Endocrine system 2019
Thyroid gland part 2

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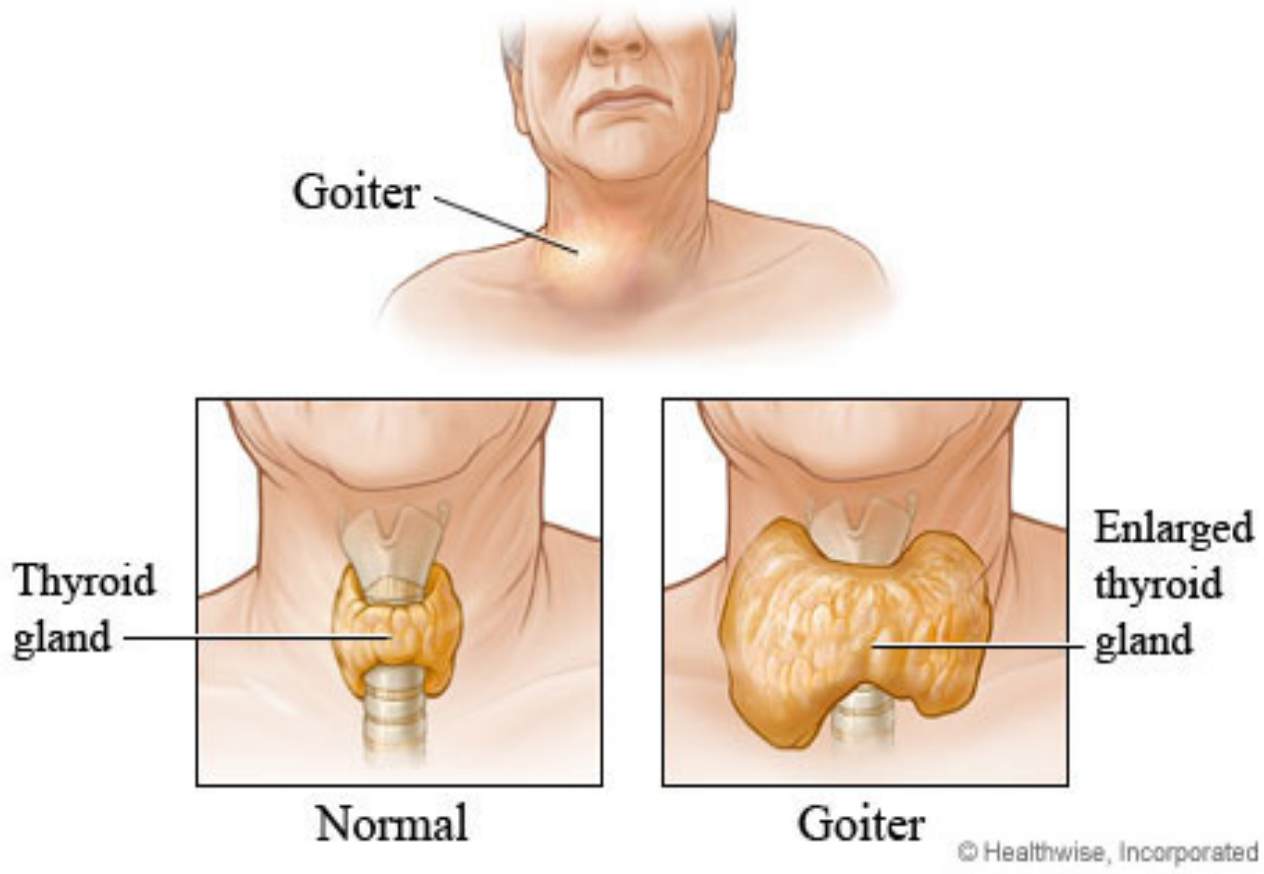
Goiter


Goiter
Thyroid gland
Enlarged thyroid gland
Normal
Goiter
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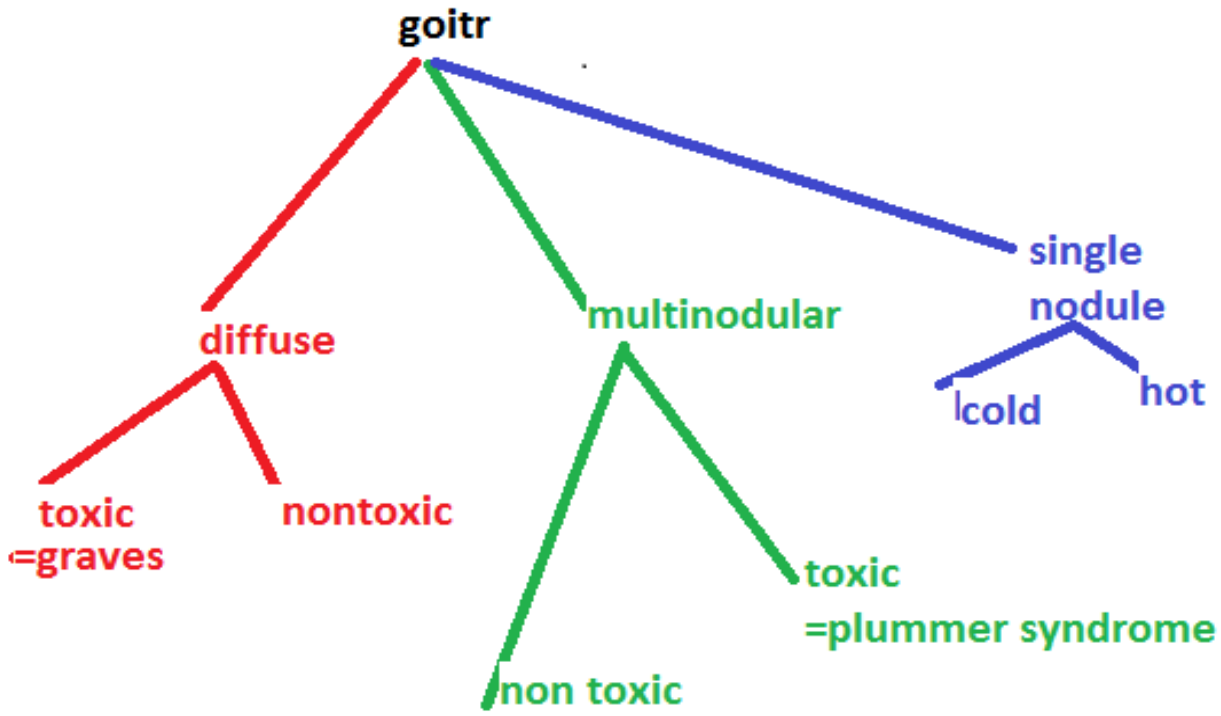
Goiter


goitr
diffuse
multinodular
single
nodule
toxic
=graves
nontoxic
cold
hot
toxic
=plummer syndrome
non toxic

Graves disease

- Named after an Irish surgeon: Robert Graves.
- Robert Invented the seconds-hand on watches and he used the timing of the pulse using the watch.
- Introduced giving food and liquids to patients with fever instead of withholding nourishment.
- One of the first doctors to introduce bedside learning.

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

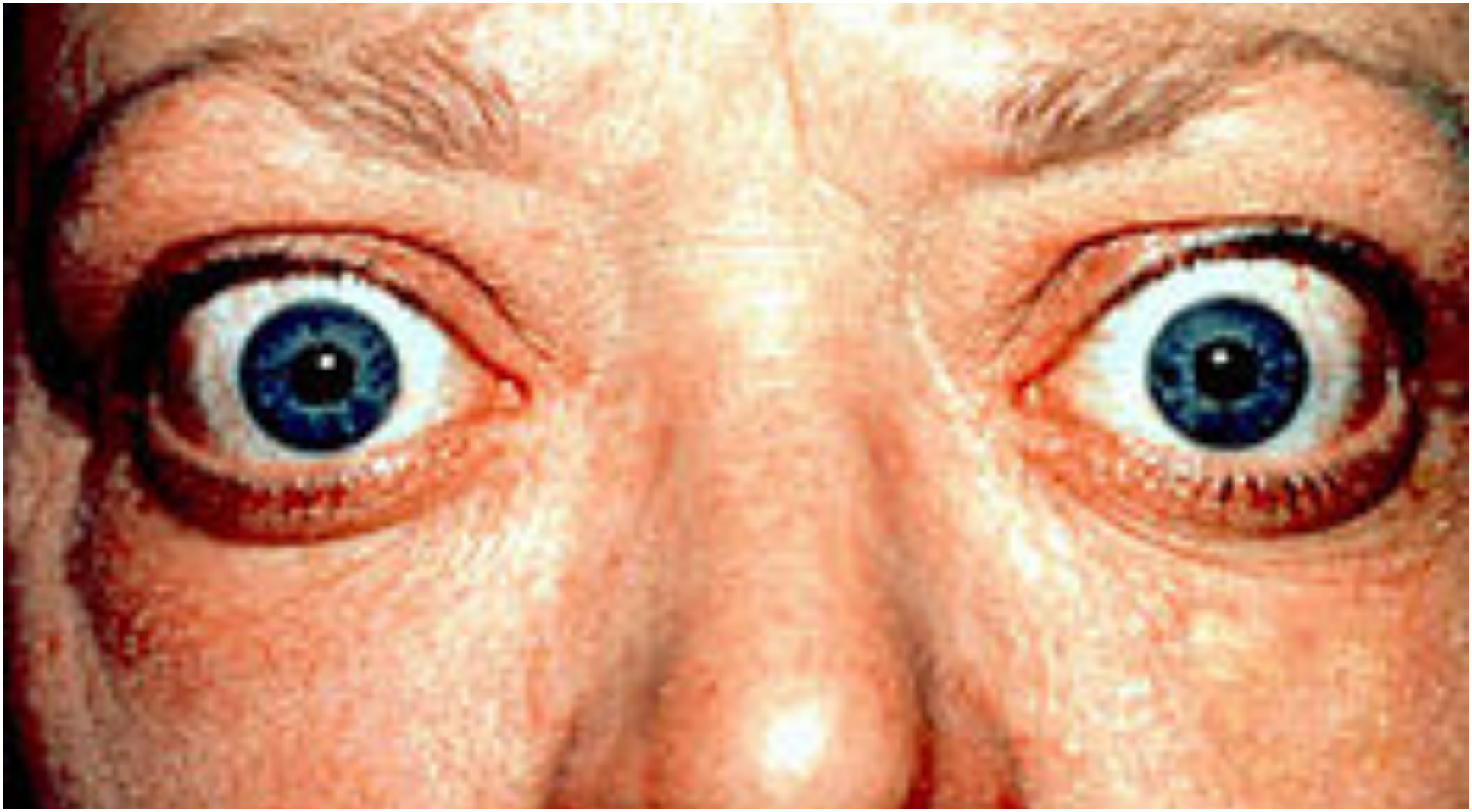
Exophthalmos is the result of increased volume of the retro-orbital connective tissues by

1. Marked infiltration of T cells with inflammatory edema
2. Accumulation of glycosaminoglycans
3. Increased numbers of adipocytes (fatty infiltration).

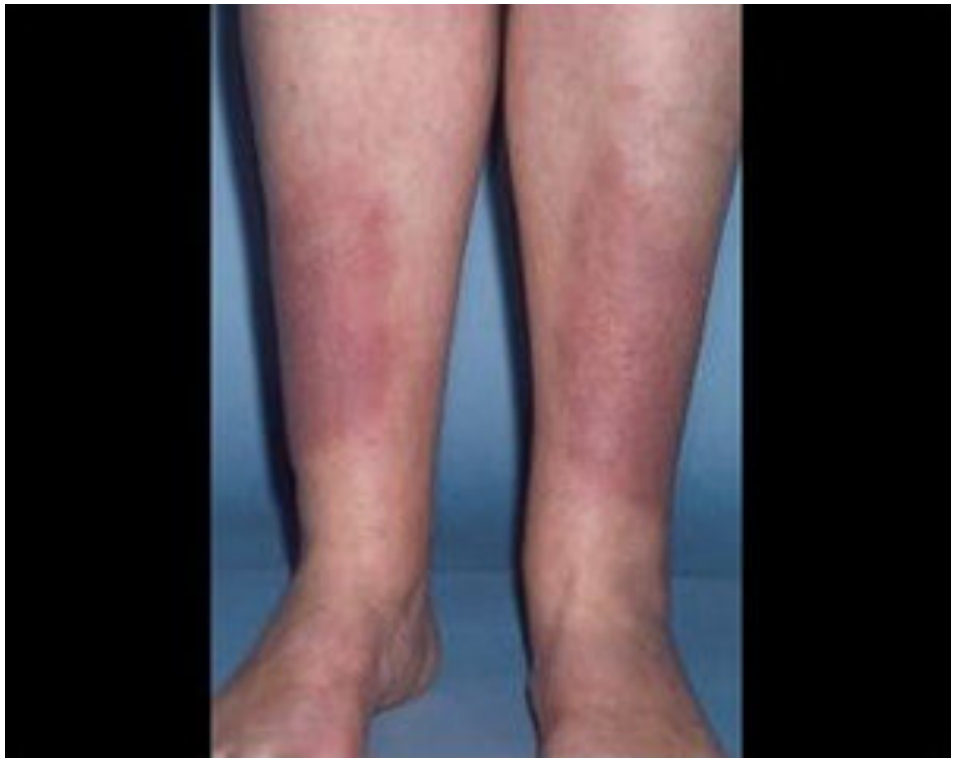
- These changes displace the eyeball forward, potentially interfering with the function of the extraocular muscles

- Exophthalmos may persist after successful treatment of the thyrotoxicosis, and may result in corneal injury.

exophthalmus



Pretibial myxedema



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

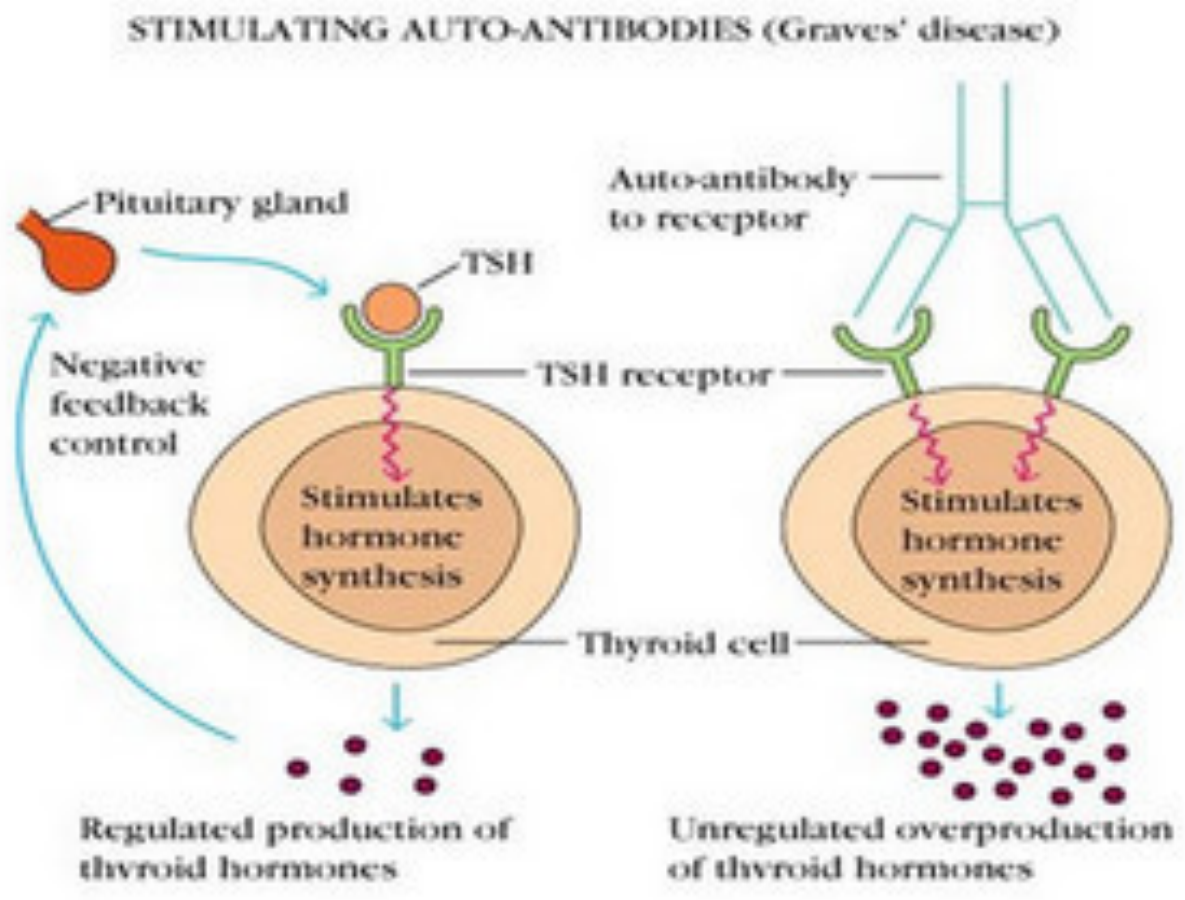
2. Thyroid growth-stimulating immunoglobulins:

- Directed against the TSH receptor, and have been implicated in the proliferation of follicular epithelium

3. TSH-binding inhibitor immunoglobulins:

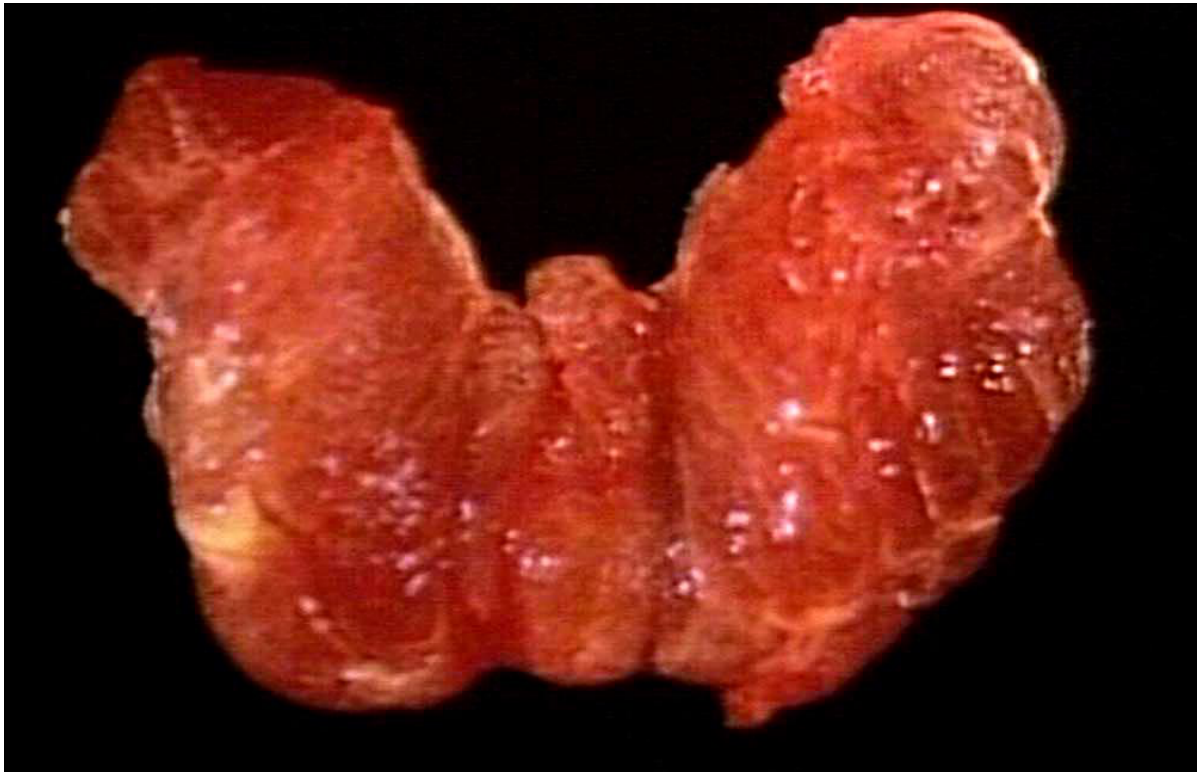
- Prevent TSH from binding to its receptor on thyroid cells and in so doing may actually inhibit thyroid cell function, a finding explains why some patients with Graves spontaneously develop episodes of hypothyroidism.

