Summary/takeaway up here

Questions about lecture content in red.

Questions relevant to material from lecture but not necessarily from the lecture are in yellow

Information from lecture in the green textbox

Information from outside sources in the black textbox

The pointy box will have information referring to what it is pointing at

The Endocrine System

APPROVED

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Lecture overview

The Endocrine System

- Pituitary gland
- Thyroid gland
- Parathyroid glands
- Endocrine Pancreas
- Adrenal glands
- Pineal gland

this lecture's main focus

she will go over a little bit of pathology here

The anterior pituitary is the main producer of hormones in the pituitary gland. The table lists the types of cells located in it and their properties.

Pituitary gland

From what germ layer does the adenohypophysis arise? What embryological structure formed from this germ layer is the precursor to the adenohypophysis?

- Two components:
- Anterior (adenohypophysis); 80%

Associated syndrome due to hyperproduction of the hormone

Pituitary cell type	Hormone	Cytoplasm characteristics	Associated syndrome
Somatotrophs	GH	acidophilic cells (eosinophilic cytoplasm)	Gigantism (children) Acromegaly (adults)
Lactotrophs (mammosomatotrophs)	Prolactin, GH	acidophilic cells	Galactorrhea and amenorrhea (females) Sexual dysfunction, infertility (males)
Corticotrophs	ACTH, MSH, POMC	basophilic cells (basophil cytoplasm)	Cushing syndrome Nelson syndrome
Thyrotrophs	TSH	pale basophilic cells	Hyperthyroidism
Gonadotrophs	FSH, LH	basophilic cells	Hypogonadism, mass effects, hypopituitarism

The posterior pituitary doesn't produce hormones. It stores and secretes oxytocin and ADH, which are produced by the hypothalamus.

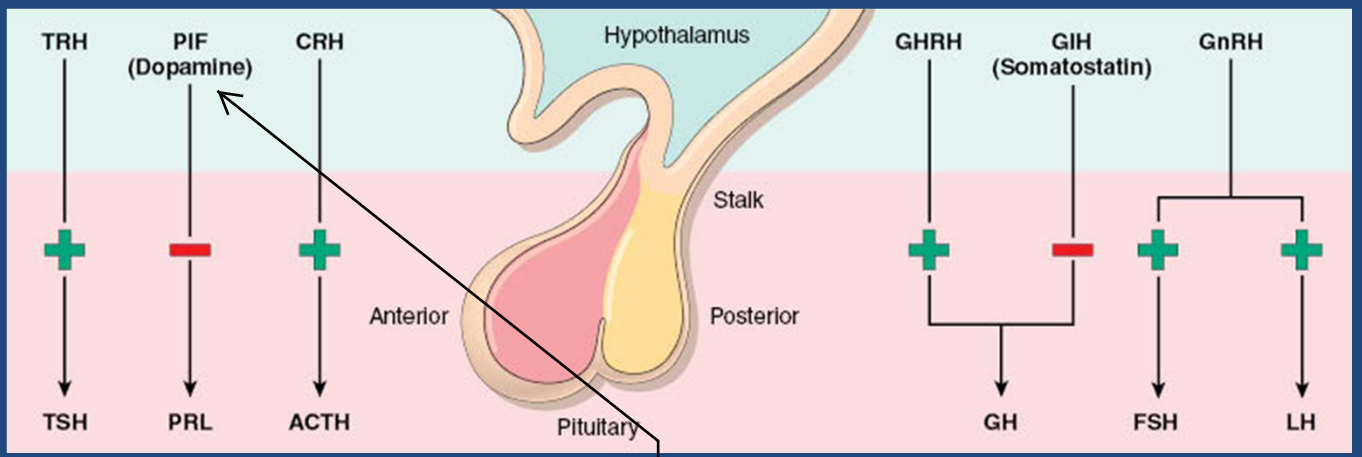
From what germ layer does the neurohypophysis arise?

Pituitary gland

- Posterior (neurohypophysis); modified glial cells extending from hypothalamus (*axon terminals*):
  - Oxytocin

    (contraction of uterine and lactiferous ducts smooth muscle)
  - Antidiuretic hormone (ADH) (vasopressin)

    (water conservation)



Note that the hypothalamus, through dopamine, has an inhibitory effect on prolactin secretion from the adenohypophysis. Thus, hyperprolactinemia results from anything that blocks dopamine from inhibiting the adenohypophysis; such things include infarction of the stalk and tumors.

Pituitary gland diseases of various etiologies can either present as too much trophic hormone (hyper-) or too little (hypo-).

Clinical manifestations of pituitary gland disease

- Hyperpituitarism (excess secretion of trophic hormones)

  most common cause of hyperpituitarism is adenoma

  - Adenomas, hyperplasia, carcinoma of anterior pituitary, etc

- Hypopituitarism (deficiency of trophic hormones)

  - Ischemic injury, surgery, radiation, inflammation

- Local mass effects

  - sella turcica abnormalities

What hormones do the neurohypophysis secrete? Where are these hormones produced?

