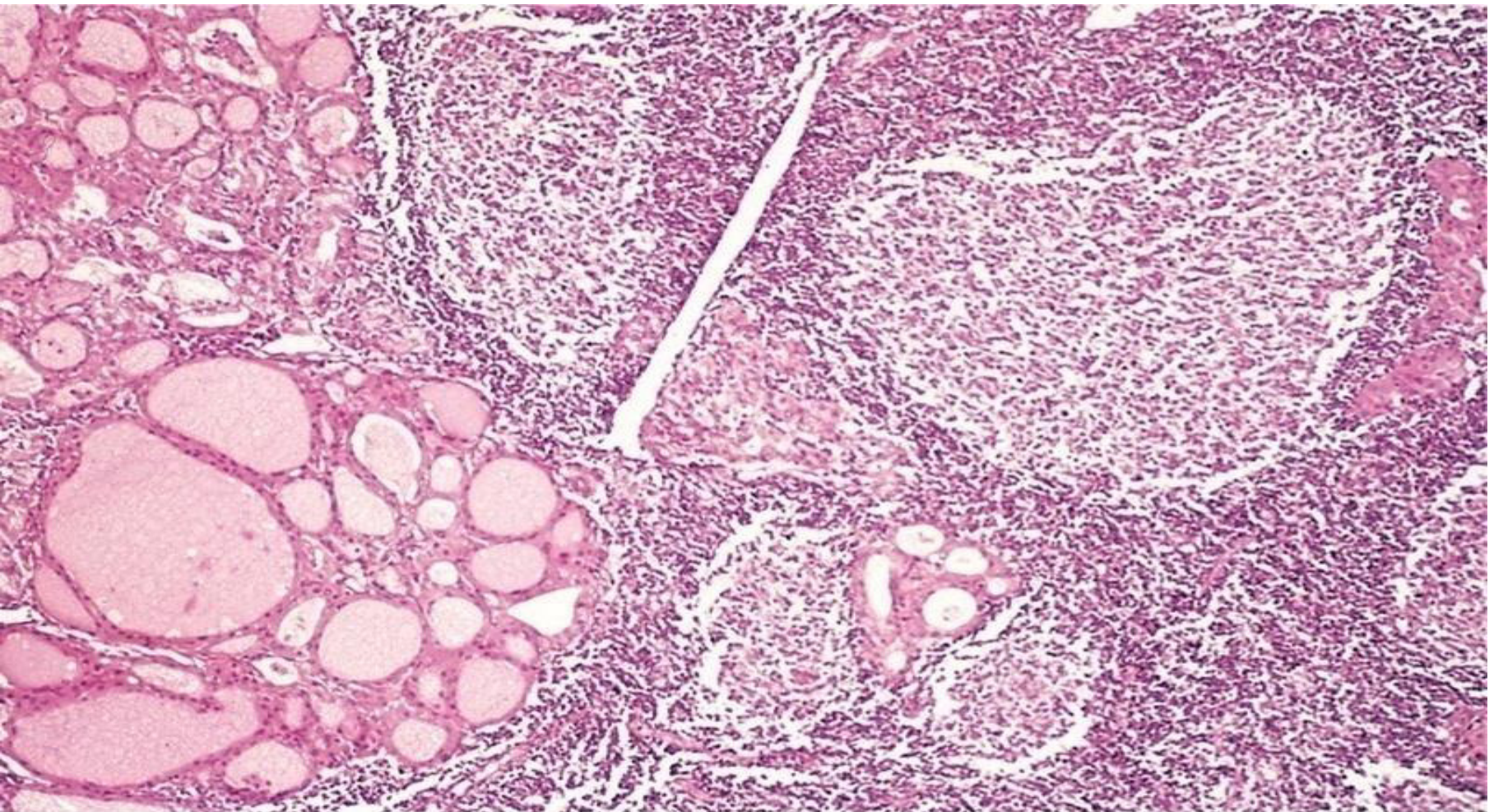
1. Infiltration by small lymphocytes, plasma cells, and well-developed germinal centers
2. The thyroid follicles are atrophic
2. Some follicles are lined by epithelial cells with abundant eosinophilic cytoplasm, termed Hürthle cells and these Hurthle cells have numerous mitochondria

- Less commonly, the thyroid is small due to extensive fibrosis (fibrosing variant) but unlike Reidel thyroiditis, the fibrosis does not extend beyond the capsule of the gland.