Note the autoantibodies in Grave's cause stimulation of hormone synthesis



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: Diffuse Symmetrical enlargement of the thyroid gland with intact capsule,



On microscopic examination,

a. The follicular cells in untreated cases are tall and crowded.

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.

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

Sporadic goiter : Less common than endemic goiter.

- 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.

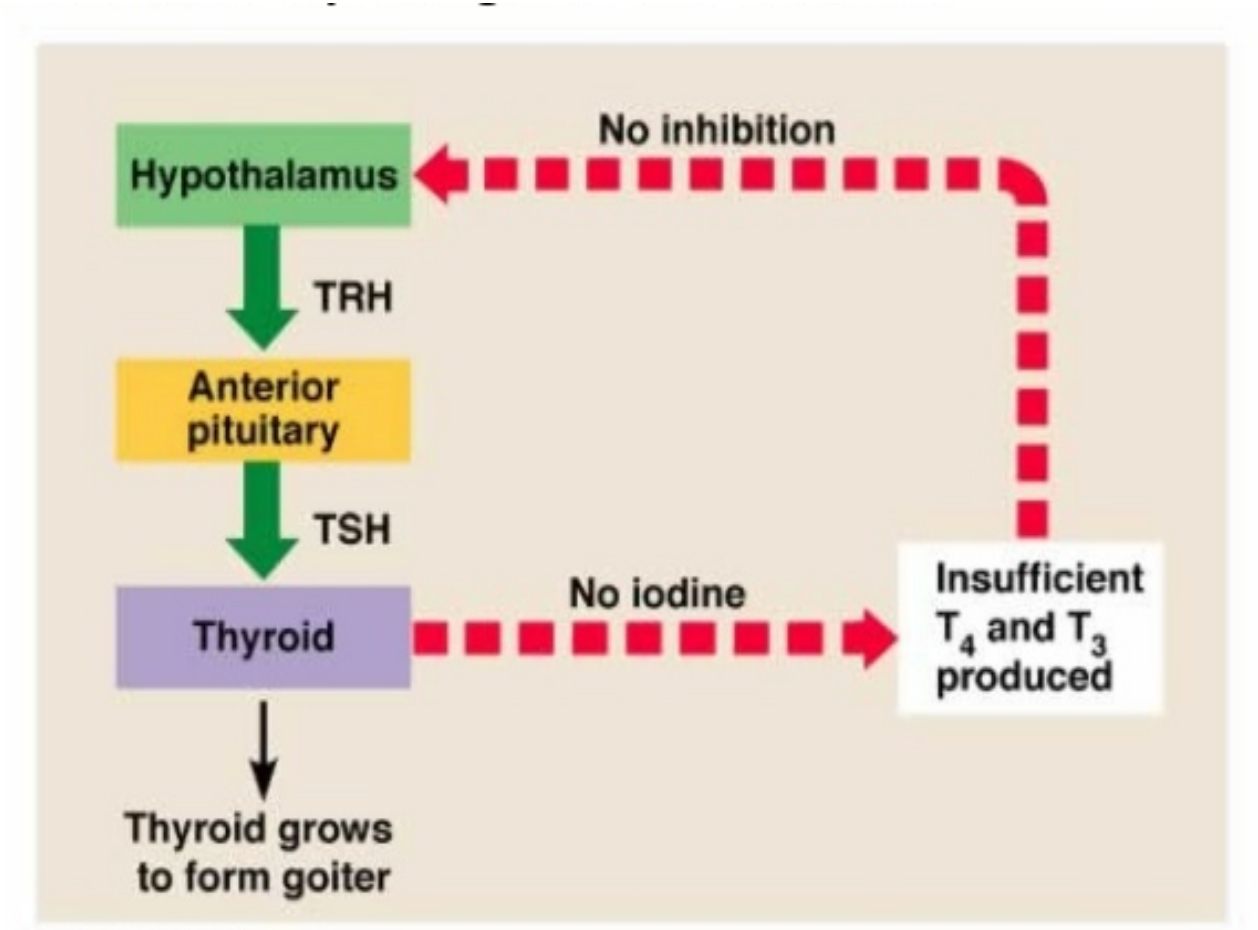
On microscopic examination,

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).

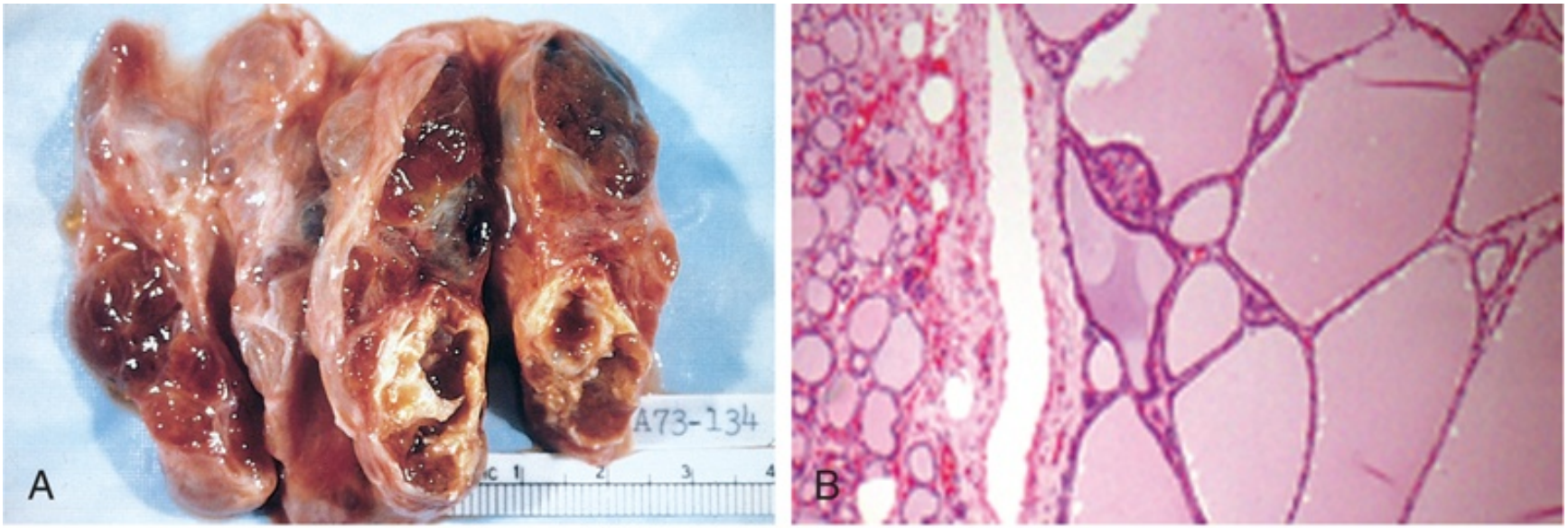
c. With time, recurrent episodes of hyperplasia and involution produce a more irregular enlargement of thee thyroid, termed multinodular goiter and virtually all long-standing diffuse goiters convert into multinodular goiters.

mechanism


Hypothalamus
No inhibition
TRH
Anterior pituitary
TSH
Thyroid
No iodine
Insufficient T_4 and T_3 produced
Thyroid grows to form goiter

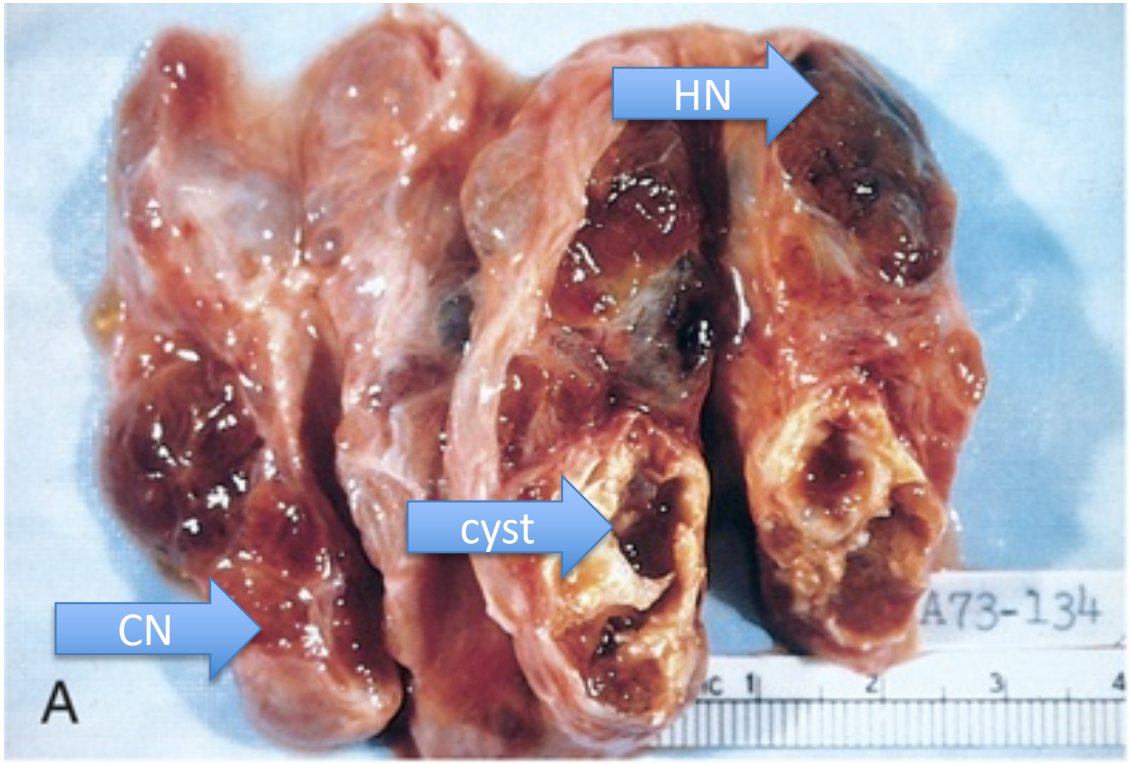
Macroscopic appearance

- Multinodular goiters cause multilobulated, asymmetrically enlarged glands . Old lesions often show fibrosis, hemorrhage, calcification

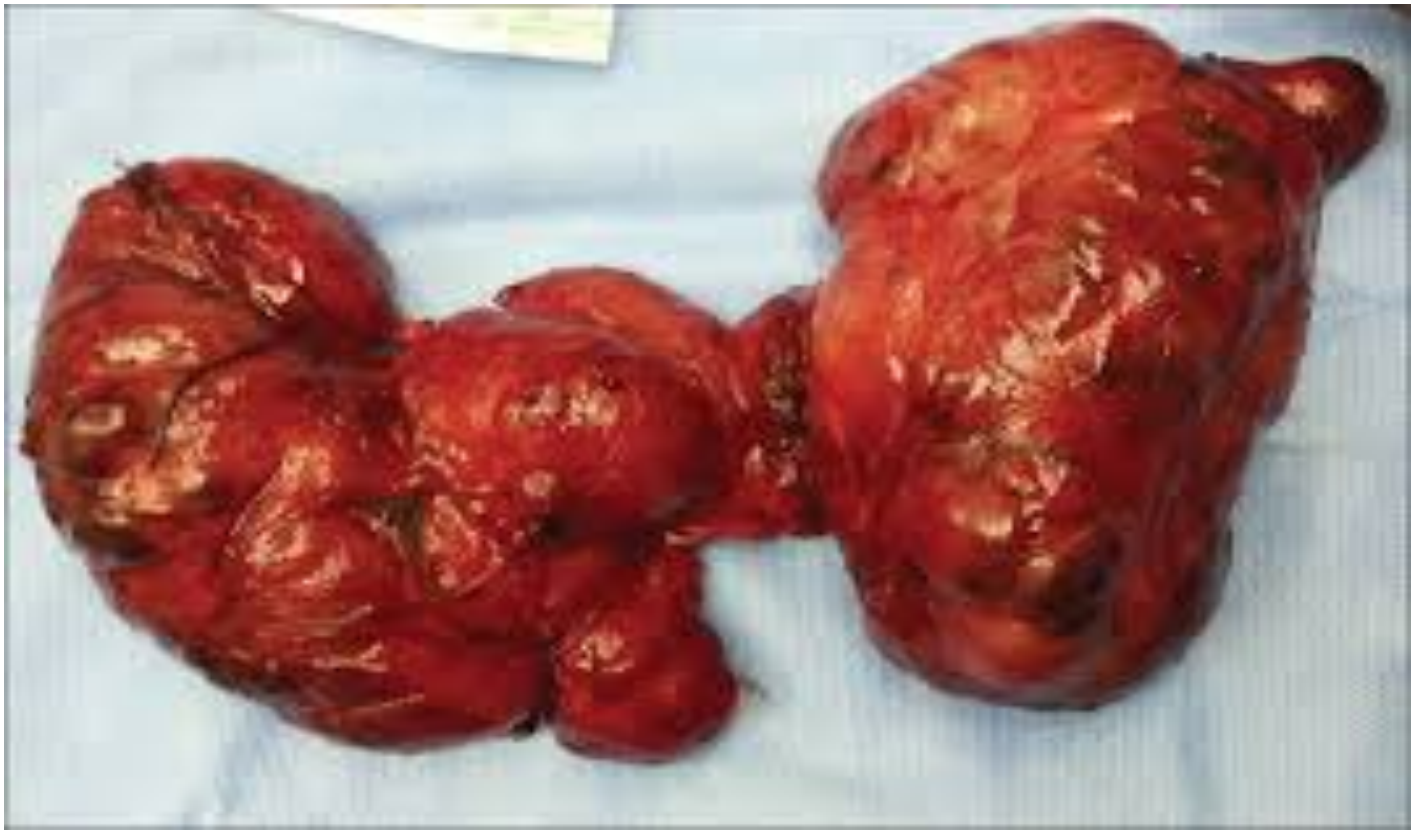


Kumar et al: Robbins Basic Pathology, 9e.