Dr. Veras is going to use clinical scenarios to illustrate the pathogenesis and presentation of pituitary disease.

Case 1

- 35 year old female presents with amenorrhea, galactorrhea, visual complaints and headache. CT scan discloses a 2 cm mass in the anterior pituitary.
- What's the most likely cause?

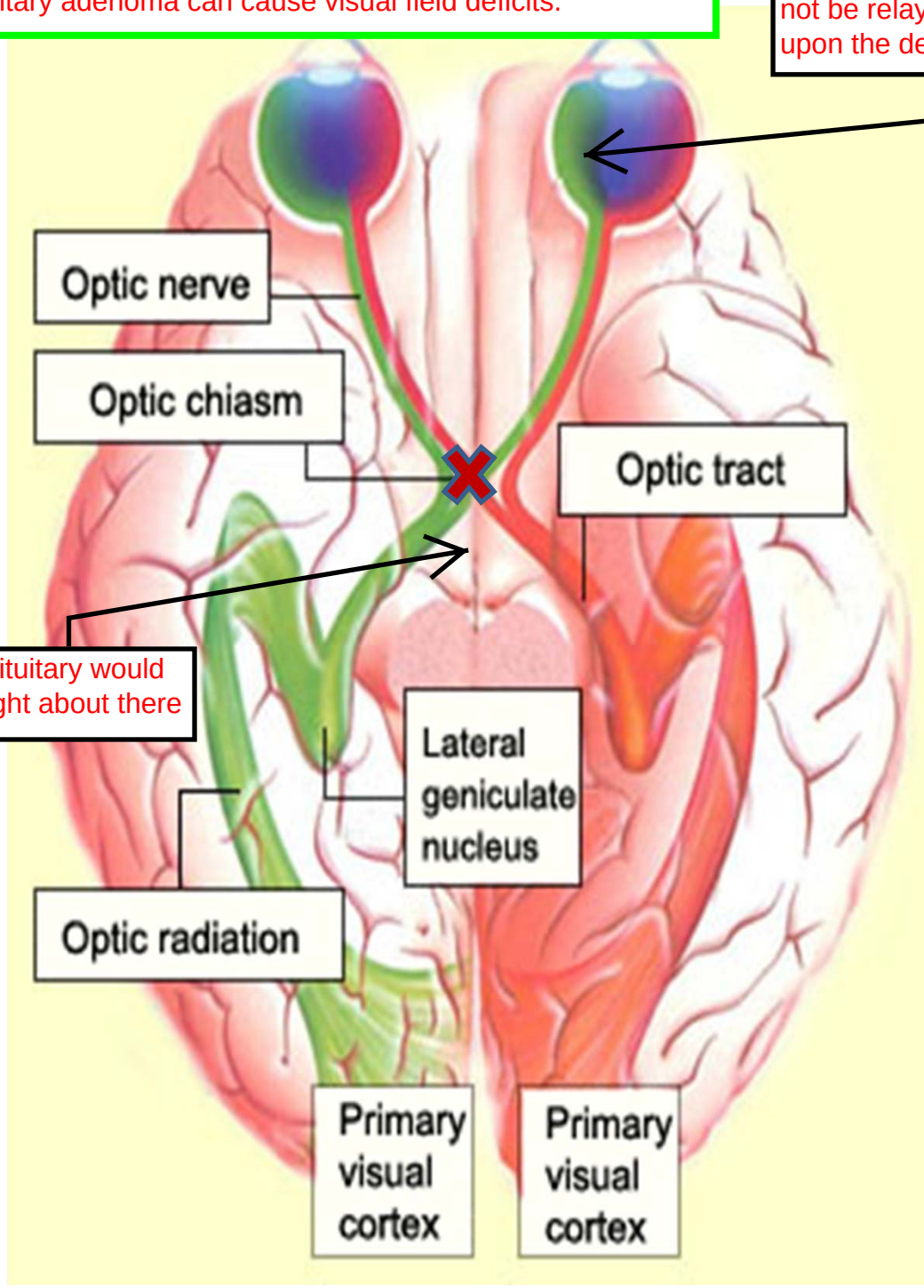
remove this text-box to reveal the answer. The sticky note expounds upon the answer.

- What could explain the "visual disturbances"?