Clinically ,

1. *Painless 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*).

Hashimoto thyroiditis



- 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

Subacute Granulomatous (de Quervain) Thyroiditis

- 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.

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.

Clinical Features :

- Acute onset characterized by neck pain (with swallowing)
- Fever, malaise, 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

Subacute Lymphocytic Thyroiditis :

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

Riedel thyroiditis,:

A rare disorder of unknown etiology,

- Characterized by extensive fibrosis involving the thyroid and contiguous structures simulating a thyroid neoplasm
- 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**

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.



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 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: Symmetrical enlargement of the thyroid gland with intact capsule,

On microscopic examination,

- a. The follicular cells in untreated cases are tall, and more crowded and may result in formation of small papillae
- 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

Laboratory findings and radiologic findings

- Elevated serum free T_4 and T_3 and depressed serum TSH
- Because of ongoing stimulation of the thyroid follicles radioactive iodine uptake is increased, and radioiodine scans show a *diffuse uptake* of iodine.

DIFFUSE AND MULTINODULAR GOITER

- Enlargement of the thyroid, or *goiter*, is the most common manifestation of thyroid disease

Mechanism :

- *The goiters reflect impaired synthesis of thyroid hormone often caused by dietary iodine deficiency and this leads to to a compensatory rise in the serum TSH, which in turn causes hyperplasia of the follicular cells and, ultimately, gross enlargement of the thyroid gland .,*

Goiters can be endemic or sporadic.

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

- The term *endemic* is used when goiters are present in more than 10% of the population in a given region.
- Such conditions are common in mountainous areas of the world, including the Himalayas and the Andes but with increasing availability of iodine supplementation, the frequency and severity of endemic goiter have declined

II. Sporadic goiter : Less common than endemic goiter.

- The condition is more common in females than in males, with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T_4 .
- It may be caused by several conditions, including the:
 - a. Ingestion of substances that interfere with thyroid hormone synthesis , such as excessive calcium and vegetables such as cabbage, cauliflower, sprouts, .
 - b. Hereditary enzymatic defects that interfere with thyroid hormone synthesis (*dyshormonogenetic goiter*).
- In most cases, the cause of sporadic goiter is not apparent.

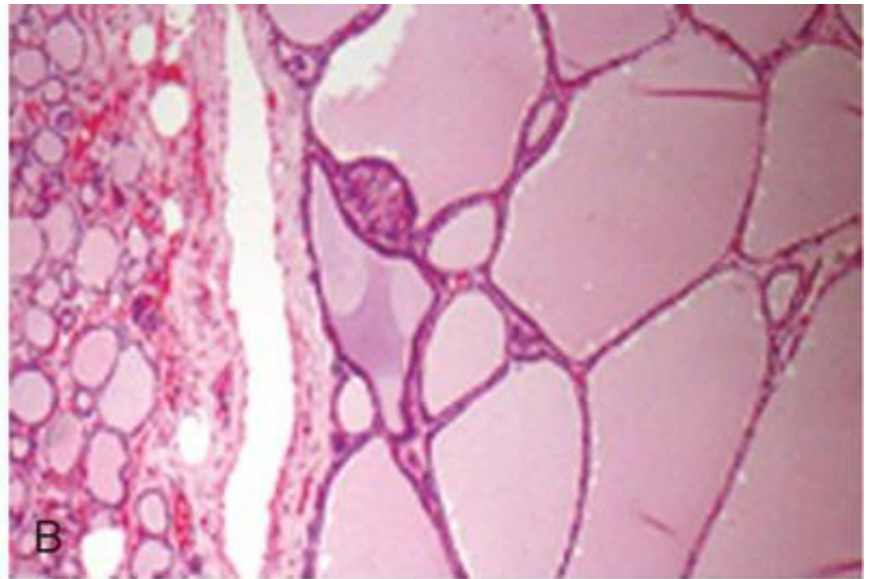
MORPHOLOGY :

- Initially, the gland is diffusely and symmetrically enlarged (diffuse goiter) but later on it becomes multinodular goiter.

On microscopic examination,

- a. The follicular epithelium may be hyperplastic in the early stages of disease or flattened and cuboidal during periods of involution.
- b. Colloid is abundant in the latter periods (colloid goiter).
- c. With time, recurrent episodes of hyperplasia and involution produce a more irregular enlargement of the thyroid, termed multinodular goiter and virtually all long-standing diffuse goiters convert into multinodular goiters.