Multinodular goiter: thyroid shows several nodules, some are hemorrhagic (HN), others contain colloid (CN) and some become cystic.



multinodular goiter



Note:

- Multinodular goiters typically are hormonally silent (no hyperthyroidism)
- however, 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 :

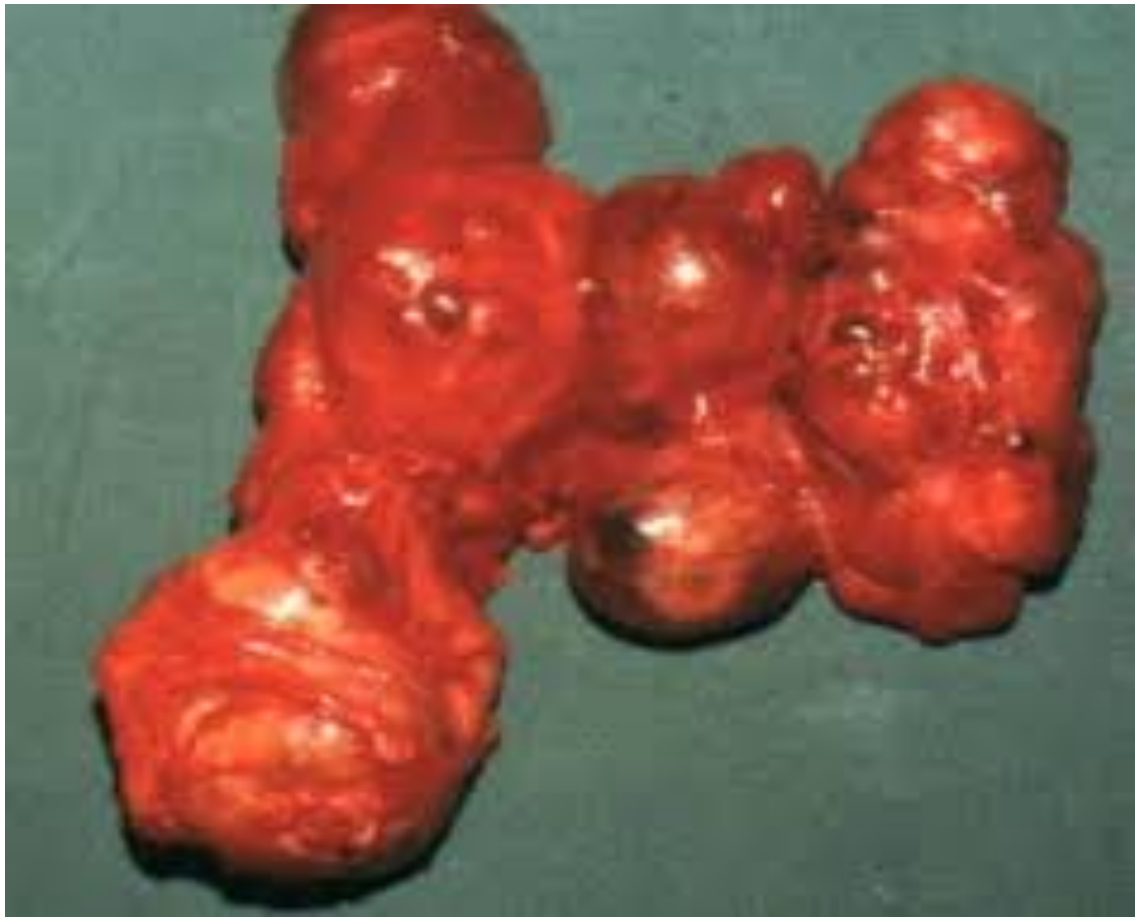
a. The dominant features are *mass effects* of the goiter

b. may cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax

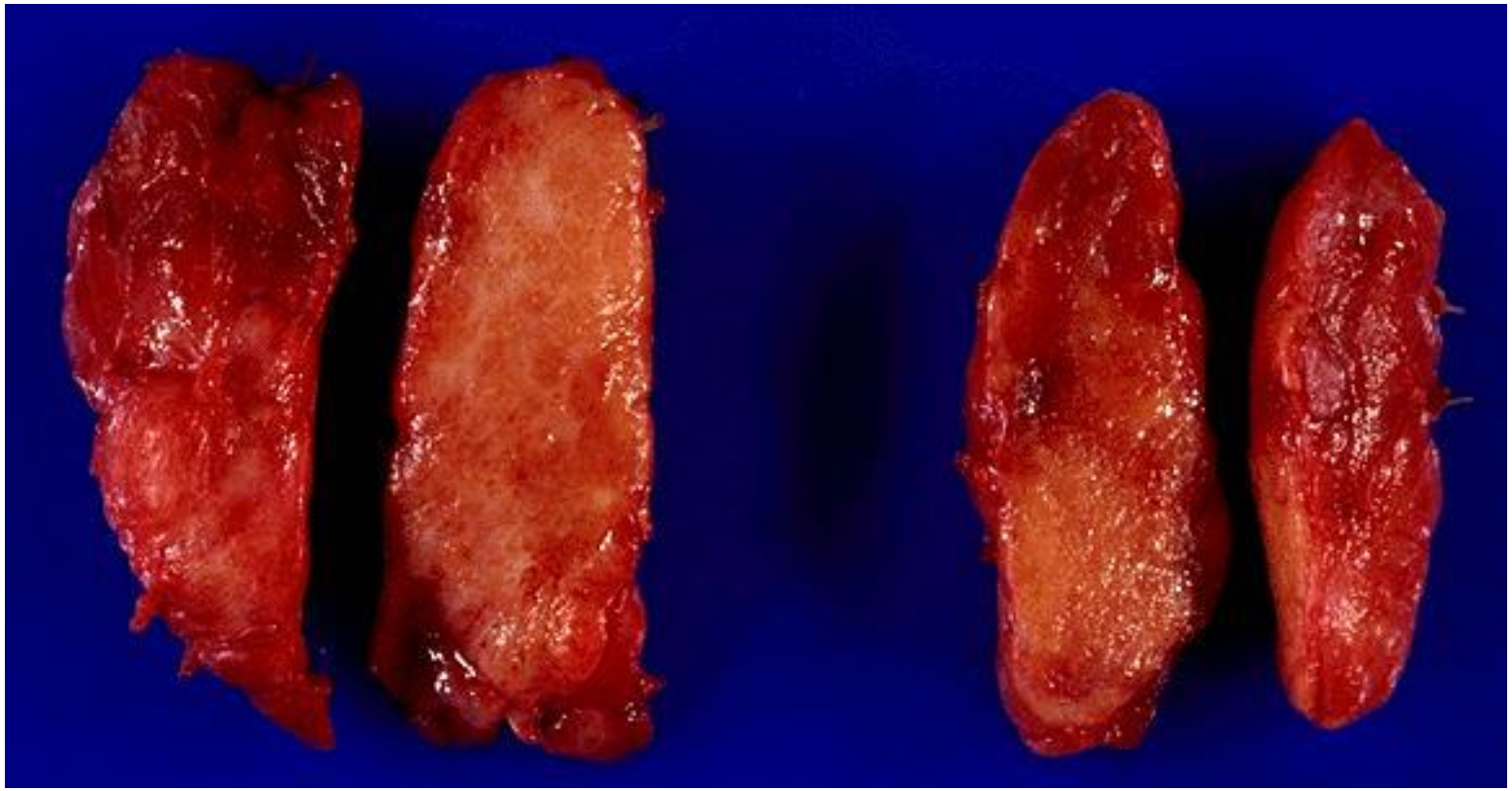
c. The incidence of malignancy in long-standing multinodular goiters is low (less than 5%) but not zero and concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (hoarseness)

QUIZ.. What's the type of goiter on these macroscopic pictures:

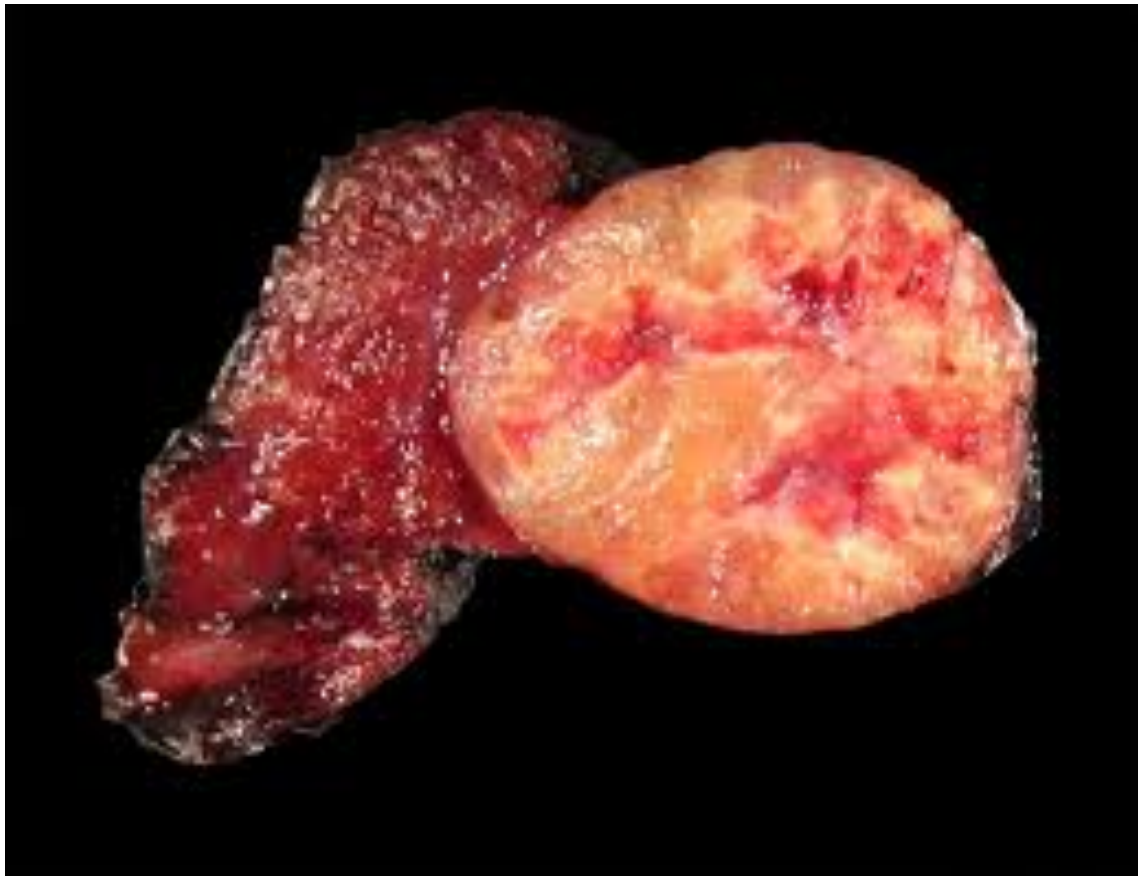
- Case A



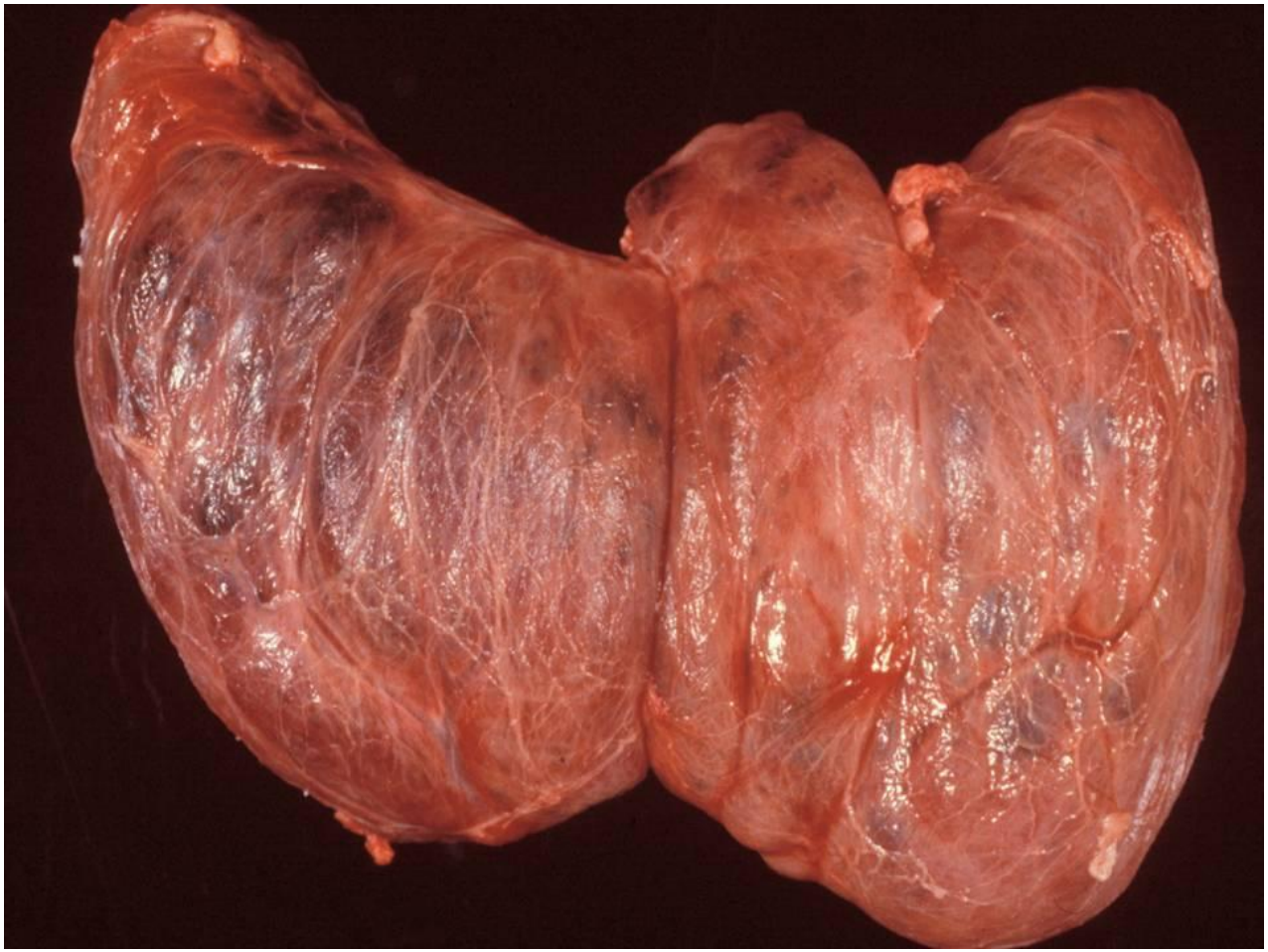
Case B



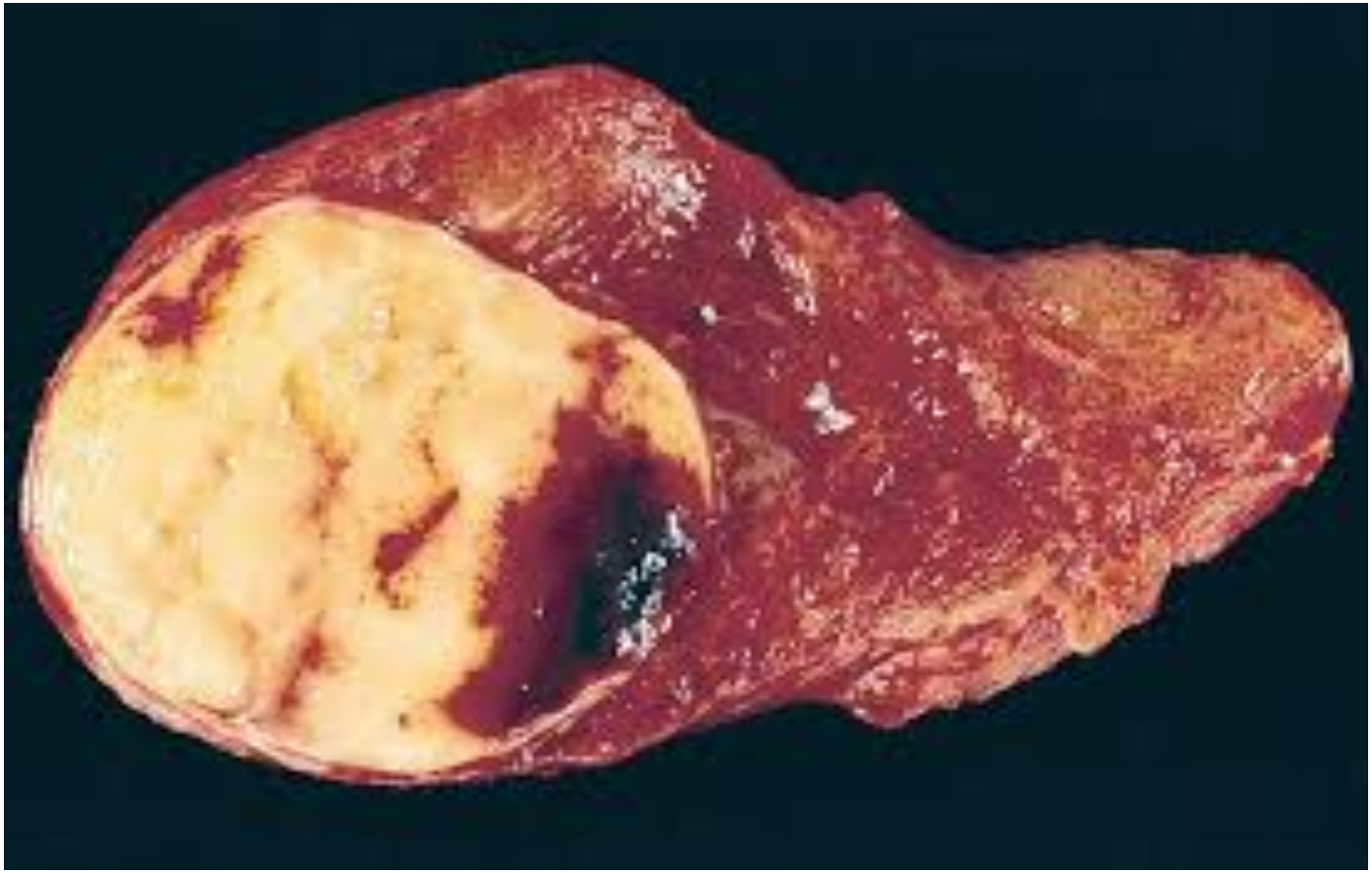
Case C



Case D



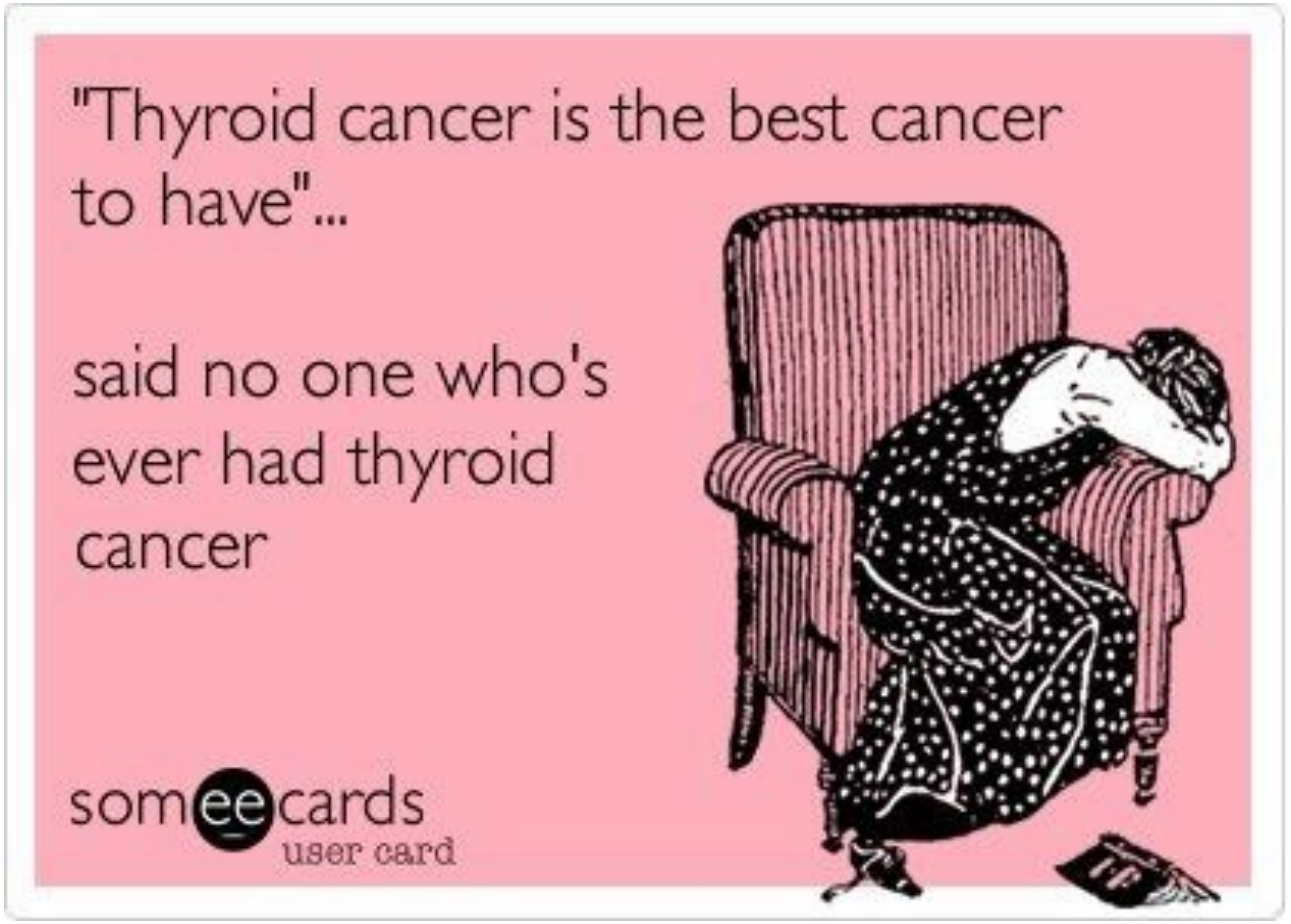
Case E



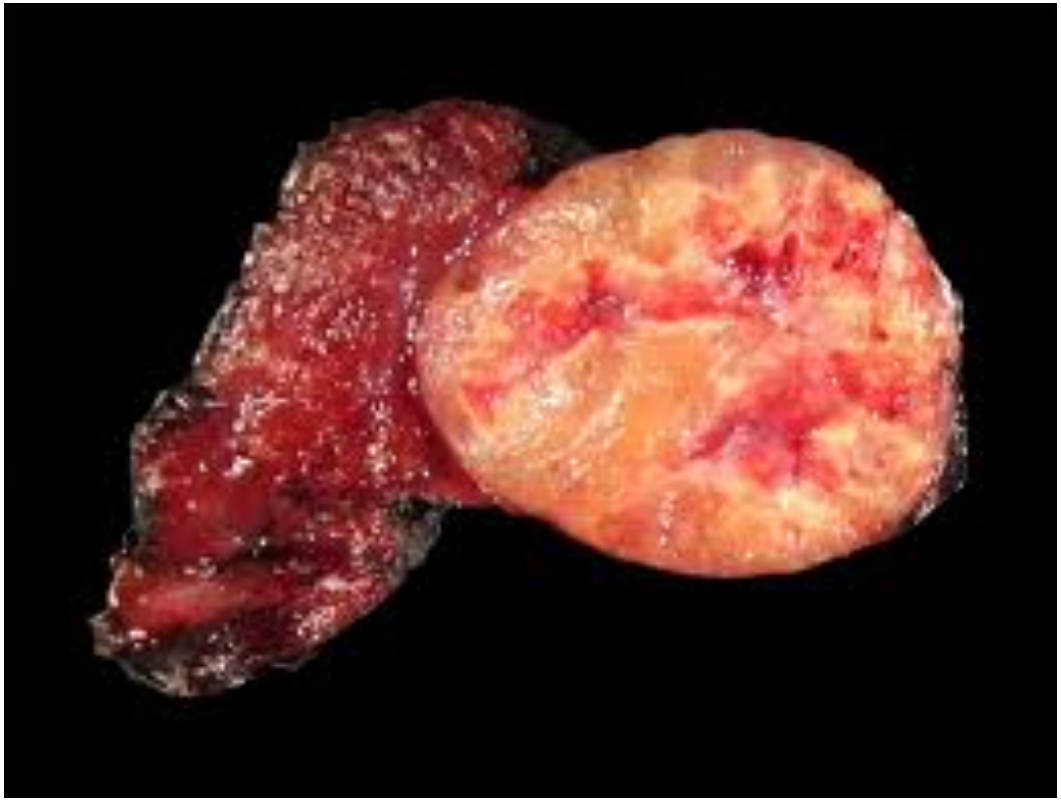
Answers

- A: multinodular.
- B and D: Diffuse
- C and E: single nodule.

Thyroid tumors



Thyroid neoplasms present as single nodules



Thyroid tumors

- Tumors of the thyroid gland can be benign or malignant.
- They are usually solitary (single not multiple)
- Benign lesions in the thyroid are commoner than malignant ones.
- Carcinomas of the thyroid are uncommon, accounting for much less than 10% of solitary thyroid nodules

Solitary thyroid nodules

- In clinical practice, if you see a patient with solitary nodule, your differential diagnosis (D Dx) will include neoplastic and non-neoplastic lesions.
- The D Dx includes:

a. Follicular adenomas

b. A dominant nodule in multinodular goiter

c. Simple cysts or foci of thyroiditis

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

a. Solitary nodules, in general, are more likely to be neoplastic than are multiple nodules.

b. Nodules in younger patients are more likely to be neoplastic than are those in older patients.

c. Nodules in males are more likely to be neoplastic than are those in females.

d. Nodules that take up radioactive iodine in imaging studies (*hot nodules*) are more likely to be benign than malignant.

Note: About 10% of *cold* nodules prove to be malignant and, malignancy is rare in *hot* nodules

Neoplastic thyroid lesions

Benign: follicular adenoma and its variants (example: Hurthle cell adenoma, atypical adenoma)

Malignant:

1.papillary carcinoma

2. Follicular carcinoma

3. medullary carcinoma

4. Anaplatic carcinoma.

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:

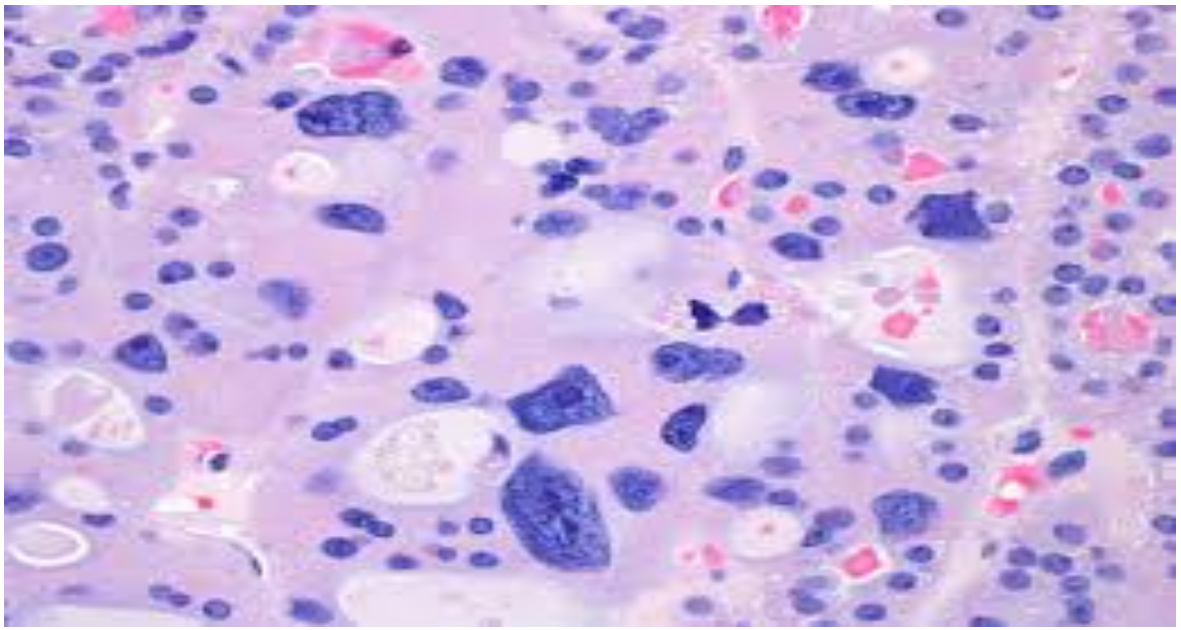
- The neoplastic cells show oxyphil or Hürthle cell change) and its behavior is not different from those of a conventional adenoma.

b. Atypical adenoma:

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

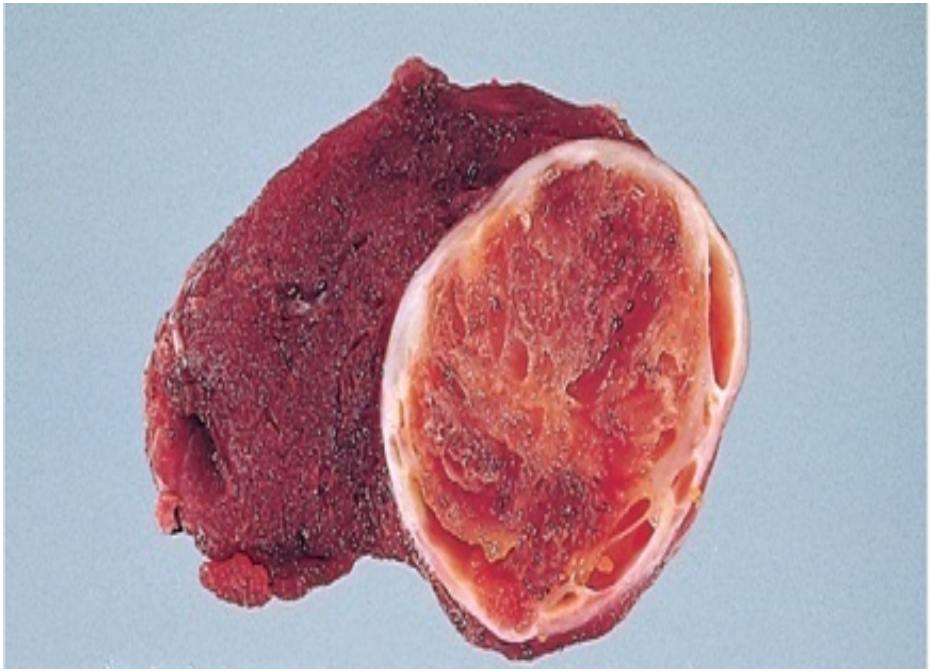
Endocrine atypia

- Note the large, hyperchromatic, pleomorphic cells. These are atypical and this atypia in endocrine glands doesn't necessarily mean malignancy.

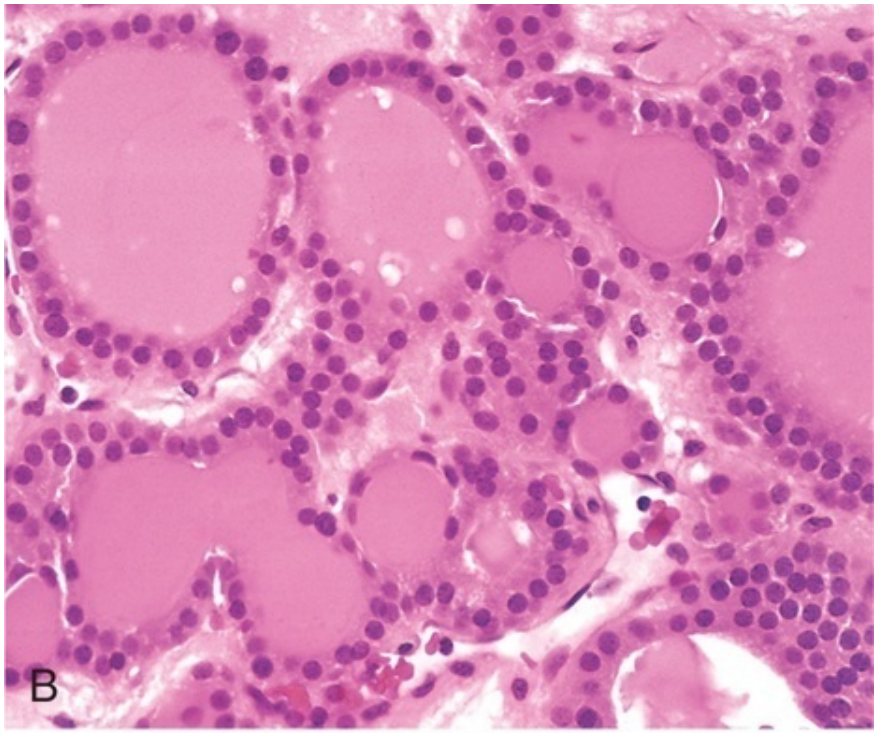


Follicular adenoma

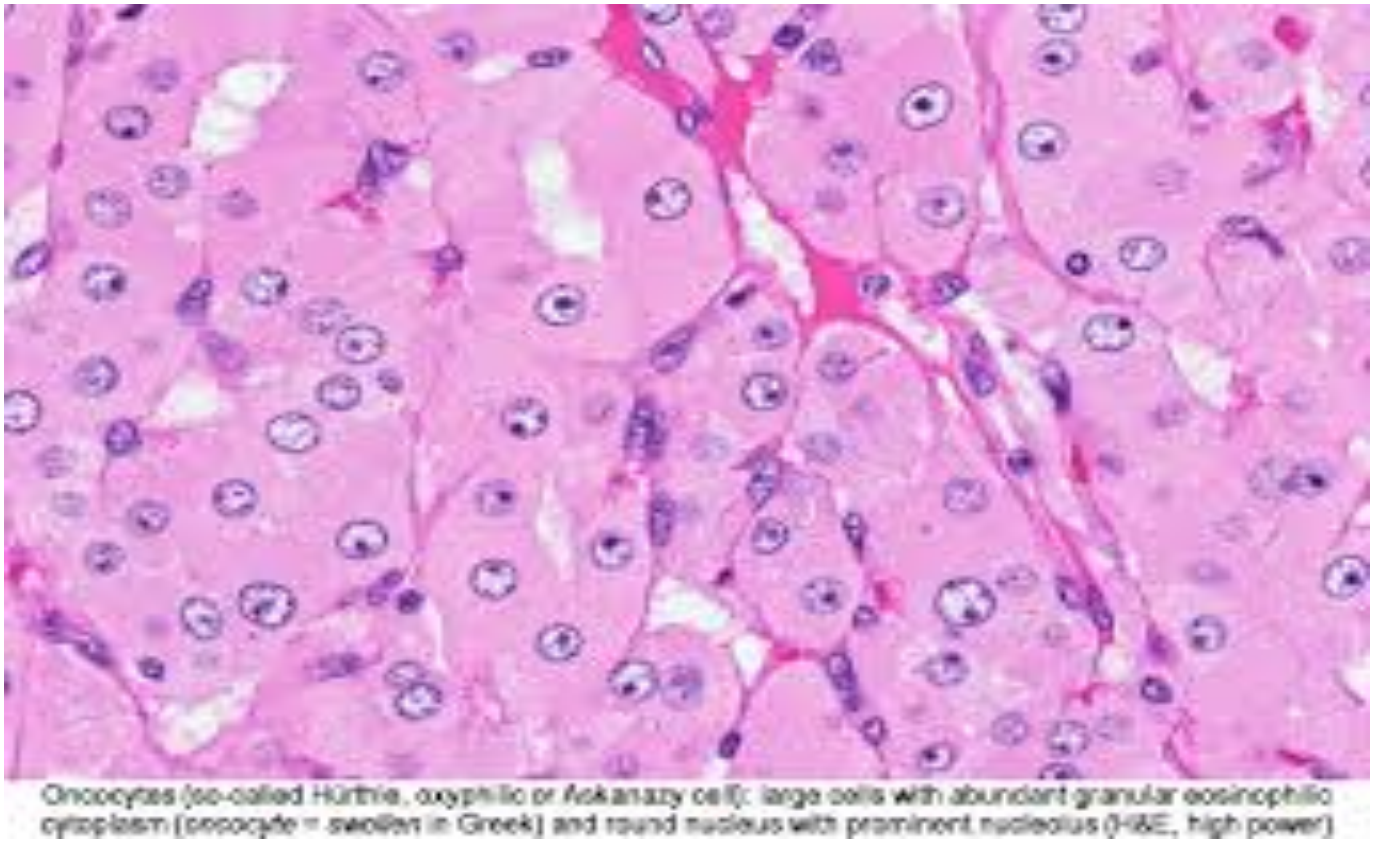
- Well demarcated, encapsulated nodules.