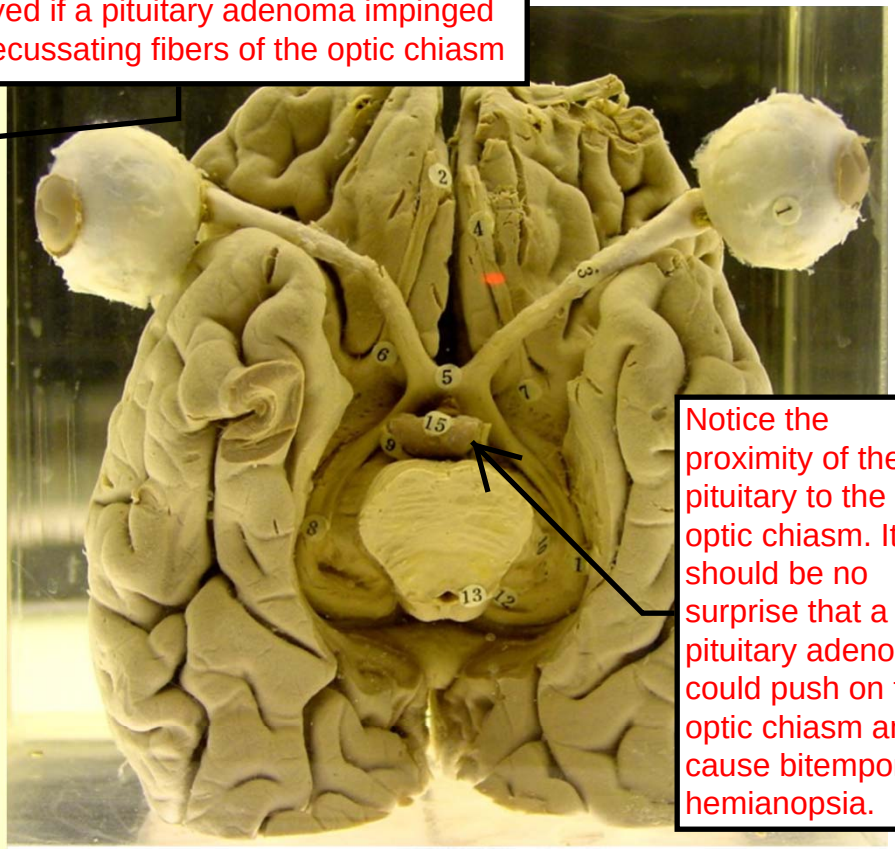
remove this text-box to reveal the answer. The sticky note expounds upon the answer.

The anatomy of the brain shows how mass effect from a pituitary adenoma can cause visual field deficits.

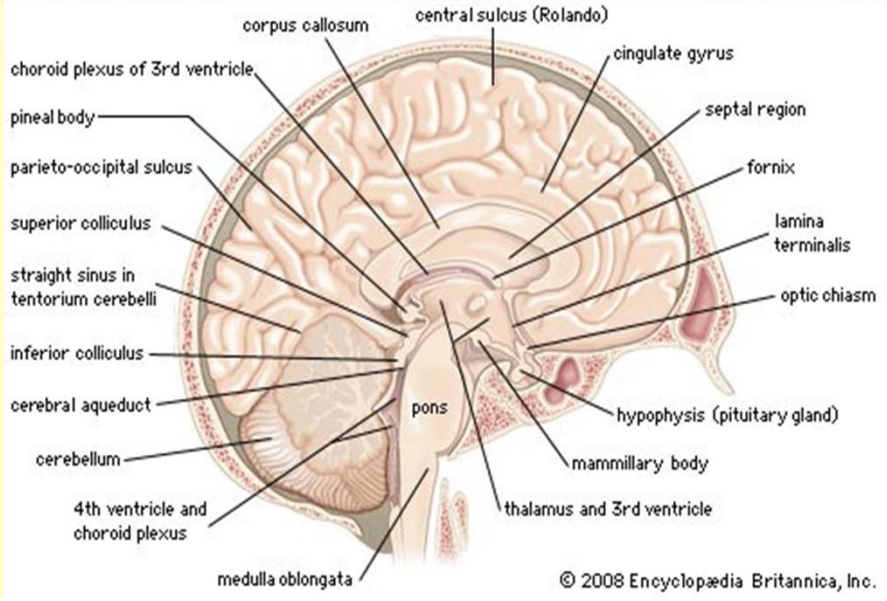
visual information coming from the part of the visual field where this text box is located would not be relayed if a pituitary adenoma impinged upon the decussating fibers of the optic chiasm



the pituitary would be right about there



Notice the proximity of the pituitary to the optic chiasm. It should be no surprise that a pituitary adenoma could push on the optic chiasm and cause bitemporal hemianopsia.