Multinodular Goiter



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- Multinodular goiters cause multilobulated, asymmetrically enlarged glands which attain massive size and old lesions often show fibrosis, hemorrhage, calcification
- Multinodular goiters typically are hormonally silent,
- 10% of patients can manifest with thyrotoxicosis due to the development of **autonomous nodules** producing hormone independent of TSH stimulation and this condition, called toxic multinodular goiter or **Plummer syndrome**

Clinical Features :

- a. The dominant features are *mass effects* of the goiter
- b. may cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax
- c. 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 (hoarseness)

Thyroid tumors :

- present as solitary nodules.

- the majority of solitary nodules of the thyroid prove to be benign :
 - a. Follicular adenomas
 - b. A dominant nodule in multinodular goiter
 - c. Simple cysts or foci of thyroiditis

- Carcinomas of the thyroid, are uncommon, accounting for much less than 10% of solitary thyroid nodules.

- Several clinical criteria provide a clue to the nature of a given thyroid nodule:

- Solitary* nodules, in general, are more likely to be neoplastic than are multiple nodules.
- Nodules in *younger* patients are more likely to be neoplastic than are those in older patients.
- Nodules in *males* are more likely to be neoplastic than are those in females.
- Nodules that take up radioactive iodine in imaging studies (*hot nodules*) are more likely to be benign than malignant.

Follicular adenomas

- Are benign neoplasms derived from follicular epithelium.
- solitary.
- The tumor is demarcated and compressed the adjacent thyroid parenchyma by a well-defined, intact capsule
- - cold nodules on scanning but might be functional.

▪
Microscopic examination of follicular adenoma,

- The cells are arranged in follicles and its variants

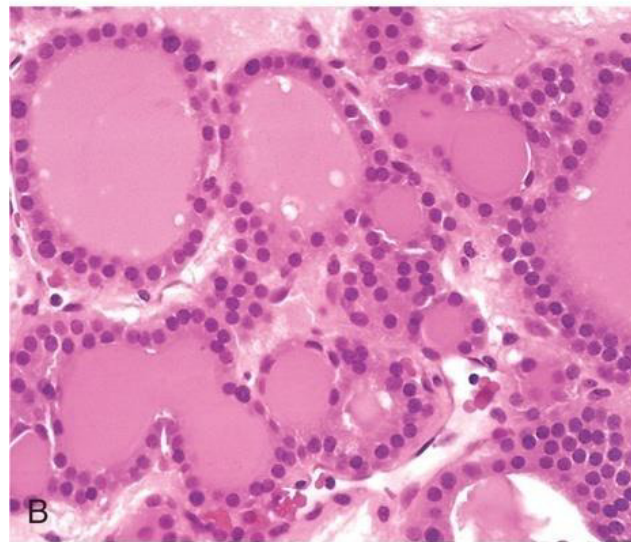
- a. Hurthle cell adenoma:

- The neoplastic cells show oxyphil or Hürthle cell change) and its **behavior is not different** from those of a conventional adenoma.

- b. Atypical adenoma:

- The neoplastic cells exhibit focal nuclear atypia, (**endocrine atypia**); and these features do not constitute evidence of malignancy

Follicular adenoma



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- Thyroid adenomas :
 - a. Carry an excellent prognosis
 - b. and do not recur or metastasize
 - c. and are *not* forerunners to carcinomas

- About 10% of *cold* nodules prove to be malignant and by contrast, malignancy is rare in *hot* nodules

Carcinomas :

- Accounting for about 1.5% of all cancers
- A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years
- ***** cases manifesting in childhood and late adult life are distributed equally between men and women
- The major subtypes of thyroid carcinoma are are
 1. Papillary carcinoma (for more than 85% of cases)
 2. Follicular carcinoma (5% to 15% of cases)
 3. Anaplastic carcinoma (less than 5% of cases)
 4. Medullary carcinoma (5% of cases)

PATHOGENESIS

A. Genetic factors

A. Papillary thyroid carcinomas:

1. rearrangements of *RET*

- The *RET* gene is not normally expressed in follicular cells but in papillary cancers, chromosomal rearrangements place the tyrosine kinase domain of *RET* under the transcriptional control of genes that are constitutively expressed in the thyroid epithelium and the novel fusion proteins so formed are known as RET/PTC and are present in 20% to 40% of papillary thyroid cancers.

-

Genetics of papillary carcinoma/ continued

The frequency of *RET/PTC* rearrangements is significantly higher in papillary cancers arising after radiation exposure.