Micro: composed of follicles similar to the normal thyroid follicles.



Hurthle cell adenoma, cells are large with abundant eosinophilic cytoplasm.



- Behavior of thyroid adenomas :

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

Thyroid carcinoma

- Account 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

Main types

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

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.

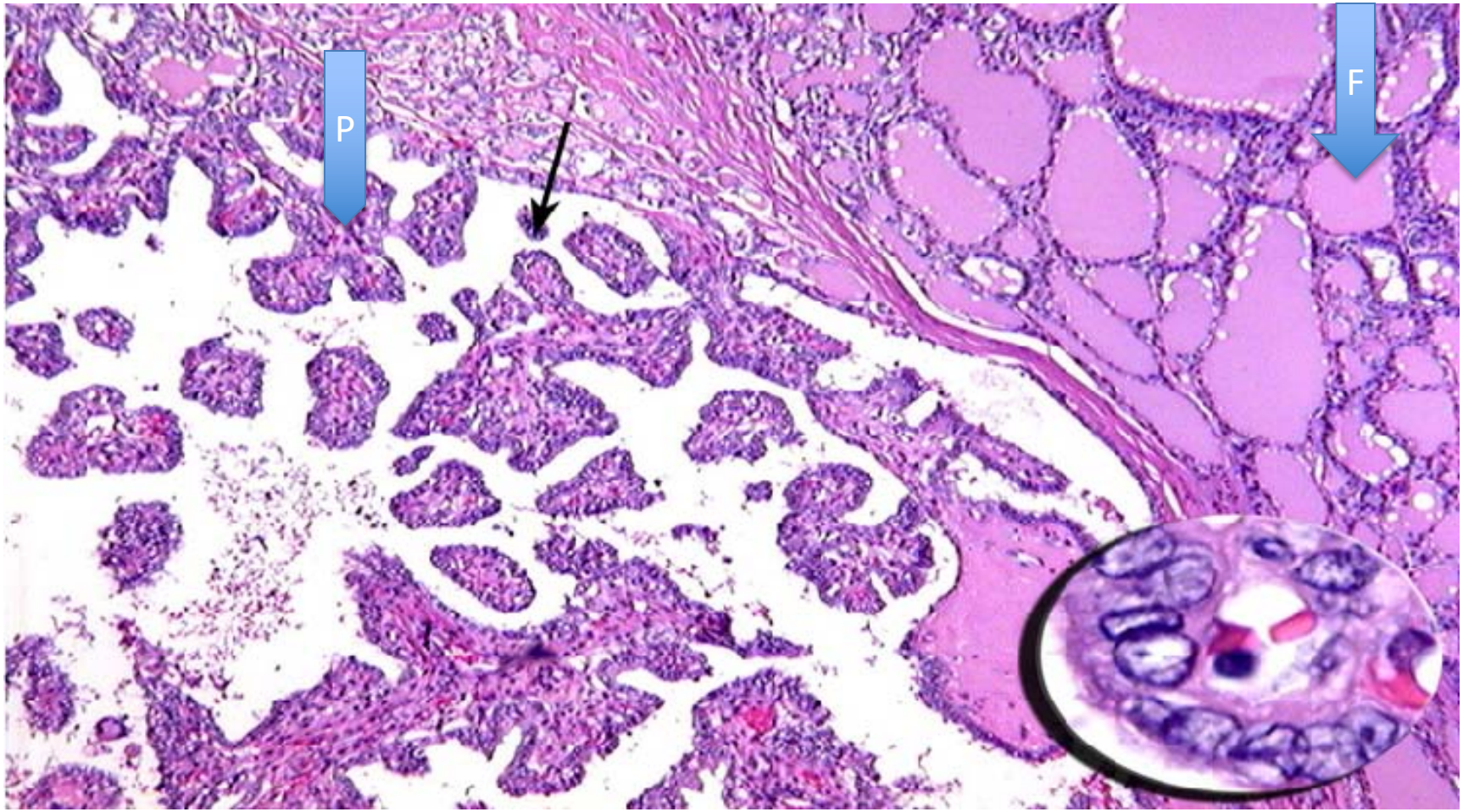
Gross: Either solitary or multifocal lesions

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

Microscopic features of papillary carcinoma

- 1. the presence of papillae.
- 2. nuclear features
- 3. Concentrically calcified structures (psammoma bodies)

Papillae (P). Note the difference from the normal follicles (F)

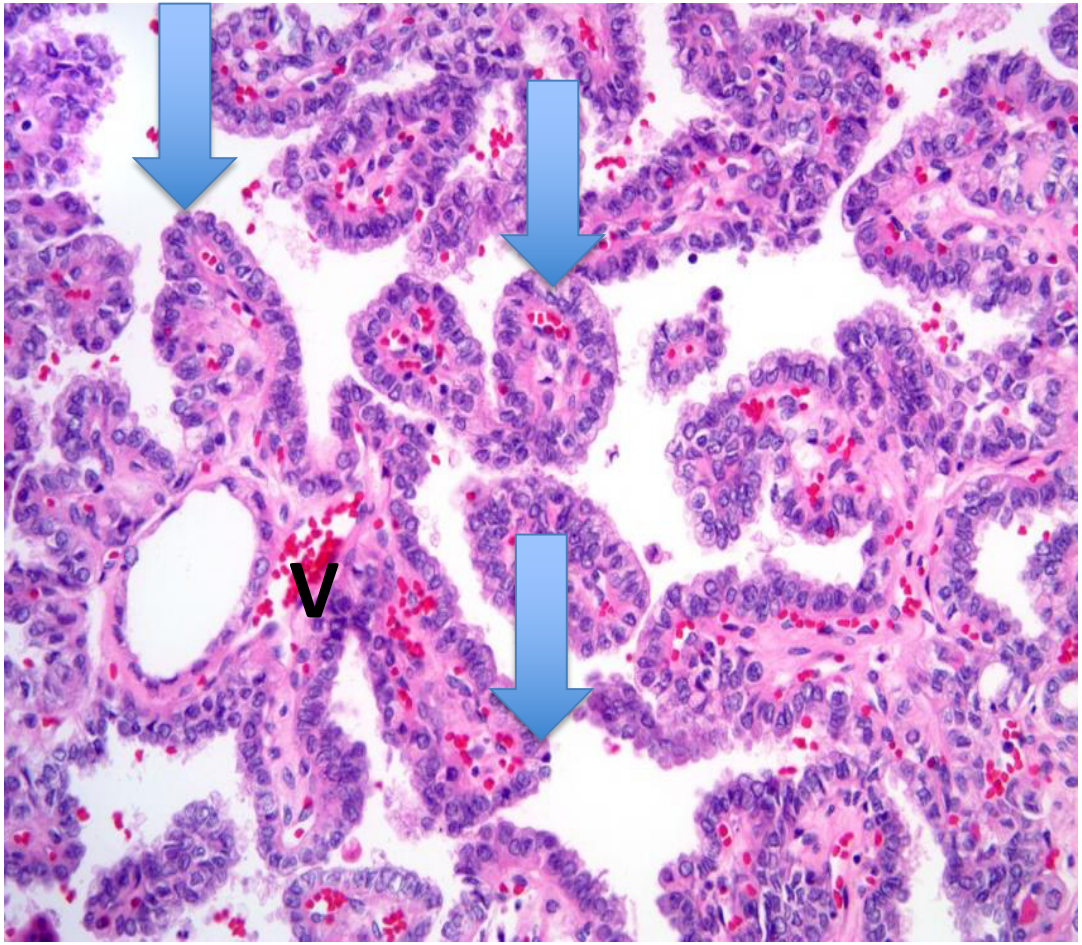


Papillae

-Papillae (arrows) are finger-like projections covered by epithelial cells (the blue dots around the papillae).

-The papillae have fibro-vascular cores (central region which is fibrous and contains blood vessels (V))

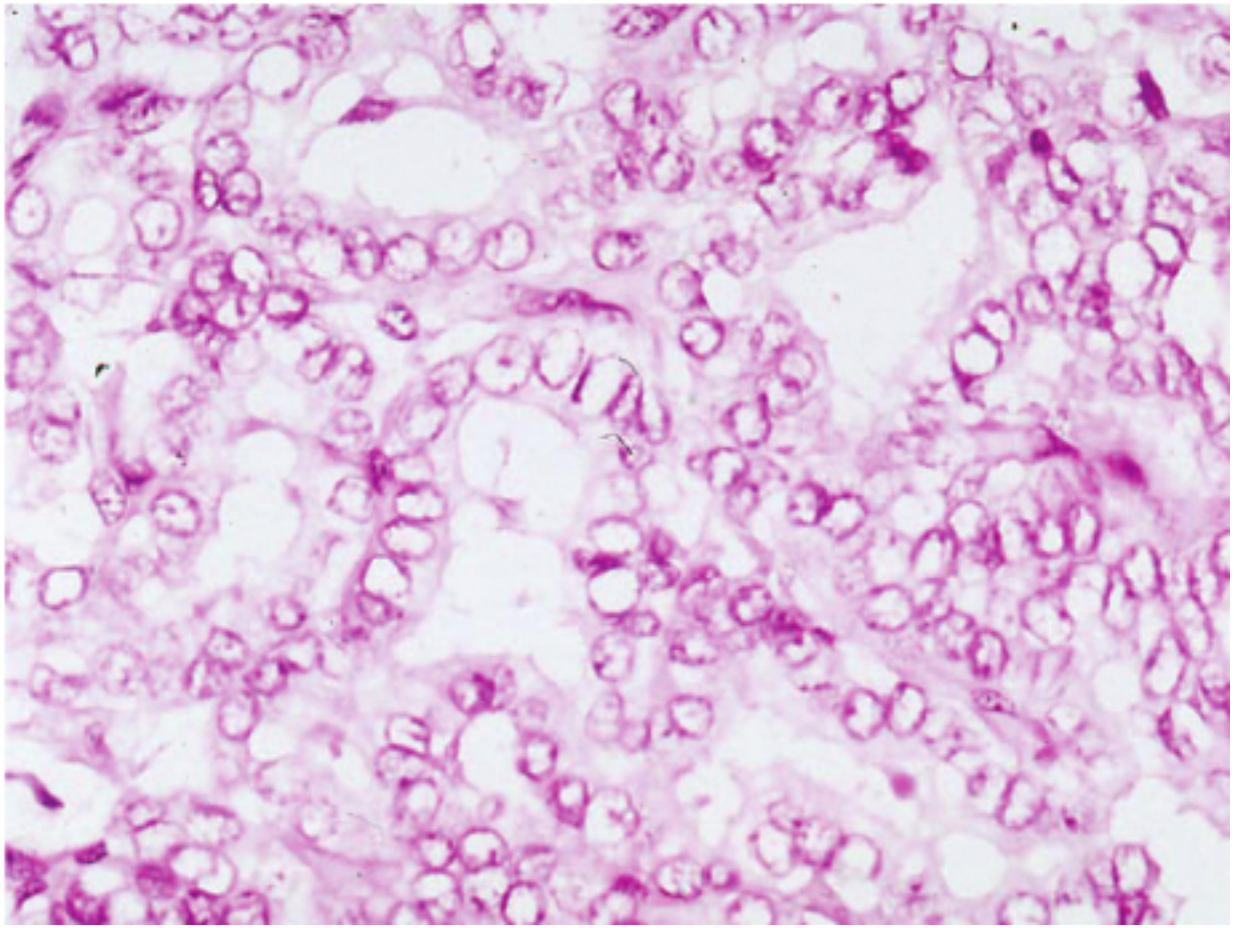
Note: all the red dots in the pic are red blood cells within the vessels.



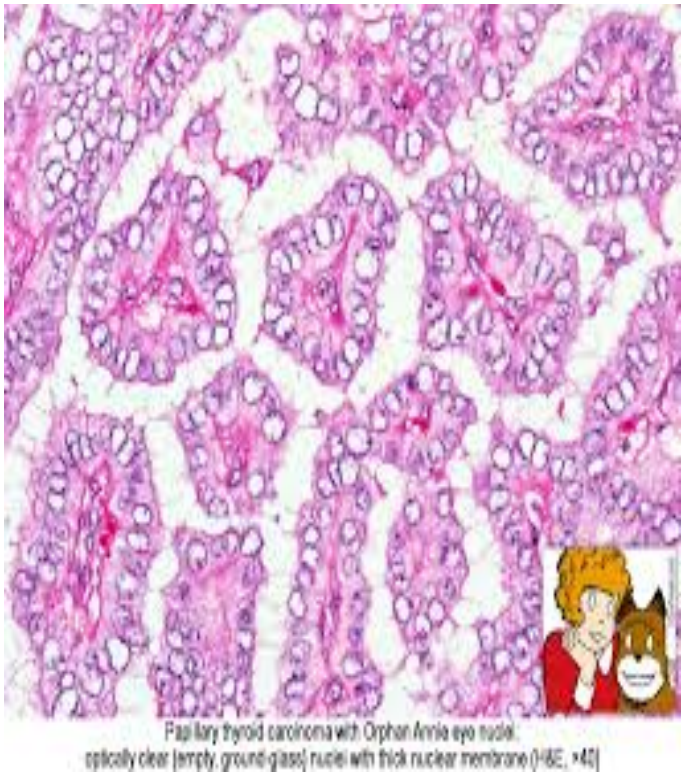
Nuclear features

1. optically clear nuclei, or "Orphan Annie eye" nuclei , seen on histological but not cytological preparations (formalin artefact)
2. Have invaginations of the cytoplasm to the nucleus (pseudoinclusions)
3. Grooves within nuclei: so the nucleus looks like a coffee bean.

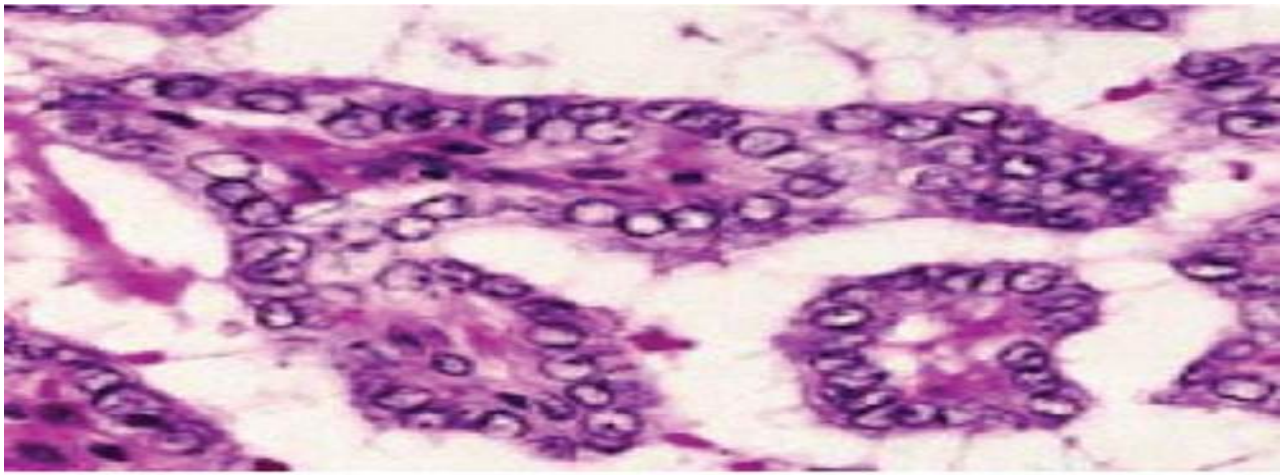
Clear nuclei: note the nuclei are white.



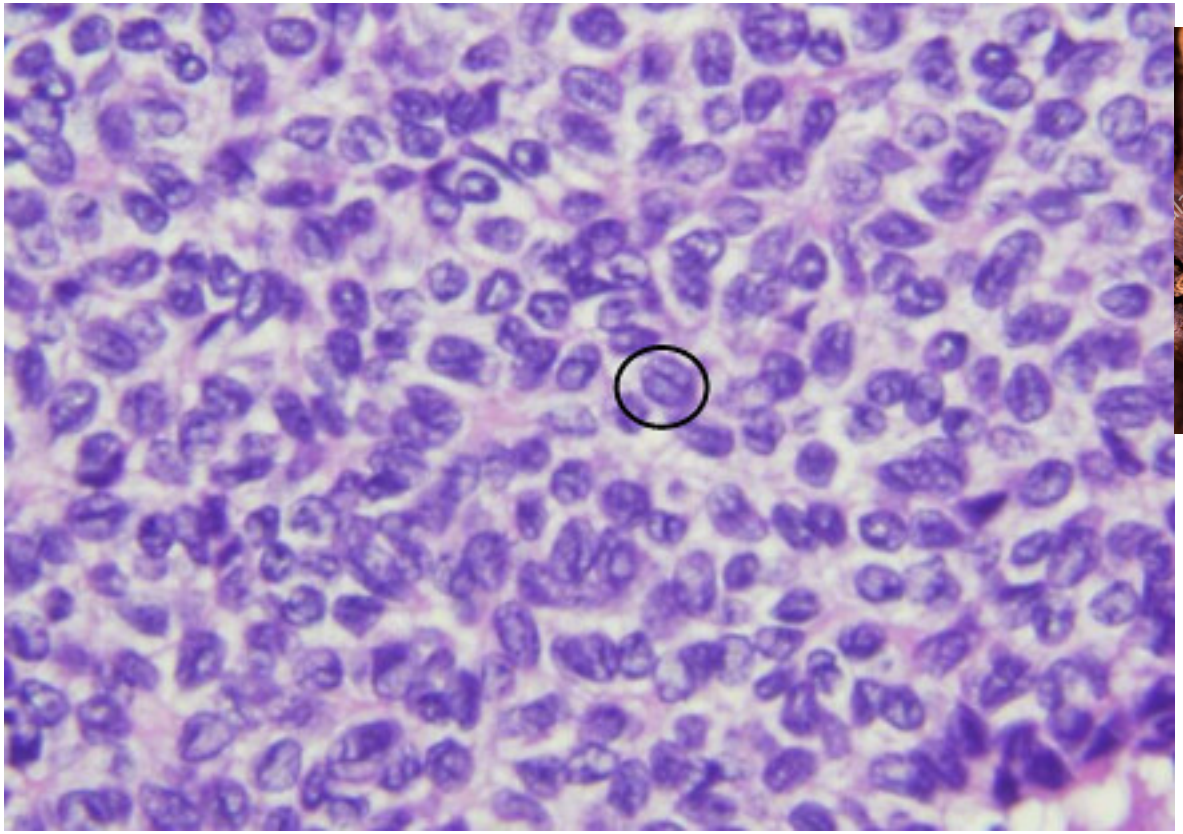
Orphan Annie eye! Because the nuclei are white and empty like Annie's character eyes!!