Just read

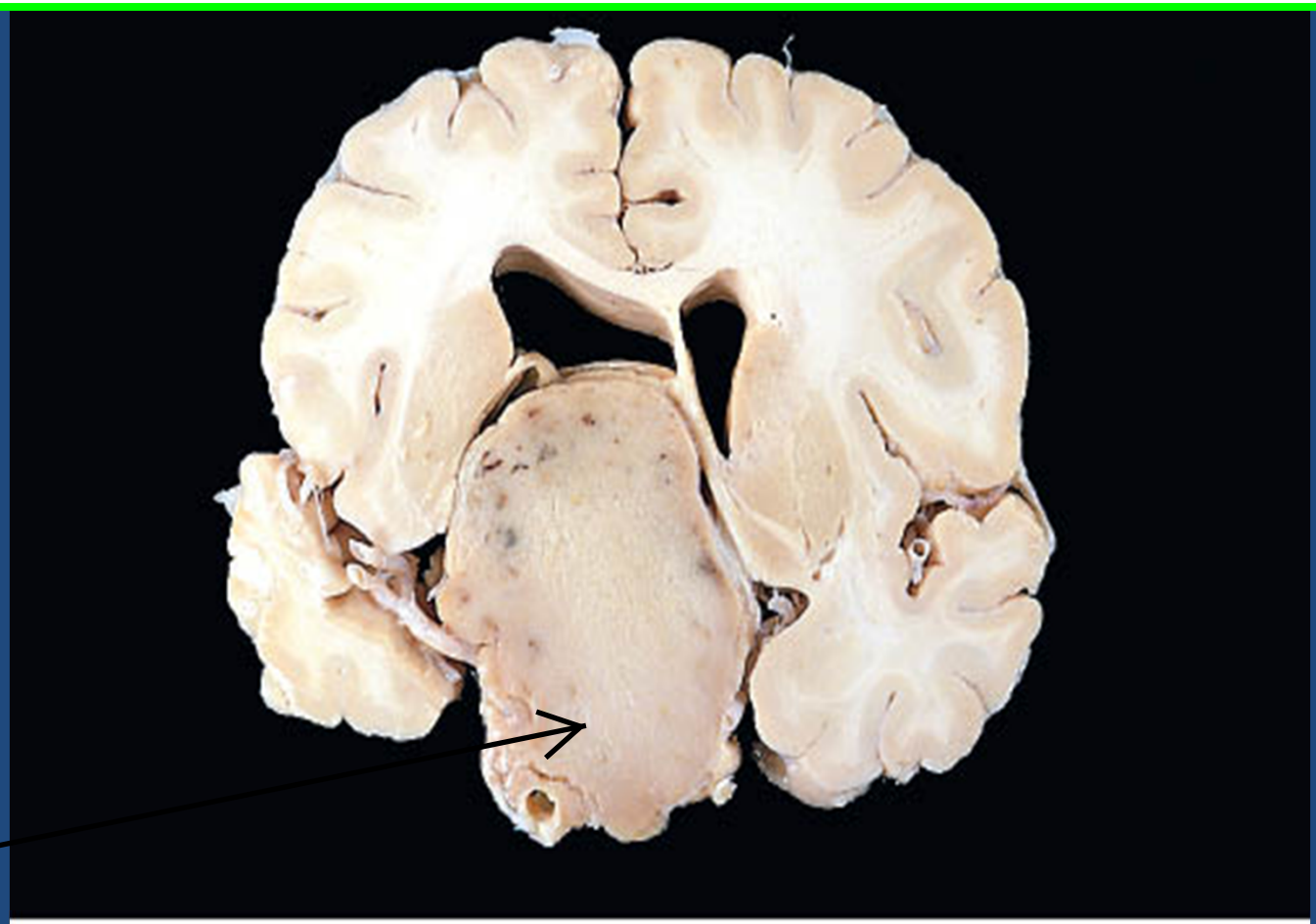
Pituitary Adenomas

- Most common cause of hyperpituitarism
- Functional or non-functional
- Affects adults (35-60)
- Microadenomas: < 1 cm
- Macroadenomas: > 1 cm
- Gross appearance: soft, well-circumscribed, and confined to sella turcica
- Microscopically: monotonous population of polygonal cells lacking significant reticulin framework.

The non-functional adenomas (i.e. no hypersecretory symptoms like galactorrhea) tend to get caught when big and cause compressive symptoms, like the bitemporal hemianopsia previously described. The functional adenomas tend to get caught when they are small since their hypersecretory symptoms are pronounced even when the tumor is not very large.

To understand what this means, go to slides 11, 12, and 13 to see the explanation of what the normal microanatomy should look like. framework