2. The second mechanism involves activating point mutations in *BRAF*, whose product is an intermediate signaling component in the MAP kinase pathway

Note: RET/PTC rearrangements and *BRAF* point mutations are not observed in follicular adenomas or carcinomas.

GENETIC FACTORS

B. Follicular thyroid carcinomas:

- a. Gain-of-function point mutations of *RAS* and *PIK3CA*,
- b. Loss-of-function mutations of *PTEN*, a suppressor gene
- c. A unique (2;3) translocation presents in one third to one half of follicular carcinomas which creates a fusion gene composed of portions of *PAX8*, a gene that is important in thyroid development, and the peroxisome proliferator-activated receptor gene (*PPARG*), whose product is a nuclear receptor implicated in cell differentiation

GENETIC FACTORS

C. Anaplastic carcinomas:

Inactivation of *TP53*, restricted to anaplastic carcinomas and may also relate to their aggressive behavior

GENETIC FACTORS

D. Medullary thyroid carcinomas:

- Arise from the C cells,.
 - a. Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) and are associated with germline *RET* proto-oncogene mutations .
 - b. *RET* mutations are also seen in approximately one half of nonfamilial (sporadic) medullary thyroid cancers.

B. Environmental Factors.

- a. The major risk factor to papillary thyroid cancer is exposure to ionizing radiation, during the first 2 decades of life.
- b. Deficiency of dietary iodine:** and by extension, an association with goiter is linked with a higher frequency of follicular carcinomas.

Papillary Carcinoma :

Is the most common form

- accounts for the majority of thyroid carcinomas associated with previous exposure to ionizing radiation.
- May occur at any age,