Papillary thyroid carcinoma with Orphan Annie eye nuclei: optically clear (empty, ground-glass) nuclei with thick nuclear membrane (H&E, ×40)

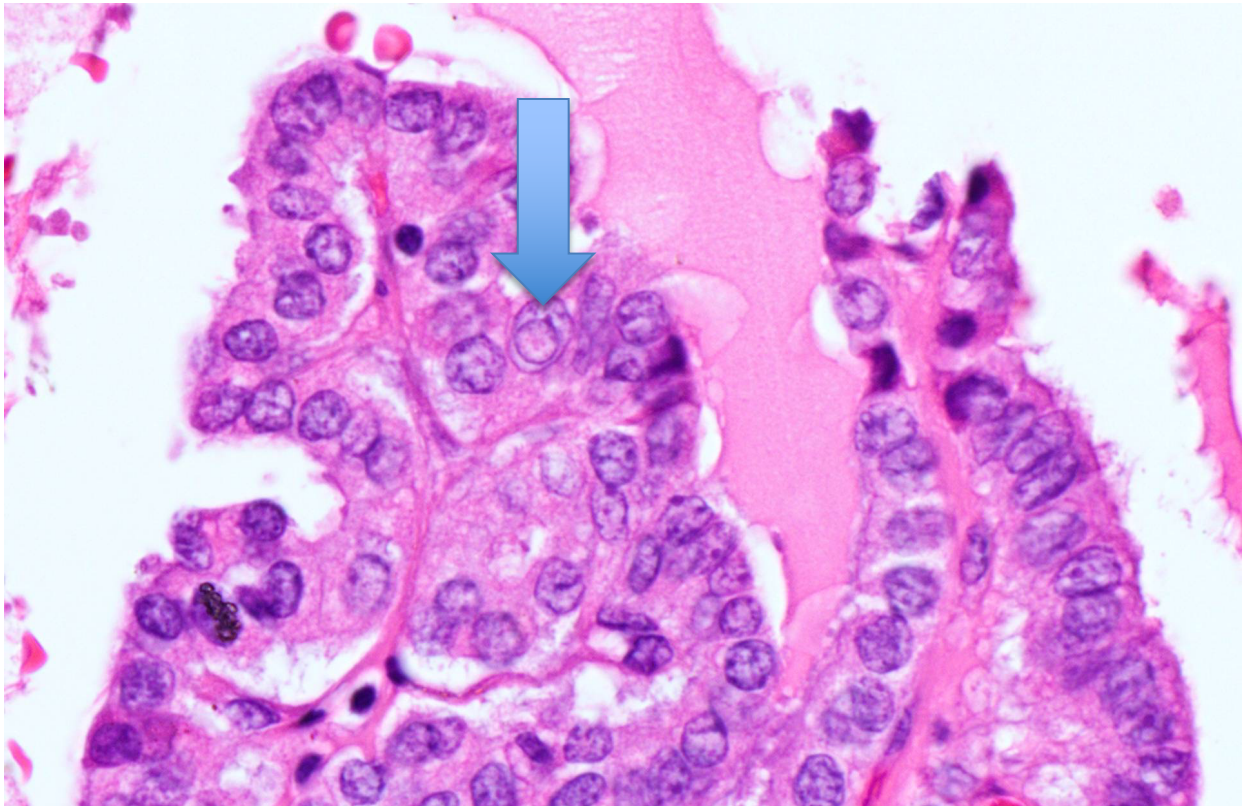
I know what you're thinking: pathological terms are funny.. You’re right



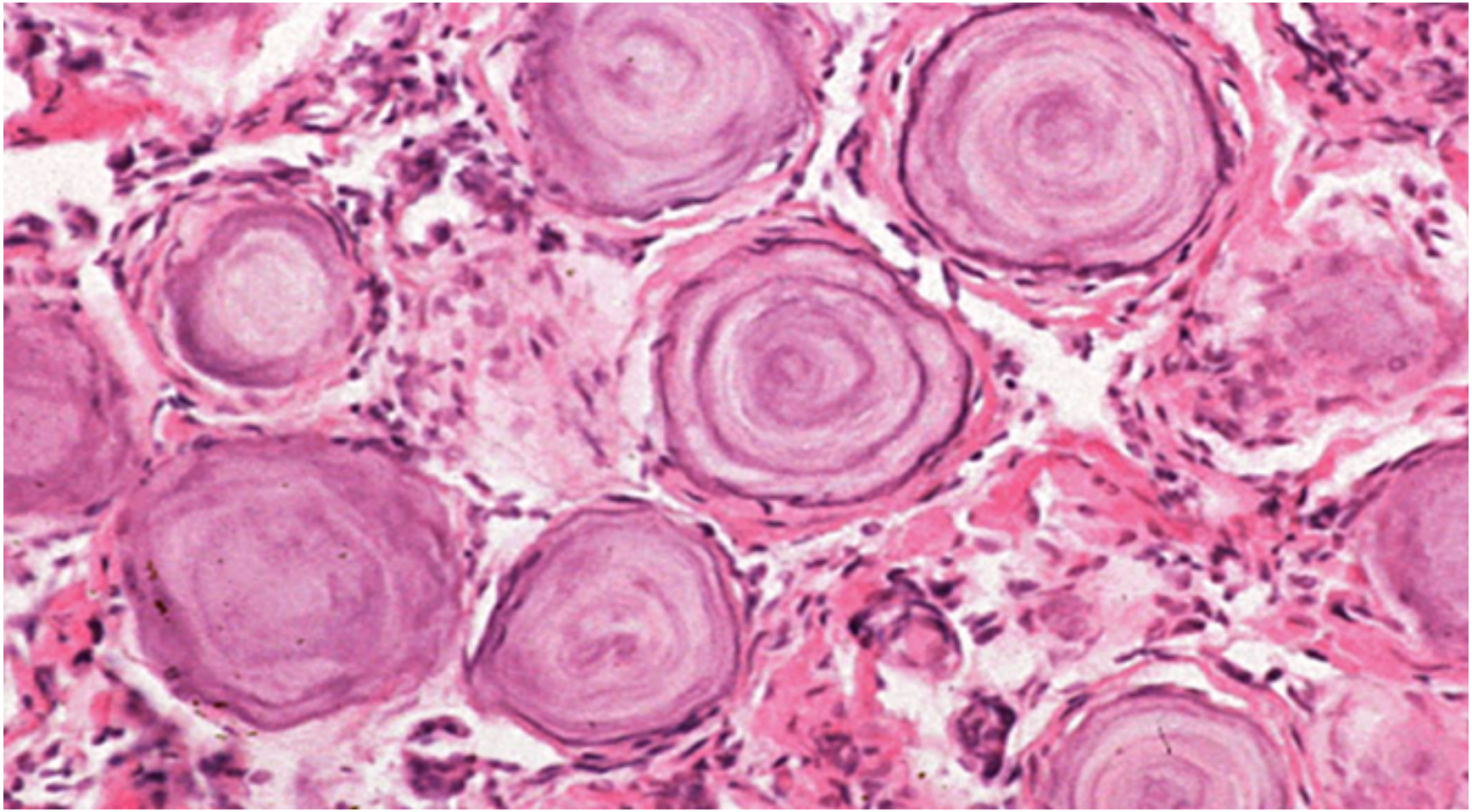
Nuclear grooves= coffee bean nuclei



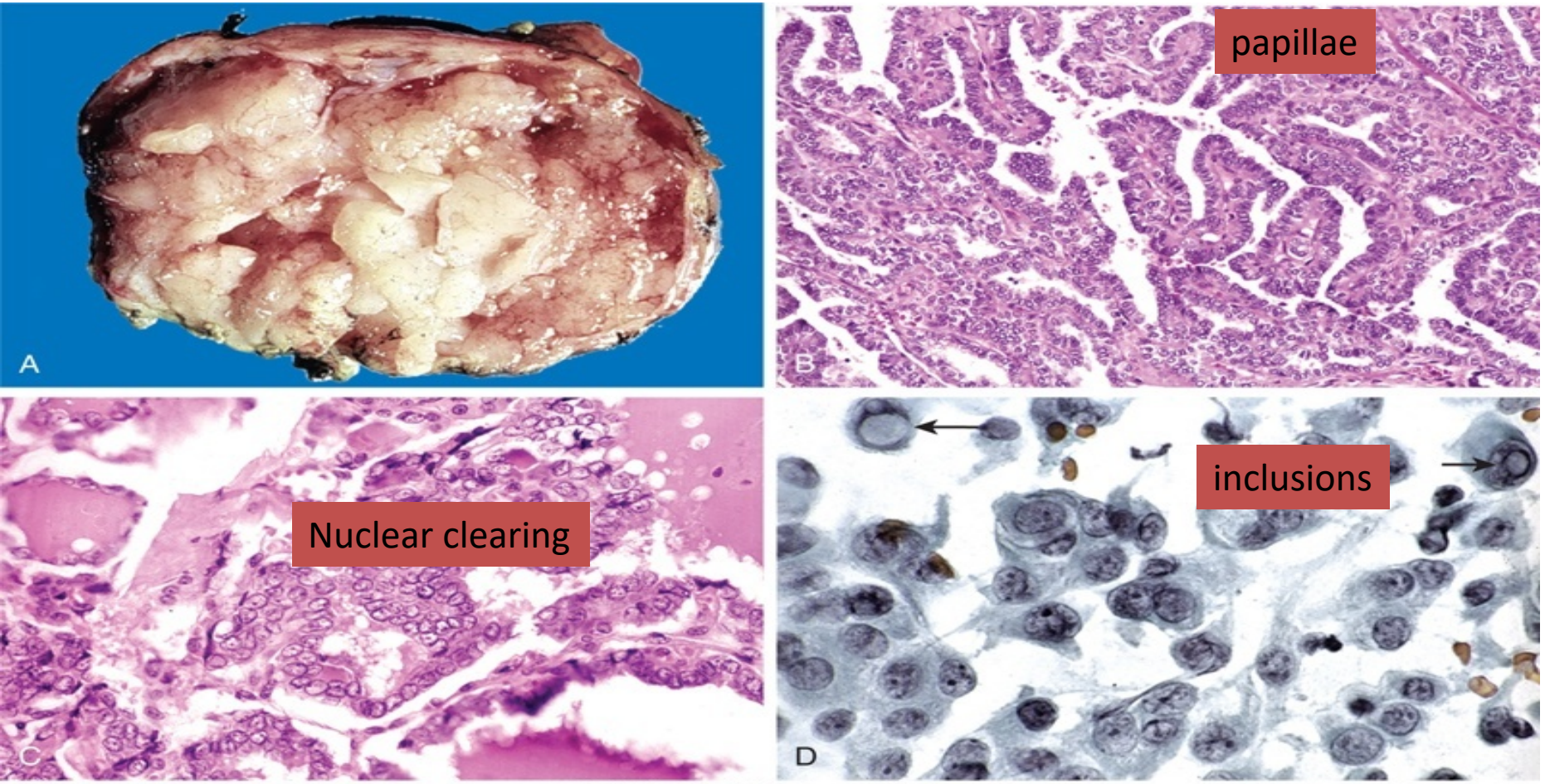
Nuclear inclusions



Psammoma bodies

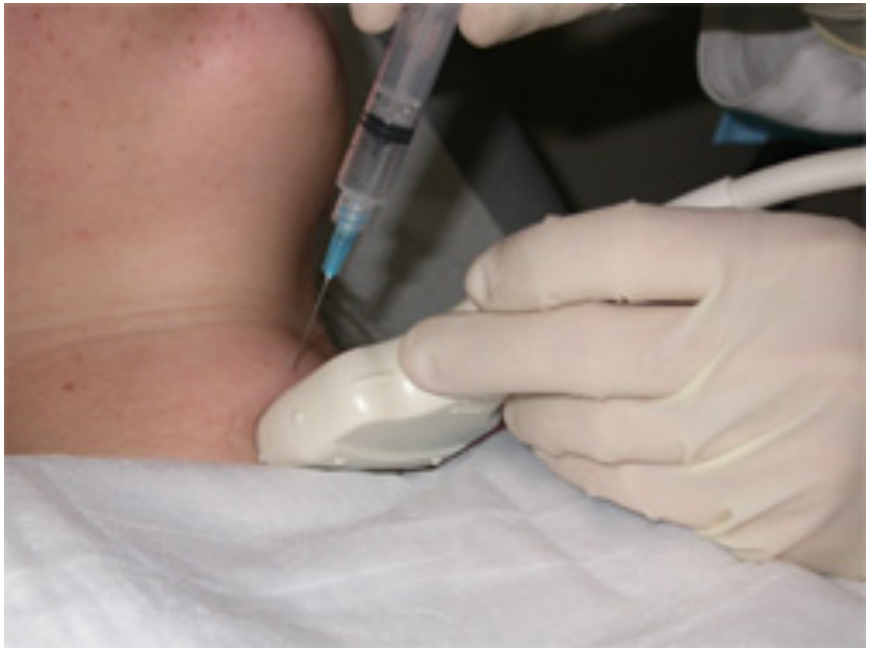


Papillary carcinoma

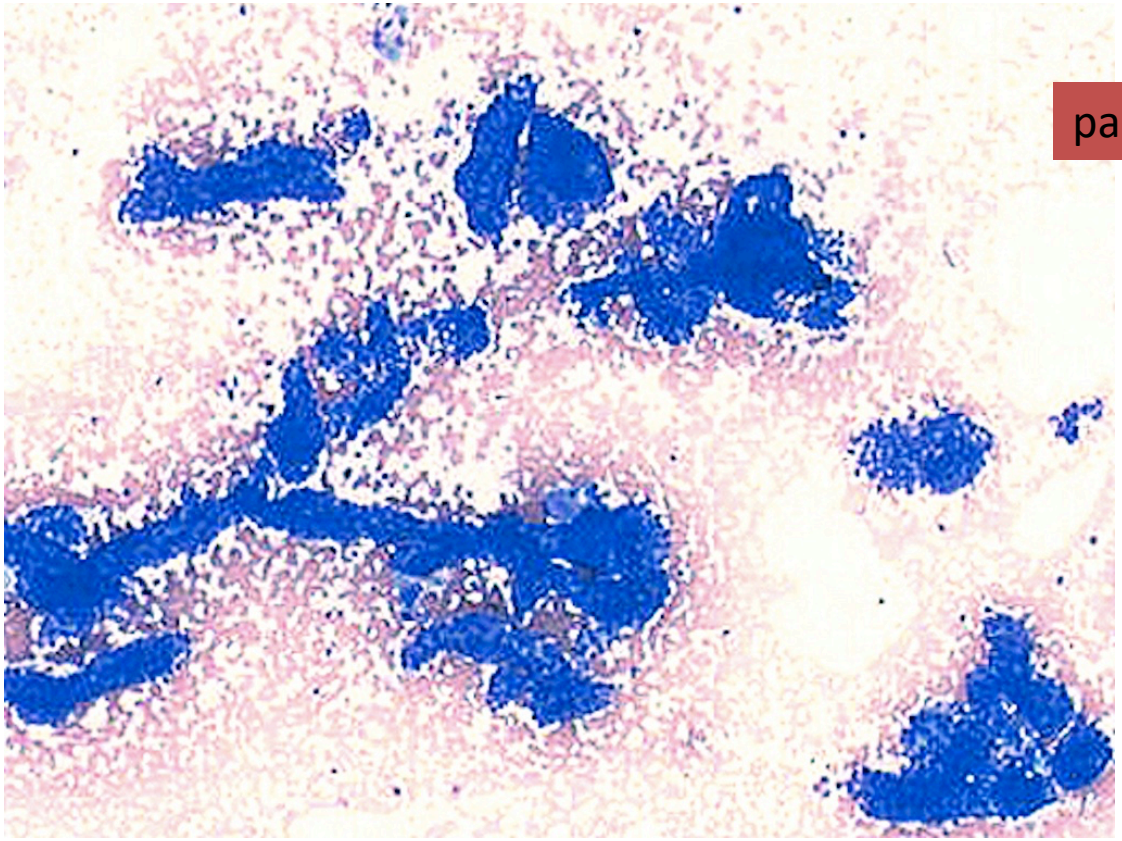


Kumar et al: Robbins Basic Pathology, 9e.