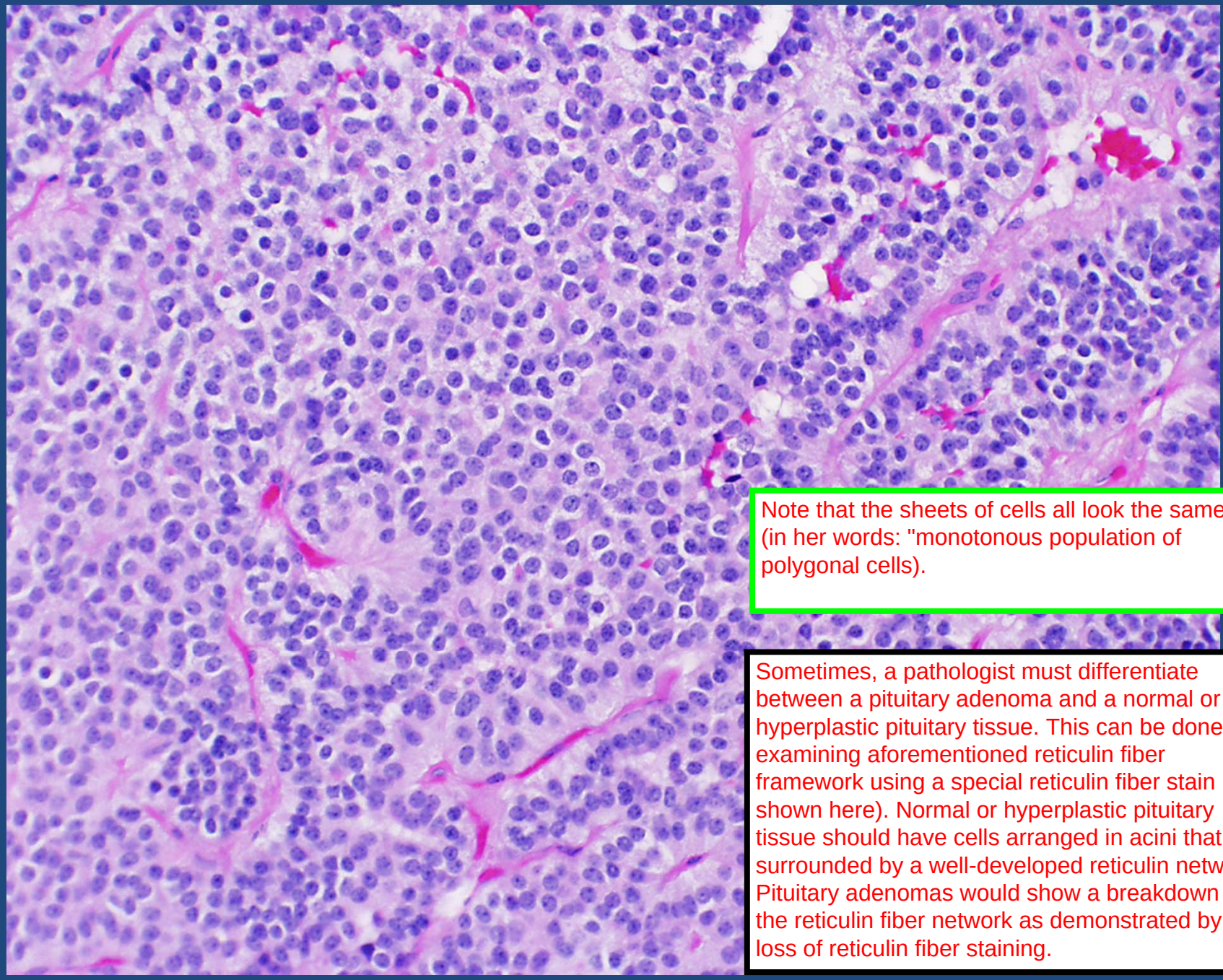
A nonfunctional adenoma, which are characteristically large. This sucker was so big it grew out of the sella tucica; Dr. Veras said that outgrowing the sella turcica is usually not the case.



Found it!

FIGURE 24–4 Pituitary adenoma. This massive, nonfunctional adenoma has grown far beyond the confines of the sella turcica and has distorted the overlying brain. Nonfunctional adenomas tend to be larger at the time of diagnosis than those that secrete a hormone.

This is the microscopic appearance of a pituitary adenoma.