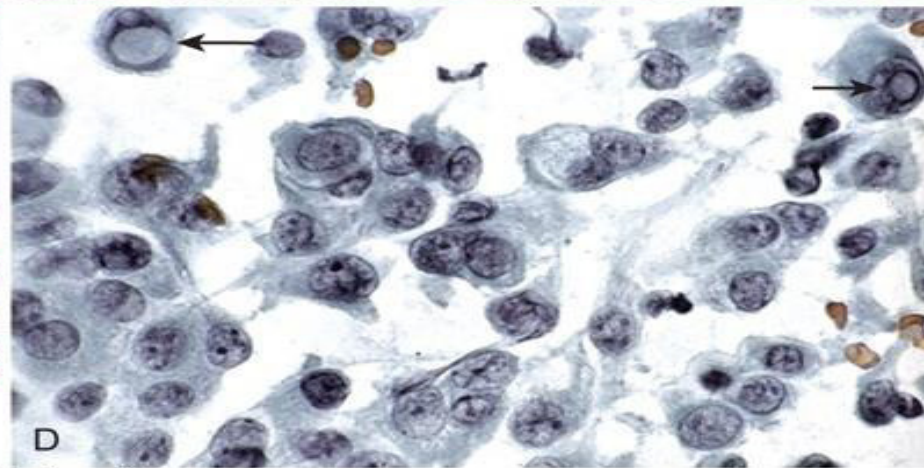
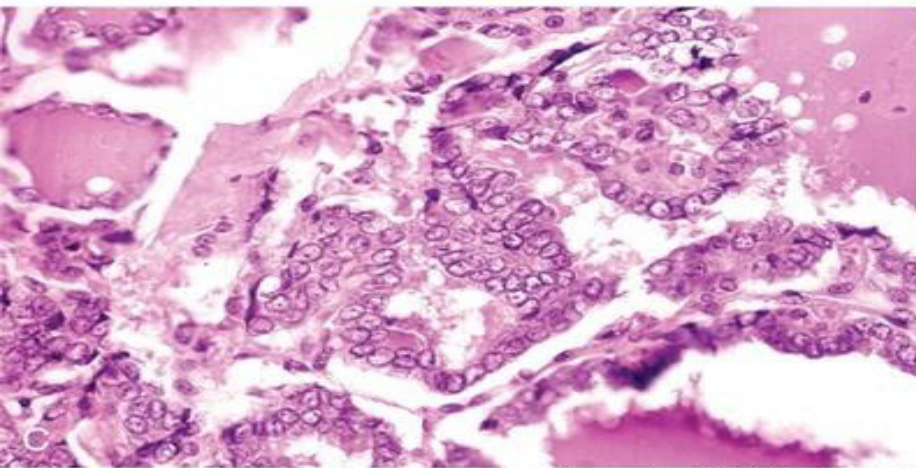
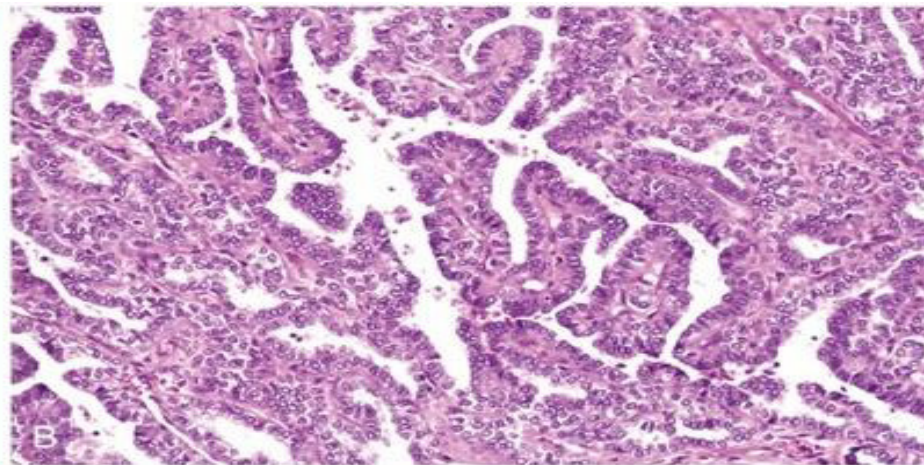
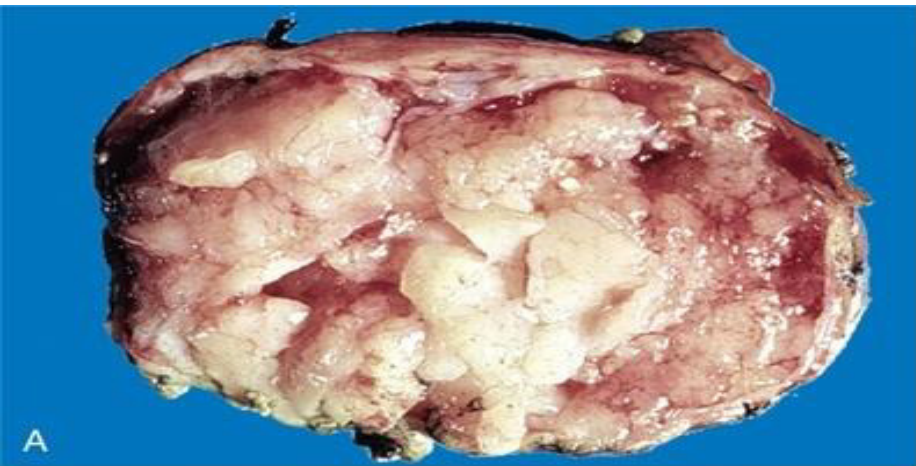
Gross: Either solitary or multifocal lesions

- Some are well circumscribed and even encapsulated; others infiltrate the adjacent parenchyma and the definitive diagnosis is made by microscopic examination