Papillary carcinoma can be diagnosed on FNA

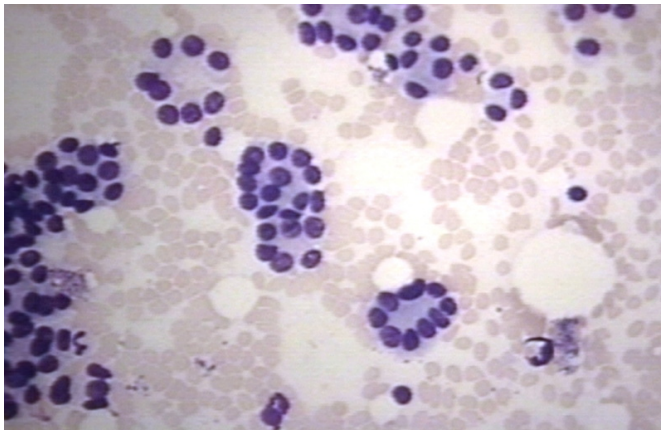


Papillae on FNA: compare to how rounded follicles are seen on the bottom pic

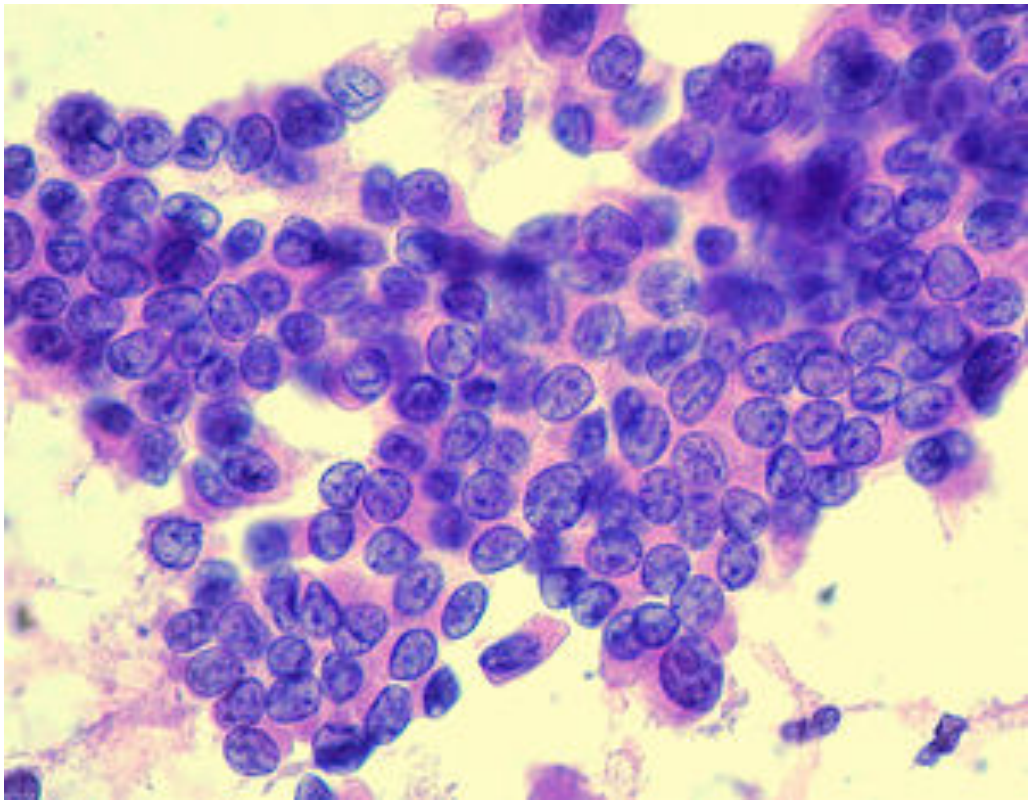


papillae

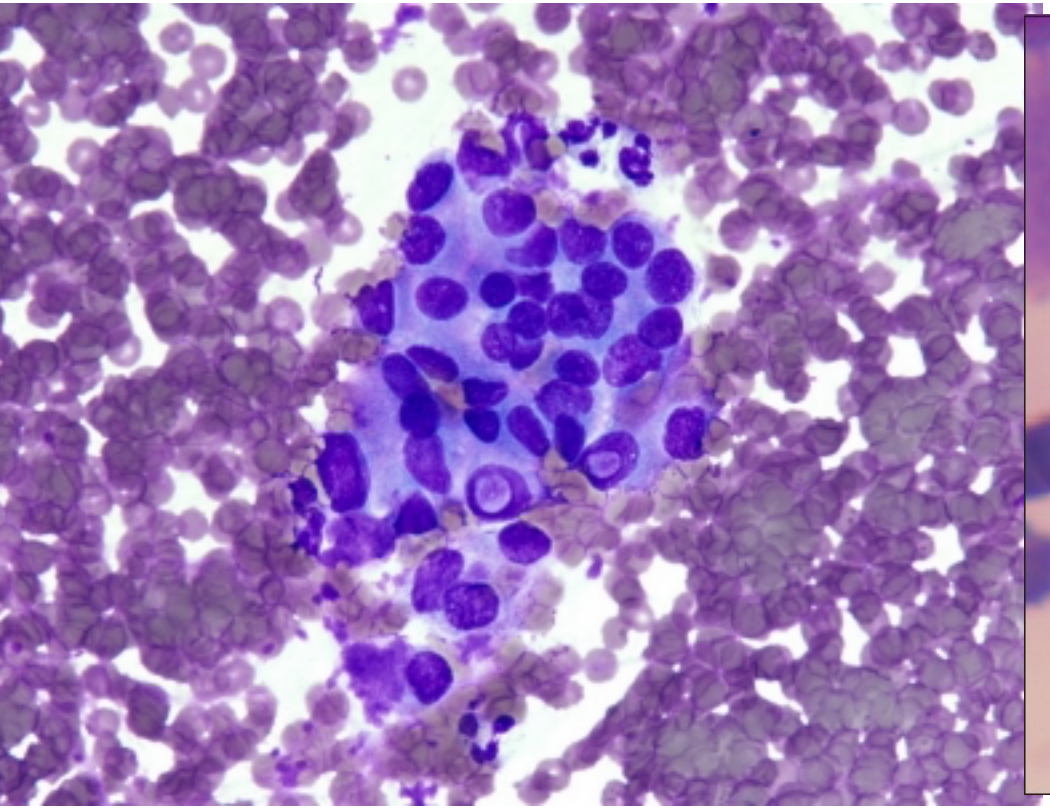
follicles

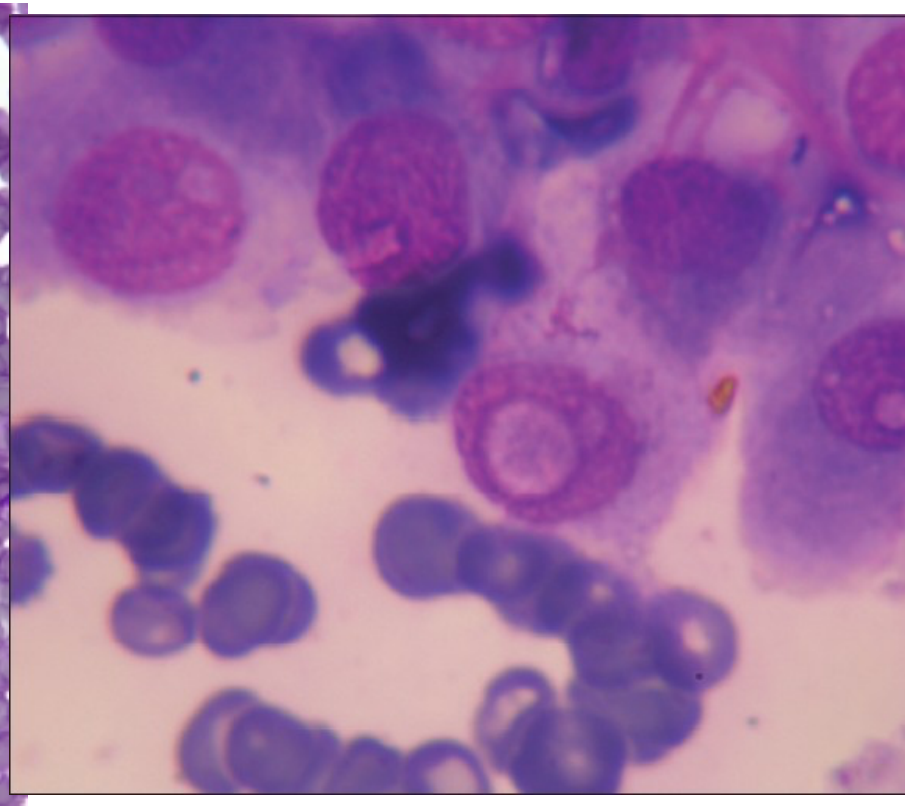


Grooves seen on FNA

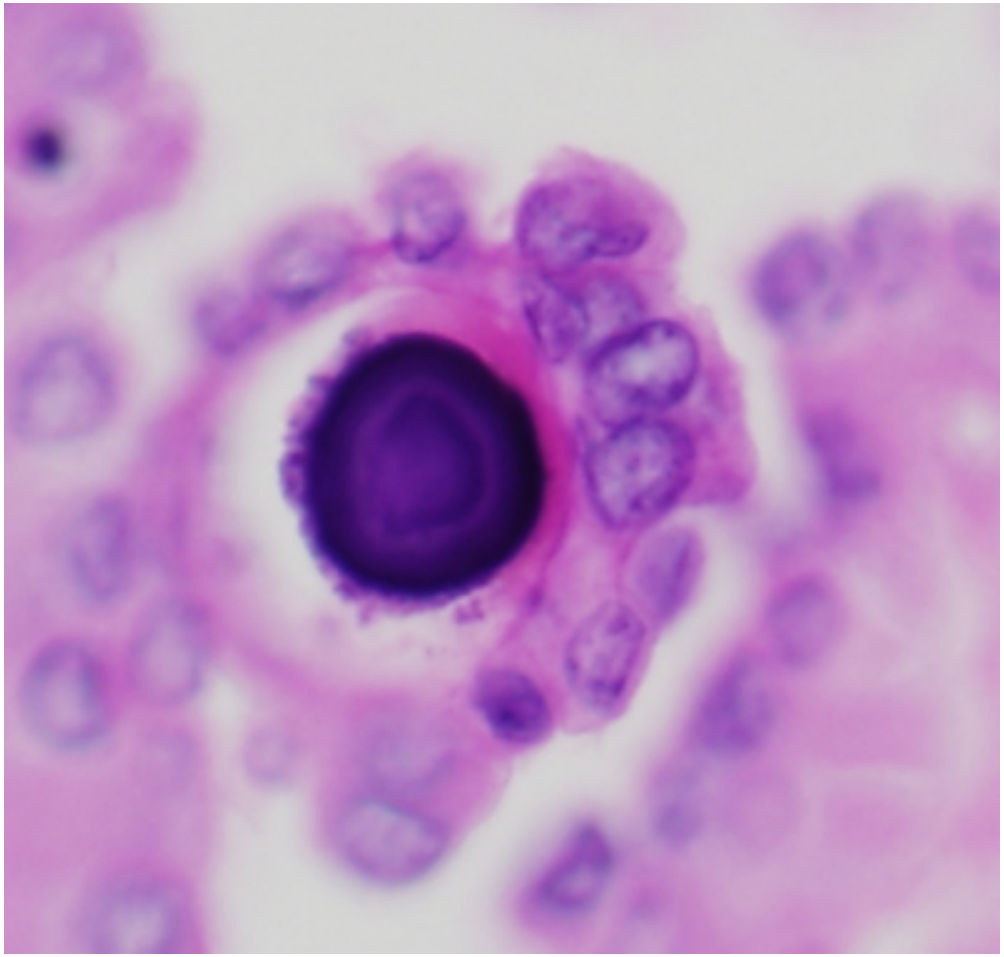


Inclusions seen on FNA





Psammoma bodies can be seen on GNA



note

- Clear nuclei are not seen in FNA because they are an artefact due to formalin.
- Formalin is used to fix *tissues* before staining them with H and E
- In cytological (FNA) preparations we use alcohol as a fixative, no formalin is used.. So no clearing artefact.

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.

Genetic factors related to papillary carcinoma

- Mainly 2 genes are involved:
- 1. BRAF amplification.
- 2. RET gene rearrangment resulting in a novel protein kinase.

- Remember from the neoplasia lectures that neoplasms occur if there is mutation increasing the effect of an oncogene or decreasing the effect of a tumor suppressor gene. Also DNA repair genes and apoptosis genes can be involved.
- In papillary thyroid carcinoma, 2 oncogenes can be upregulated: BRAF via amplification and RET (tyrosine kinase) via translocation (or rearrangement).

1. BRAF

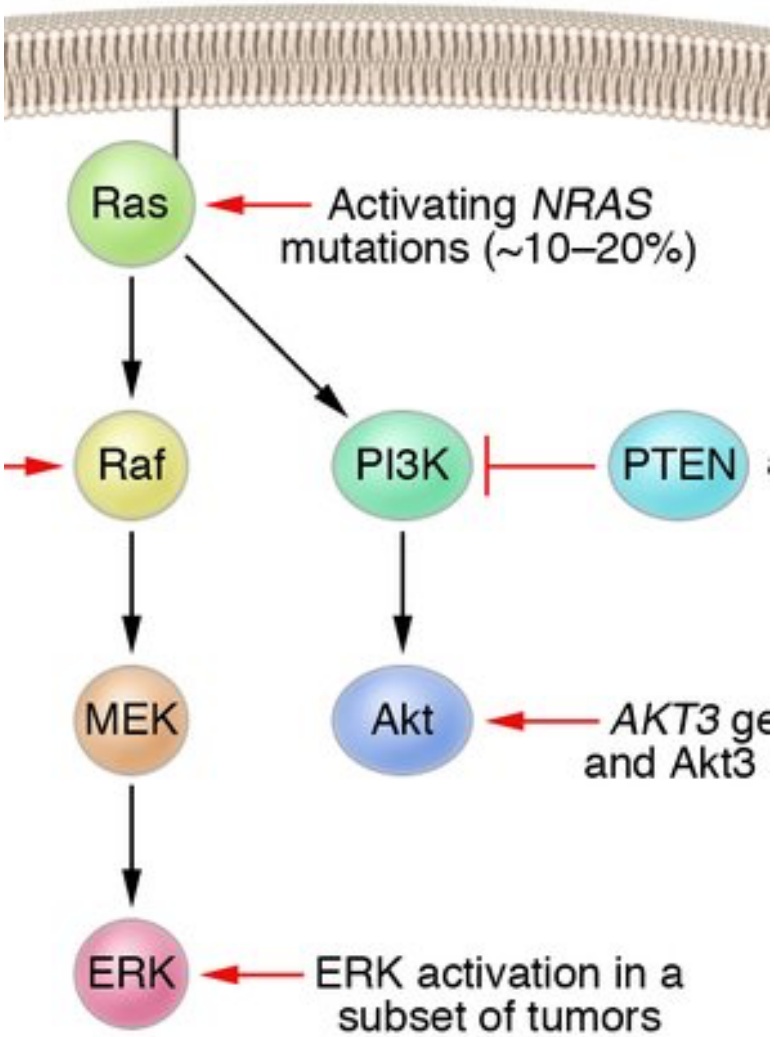
activating point mutations in *BRAF* can be seen in papillary thyroid carcinoma.

BRAF as an oncogene.. See next slide

Remember that RAS is the most commonly mutated oncogene.

RAS acts via second messeanges .. RAF is one of them

BRAF (of the RAF family genes) is an oncogene in the RAS pathway.



RET rearrangement= translocation

- The *RET* gene is not normally expressed in follicular cells but in papillary cancers, chromosomal rearrangements place the tyrosine kinase domain of *RET* resulting in a novel kinase .
- RET rearrangement is present in 20% to 40% of papillary thyroid cancers.

RET/PTC

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

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

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

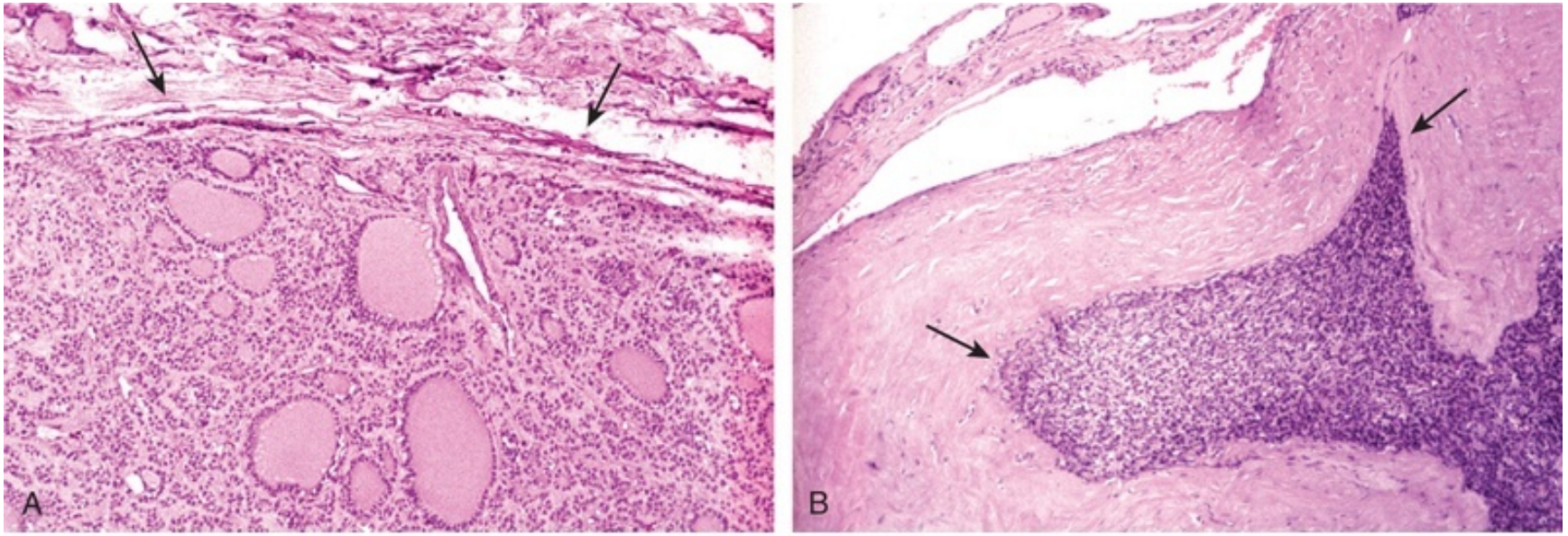
b. Minimally invasive that may be impossible to distinguish from follicular adenomas on gross examination and the .