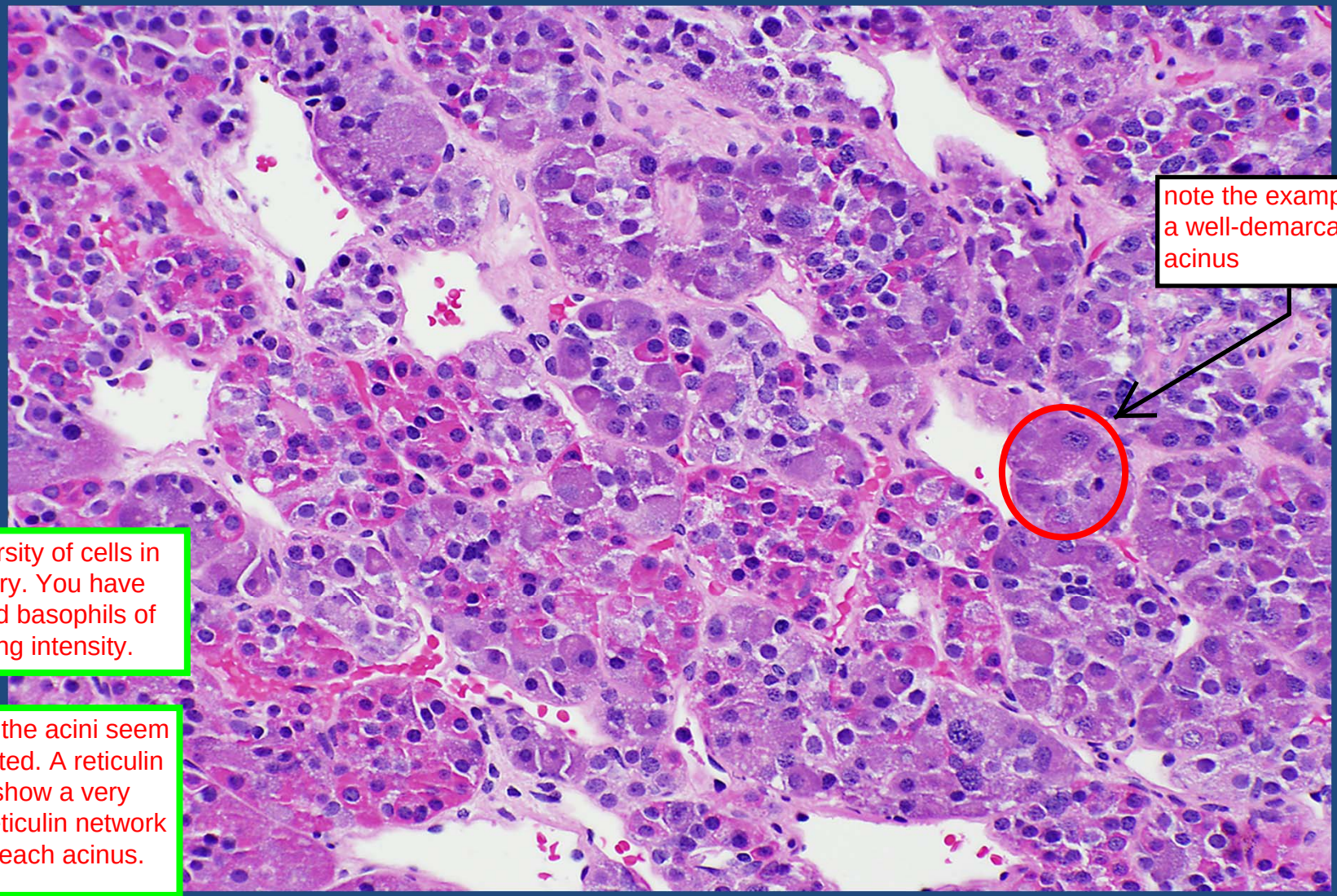


Note that the sheets of cells all look the same (in her words: "monotonous population of polygonal cells).

Sometimes, a pathologist must differentiate between a pituitary adenoma and a normal or hyperplastic pituitary tissue. This can be done by examining aforementioned reticulin fiber framework using a special reticulin fiber stain (not shown here). Normal or hyperplastic pituitary tissue should have cells arranged in acini that are surrounded by a well-developed reticulin network. Pituitary adenomas would show a breakdown of the reticulin fiber network as demonstrated by a loss of reticulin fiber staining.

This is normal pituitary tissue noted for its diverse cells, well-demarcated acini, and a robust reticulin network (which would be best seen with a special reticulin fiber stain).

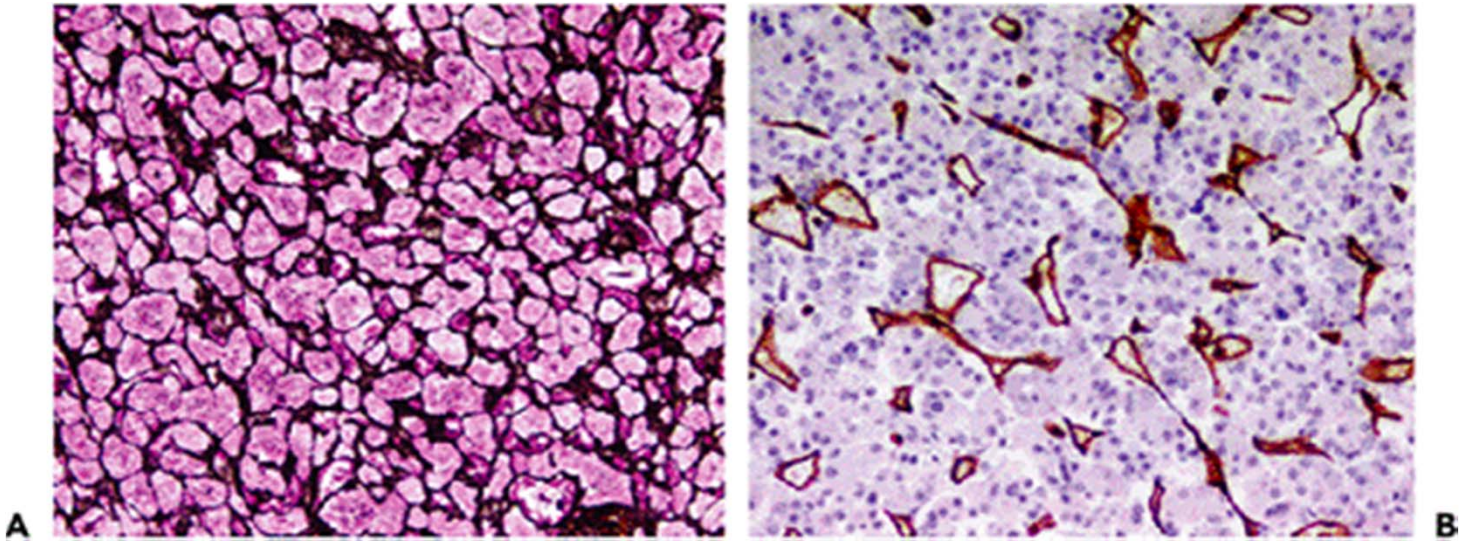
Normal pituitary acinar checkerboard



Note the diversity of cells in normal pituitary. You have acidophils and basophils of various staining intensity.