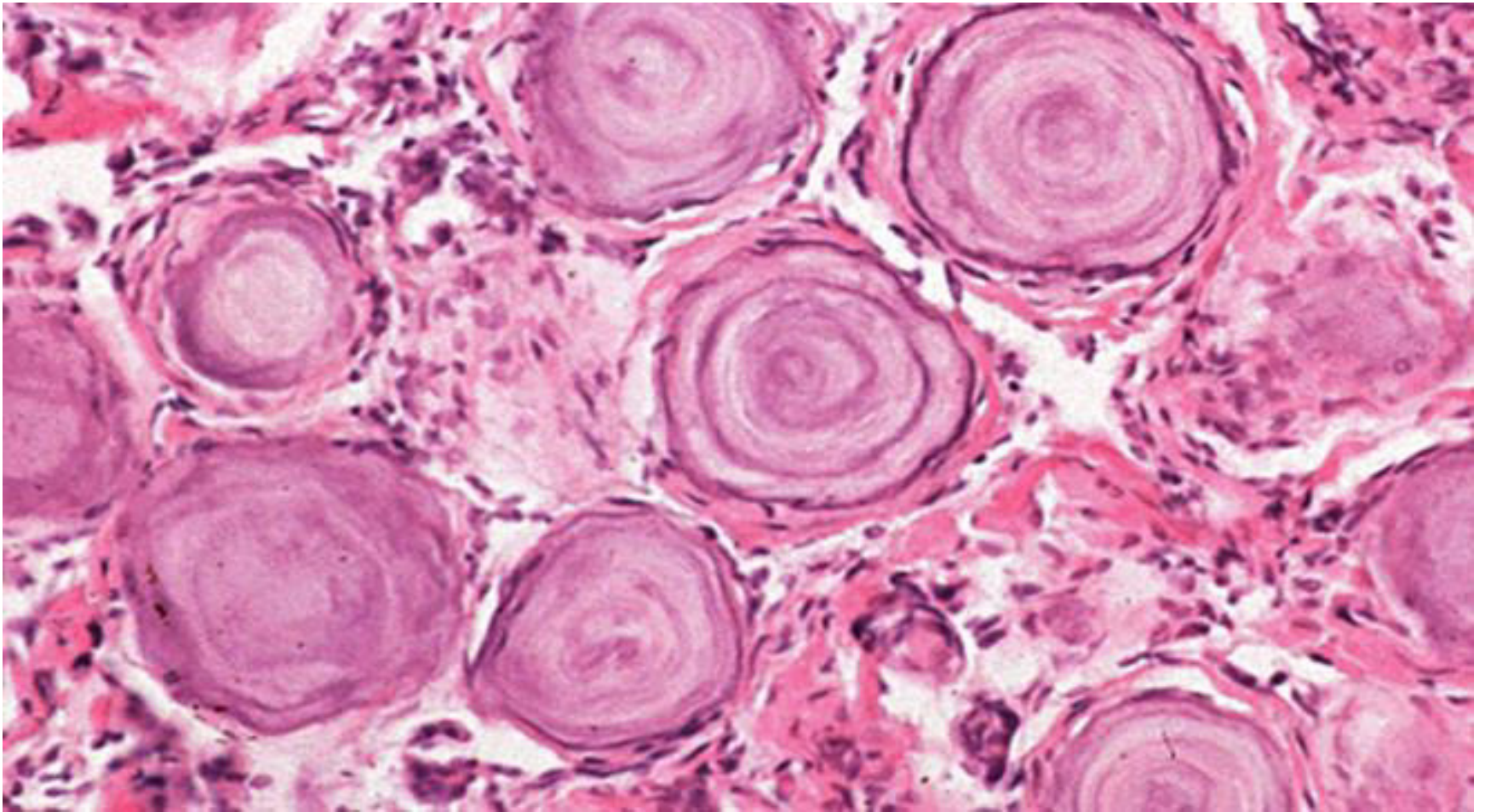
Microscopically: The diagnosis of papillary carcinoma is based on nuclear features even in the absence of a papillary architecture.

1. The nuclei of papillary carcinoma cells show:
 - a. optically clear nuclei, or "Orphan Annie eye" nuclei , seen on histological but not cytological preparations (formalin artefact)
 - b. Have invaginations of the cytoplasm to the nucleus (pseudoinclusions)
2. papillary architecture is common
3. Centrally calcified structures(psammoma bodies)
4. Foci of lymphatic permeation by tumor cells are present, but invasion of blood vessels is relatively uncommon
5. Metastases to cervical lymph nodes in half of cases.

Papillary carcinoma



Psammoma bodies



Clinical Features of papillary carcinomas

- a. Are nonfunctional tumors manifest as painless masses in the neck, either within the thyroid or as metastasis in a cervical lymph node
- b. Are indolent lesions, with 10-year survival rates of 95%.
- c. The presence of isolated cervical nodal metastases does not have influence on good prognosis of these lesions.
- d. In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly to lung.

Follicular Carcinoma :

- More common in women and in areas with dietary iodine deficiency .**
- The peak incidence between the ages of 40 and 60 years**