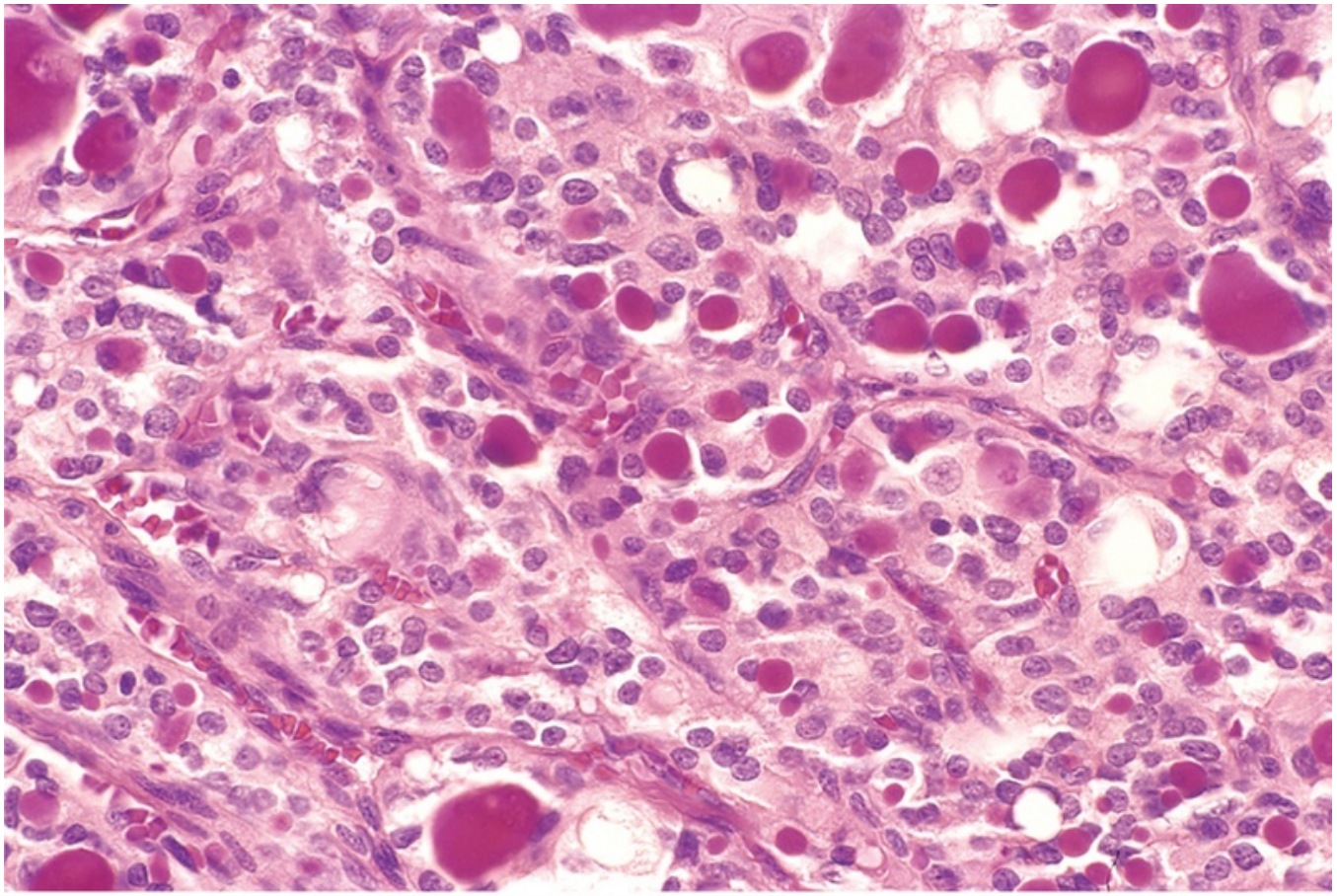
- requires extensive histologic sampling to exclude capsular and/or vascular invasion

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





GENETIC FACTORS

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**

,

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.**

GENETIC FACTORS

Anaplastic carcinomas:

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

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
- 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.

GENETIC FACTORS

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 .

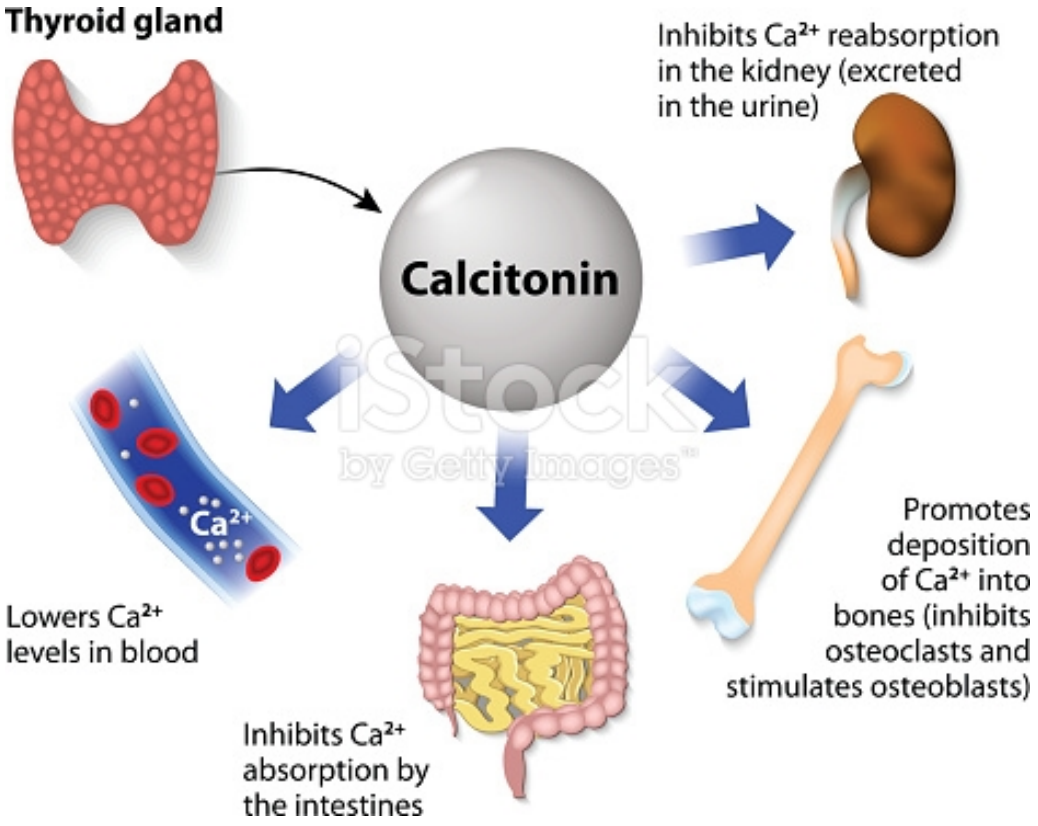
b. RET mutations are also seen in approximately one half of nonfamilial (sporadic) medullary thyroid cancers.

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.

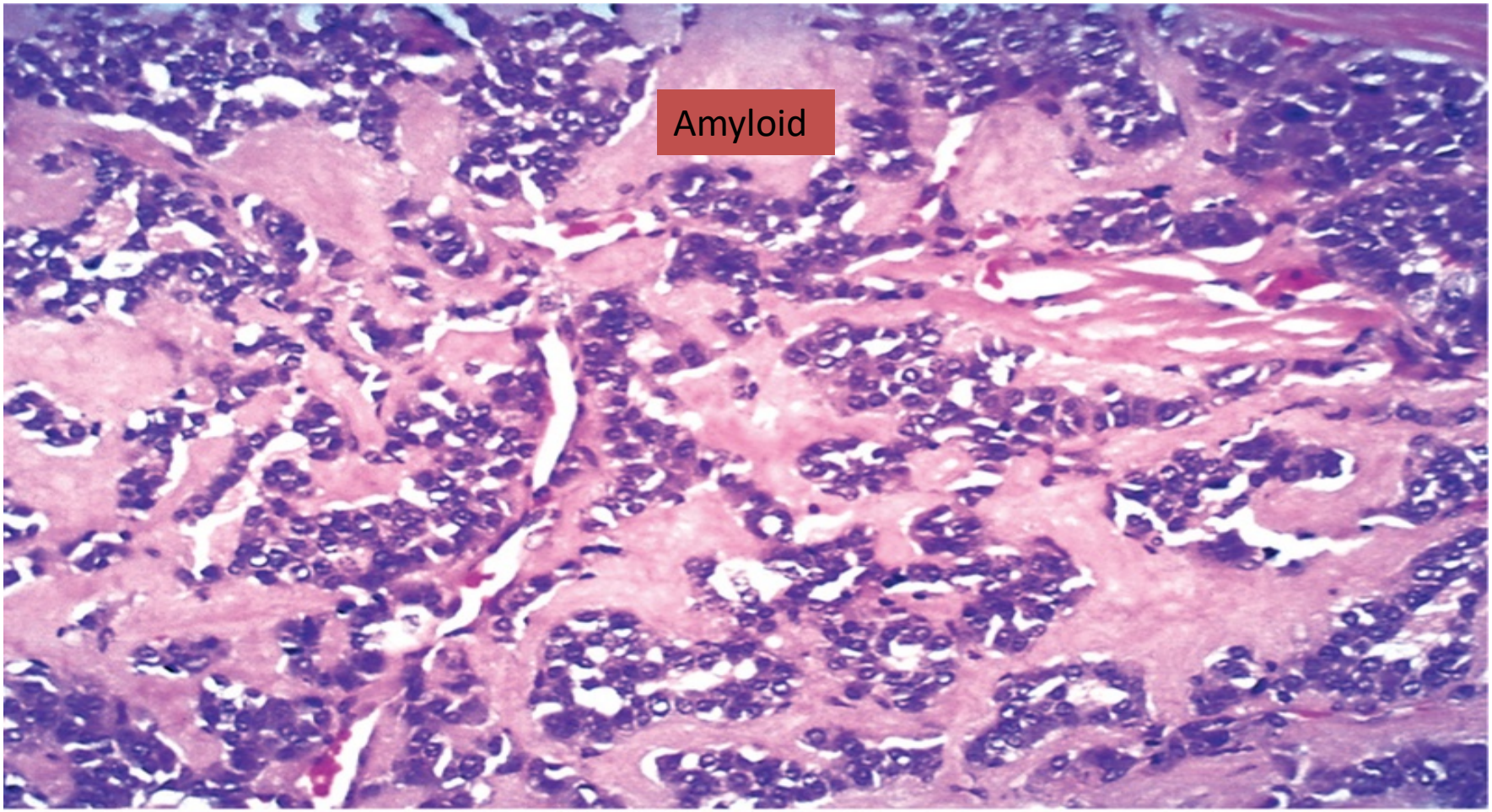
medullary


Thyroid gland
Inhibits Ca^{2+} reabsorption in the kidney (excreted in the urine)
Calcitonin
Ca^{2+}
Lowers Ca^{2+} levels in blood
Inhibits Ca^{2+} absorption by the intestines
Promotes deposition of Ca^{2+} into bones (inhibits osteoclasts and stimulates osteoblasts)

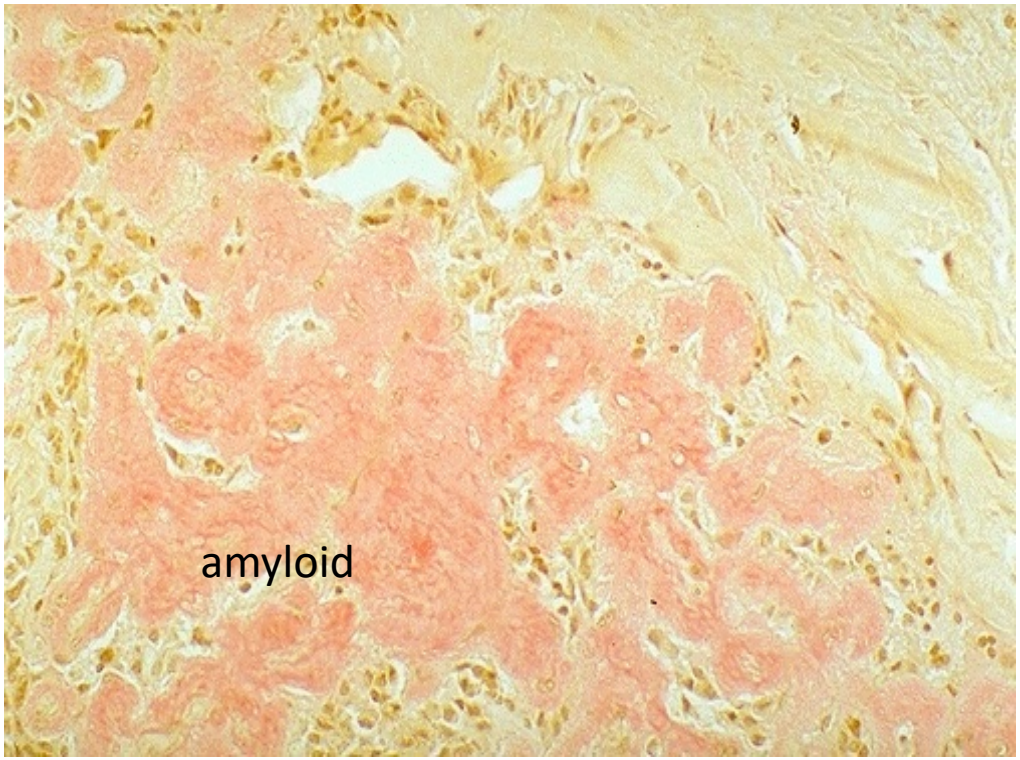
- Because medullary carcinoma secrete calcitonin; this calcitonin can accumulate and form amyloid protein.

- Amyloid: is several, chemically different proteins that share similar physical characteristics.. They can accumulate and form pink material called amyloid.. See next pic.

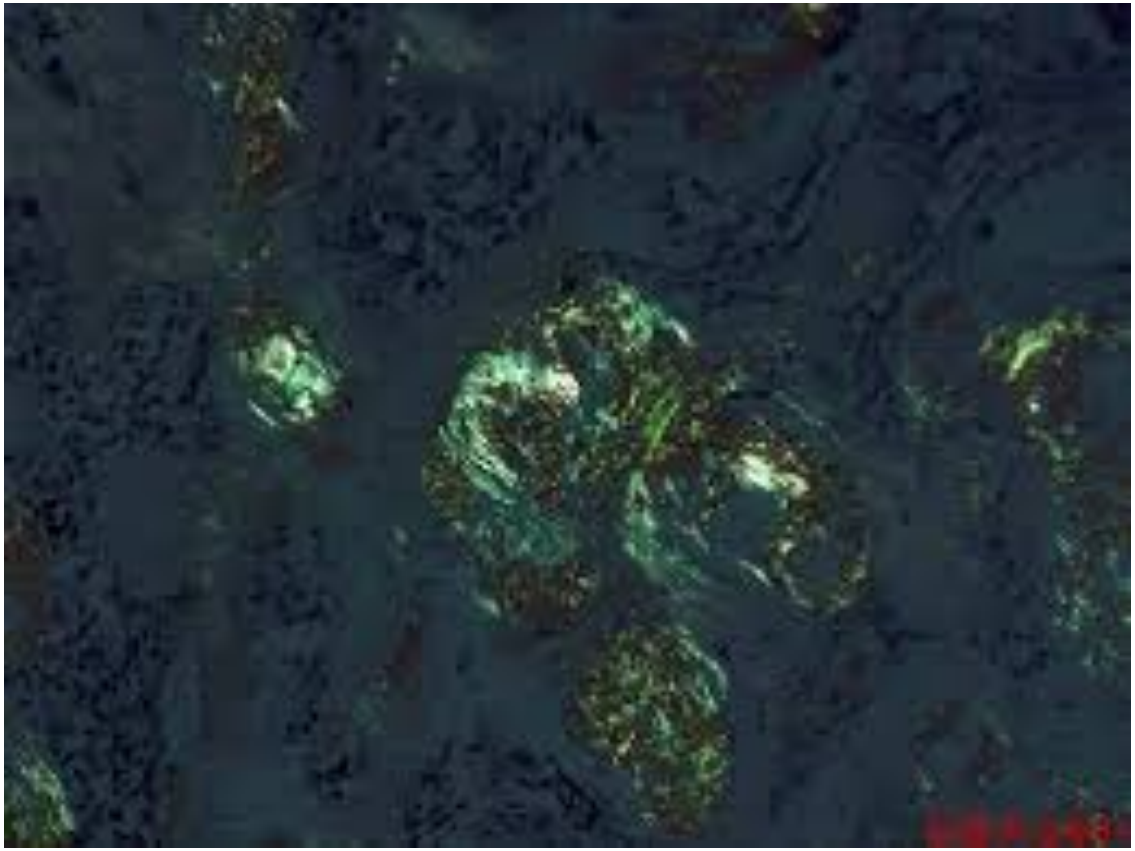
Medullary carcinoma



Amyloid stains with Congo red stain



With polarized light, amyloid gives this apple green color when stained with congo red




Thank you!