Look at how the acini seem to be separated. A reticulin stain would show a very nice intact reticulin network surrounding each acinus.

I inserted this slide to show you what a reticulin stain would look like in a normal pituitary vs an adenoma



Normal pituitary
w/ intact reticulin
network surrounding
the acini

Pituitary adenoma
w/ the breakdown of
the reticulin network
around the acini

What is the size of a microadenoma? What is the size of a macroadenoma?

Starting to go into some specific pituitary adenomas.
Prolactinoma ----> hyperprolactinemia

Few words about specific adenomas

- Prolactinomas:
  - Most common pituitary adenoma
  - Tendency for calcification ("pituitary stone")
- Causes of hyperprolactinemia:
- Prolactinoma, pregnancy, lactotroph hyperplasia (inhibition of dopamine secretion)

Dopamine(inhibitory)  prolactin

Tx: dopamine receptor agonists

Simulate dopaminergic inhibition of the adenohypophysis to decrease prolactin secretion.

Any time you have inhibition of dopamine secretion (e.g. stalk damage or apoplexy) you get hyperprolactinemia.

Talking about growth hormone cell adenomas

Few words about specific adenomas

CLINICAL PRESENTATION:
Adults: acromegaly
Children: gigantism

- Growth hormone cell adenomas:
- Second most common
- Elevated GH  hepatic secretion of insulin-like growth factor (IGF-1)
- Dx: failure to suppress GH after oral glucose dose
- Tx: somatostatin analogs

Somatostatin secreted by the periventricular nucleus inhibits GH secretion and acts as a counter to GHRH

Remember that GH is stimulated during hypoglycemia because it causes hepatic gluconeogenesis and reduced hepatic glucose uptake. On the other hand, hyperglycemia suppresses GH secretion because we already have enough blood glucose. In a pituitary adenoma, these feedback loops are lost so an oral glucose challenge would not yield the expected decrease in GH.

Acromegaly due to growth hormone cell adenoma. Before and after.

Fig. 282.

Mrs. A. B., aged twenty years, showing normal appearance of the patient.

Same patient, aged forty-two years, affected with acromegaly.

(Pershing.)

Talking about ACTH cell adenomas

Few words about specific adenomas

released from the adrenal cortex, hence, CORTisol

- ACTH cell adenomas:
- ACTH ⟹ cortisol (adrenal) ⟹ Cushing's dz
- Removal of adrenals in Cushing's sd ⟹ large adenomas ⟹ Nelson syndrome

- Pituitary carcinomas:
  - rare
  - functional (ACTH or prolactin)

Cushing's disease is pituitary in origin, and is defined as excess ACTH secretion from the pituitary.

Cushing's syndrome is simply a result of excess glucocorticoid whether it is pituitary or adrenal in origin.
Thus, Cushing's disease is one cause of Cushing's syndrome but not vice versa.

Nelson syndrome: Removal of the adrenal glands leads to no more cortisol to inhibit ACTH production by negative feedback. Thus, ACTH cell adenomas grow unchecked. This presents as muscle weakness due to excess ACTH and skin hyperpigmentation due to excess melanocyte stimulating hormone, which is also increased because it is one of the products of POMC, a precursor to ACTH.

These are some causes of *hypo*pituitarism. She just mentioned the two highlighted ones and didn't say much more.

Hypopituitarism

- Causes:
  - Tumors, mass lesions, brain injury, subarachnoid hemorrhage
  - Pituitary surgery or radiation
  - Pituitary apoplexy (neurosurgical emergency)
  - Ischemic necrosis of pituitary and Sheehan sd: postpartum necrosis of anterior pituitary
  - Rathke cleft cyst
  - Empty sella syndrome (primary vs. secondary)
  - Hypothalamic lesions
  - Inflammatory disorders

This is usually a postpartum complication after extensive bleeding. It results in necrosis of the anterior pituitary and deficiency of all the hormones secreted by the adenophypophysis

What is the most common pituitary adenoma? What is the second most common?

Problems in the posterior pituitary concern ADH (either deficency or excess)

Posterior Pituitary syndromes

Problem with inadequate ADH production or secretion

- Diabetes insipidus: ADH deficiency
  - Central (hypothalamic) vs. Nephrogenic (renal tubular unresponsiveness to ADH)
  - Polyuria and increased thirst
  - Dilute urine with low specific gravity
  - High serum sodium and osmolality

Nothing wrong with secretion of ADH, the pituitary, or hypothalamus. The kidney is the problem in that it has tubular damage, nonfunctional ADH receptors, or nonfunctional

- Syndrome of inappropriate secretion of ADH (SIADH)
  - Hyponatremia
  - Small cell carcinoma of lung (ectopic ADH secretion)

You retain too much water! This essentially dilutes your sodium concentration.