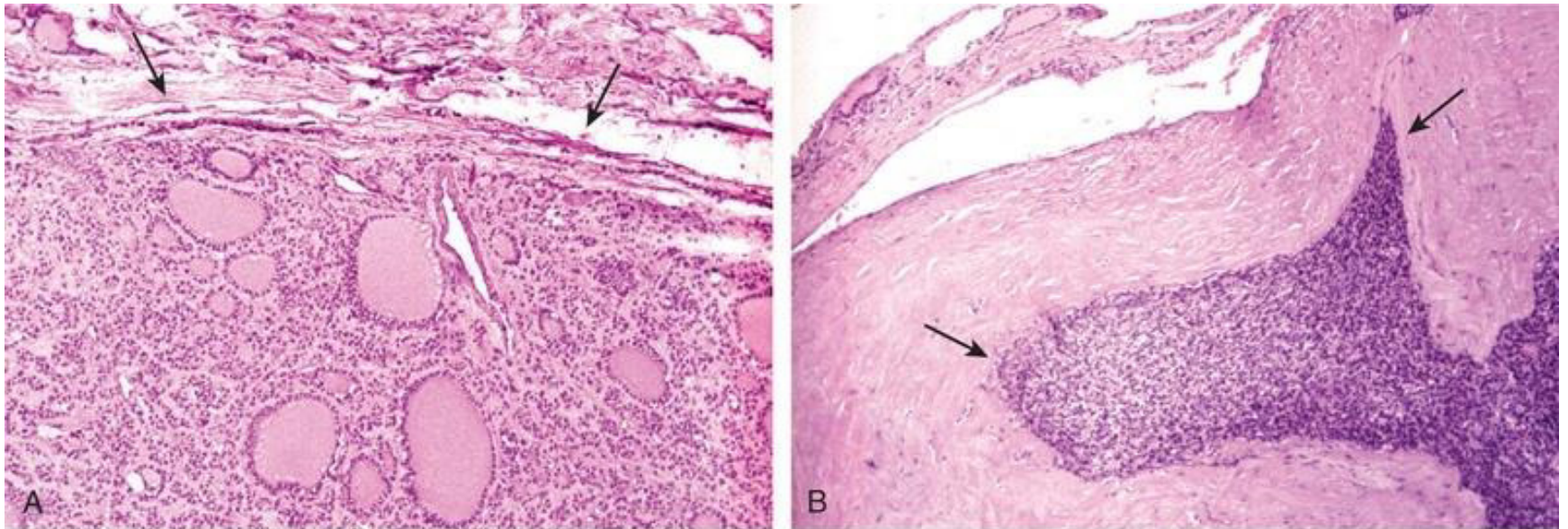
On microscopic examination,

- Are composed of fairly uniform cells forming small follicles,**
- In other cases, follicular differentiation is less apparent**
- It may be**
 - a. widely invasive, infiltrating the thyroid parenchyma and extrathyroidal soft tissues, or**
 - b. Minimally invasive that may be impossible to distinguish from follicular adenomas on gross examination and the .**
- requires extensive histologic sampling to exclude capsular and/or vascular invasion**

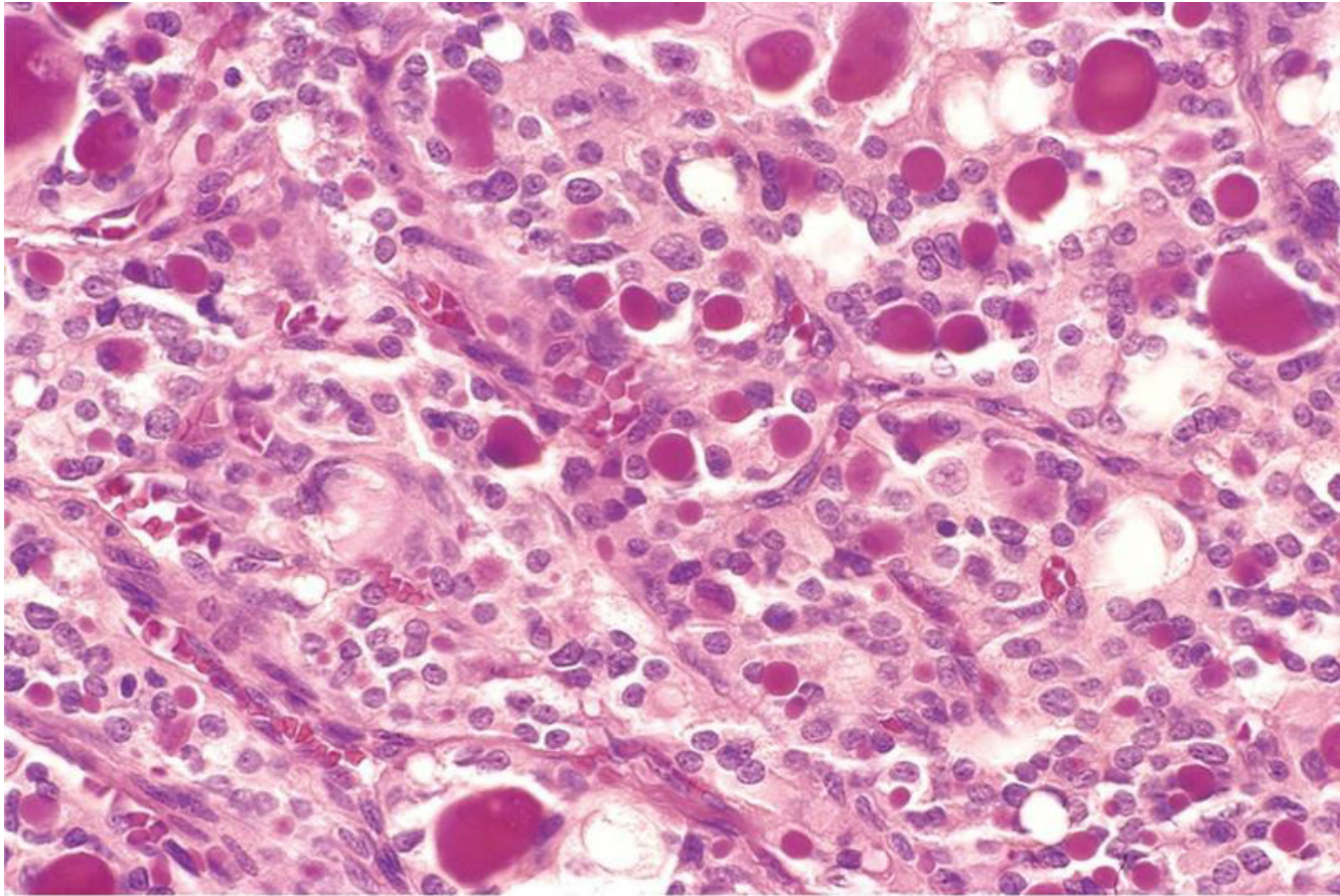
Clinical Features

- Manifest most frequently as solitary *cold thyroid nodules*.
- Tend to metastasize through the bloodstream (*hematogenous dissemination*) to lungs, bone, and liver.
- Regional nodal metastases are uncommon .
- As many as half of patients with widely invasive carcinomas succumb to their disease within 10 years, while less than 10% of patients with minimally invasive follicular carcinomas die within the same time span.

Follicular carcinoma



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3. Anaplastic Carcinoma

- Are undifferentiated tumors of the thyroid epithelium,
- The mean age of 65 years.
- They are aggressive, with a mortality rate of 100%.
- Approximately a quarter of patients have a past history a well-differentiated carcinoma, and a 1/4th harbor a well-differentiated tumor in the resected specimen.
- Metastases to distant sites are common, but death occurs in less than 1 year as a result of aggressive local growth which compromise of vital structures in the neck.

4. Medullary Carcinoma

- neuroendocrine neoplasms.
- Secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up evaluation of patients.
- In some cases, the tumor cells elaborate somatostatin, serotonin, and vasoactive intestinal peptide (VIP)

- Are sporadic in about 70% of cases and the remaining 30% are *familial* cases
 - a. Occurring in the setting of MEN syndrome 2A or 2B,
 - b. or familial medullary thyroid carcinoma without an associated MEN syndrome

Note: Both familial and sporadic forms demonstrate activating *RET* mutations.

Cases associated with MEN-2A or MEN-2B show multicentric C cell hyperplasia in the surrounding thyroid parenchyma, a feature usually absent in sporadic lesions.

These foci are believed to represent the precursor lesions from which medullary carcinomas arise.

Clinical Features

- The sporadic cases manifests most often as a mass in the neck, sometimes associated with compression effects such as dysphagia or hoarseness.
- In some instances, the initial manifestations are caused by the secretion of a peptide hormone (e.g., diarrhea caused by the secretion of VIP).

- Screening of the patient's relatives for elevated calcitonin levels or *RET* mutations permits early detection of tumors in familial cases. ,
- All members of MEN-2 carrying *RET* mutations are offered prophylactic thyroidectomies to prevent the development of medullary carcinomas
- Often, the only finding in the resected thyroid of these asymptomatic carriers is the presence of C cell hyperplasia or small (<1 cm) *micromedullary* carcinomas.
- Recent studies have shown that specific *RET* mutations correlate with an aggressive behavior in medullary carcinomas.

Medullary carcinoma