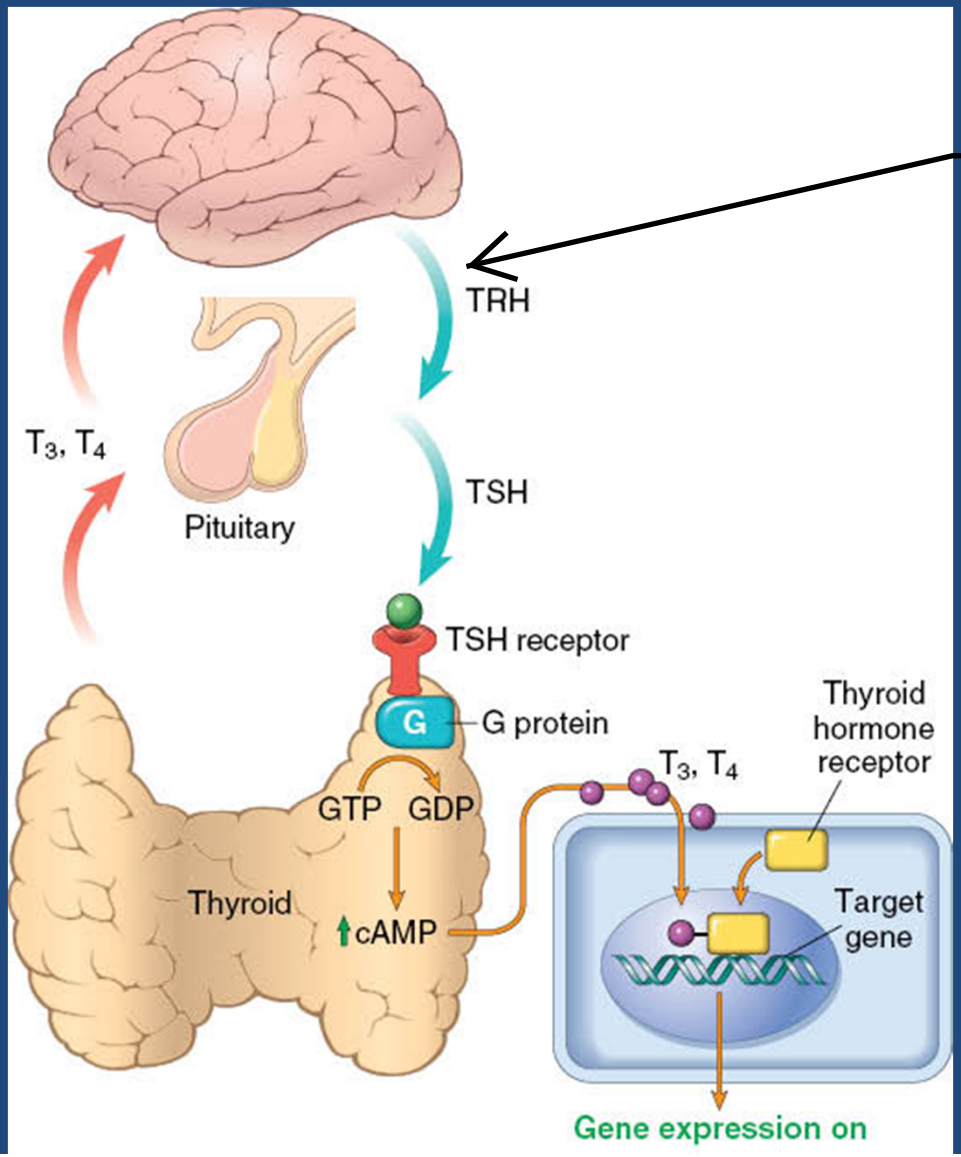
What other endocrine paraneoplastic syndrome is associated with small cell carcinoma of the lung?

The thyroid gland is under control of the pituitary and regulatory feedback loops.

Will exogenous ADH correct the hyponatremia in nephrogenic diabetes mellitus?

Thyroid gland

Blue arrows indicate induction of secretion. Red arrows indicate inhibition of secretion as a means of negative feedback regulation.



The thyroid's primary metabolically active hormonal secretions are T3 and calcitonin.

Thyroid gland

T3 is much more metabolically active than T4. The main effect of T3 is to raise the basal metabolic rate of the body.

- Thyroid follicular cells: convert thyroglobulin into T4 (thyroxine) and triiodothyronine (T3)
- Parafollicular cells (C cells): calcitonin (absorption of calcium by skeletal system and prevent resorption of bone by osteoclasts)

Calcitonin conserves calcium in bone. It has the opposite effect of parathyroid hormone.

Hyperthyroidism: Too much T3, the metabolically active thyroid hormone.

Hyperthyroidism (thyrotoxicosis)

- Elevated free T3 and T4
- Causes:
  - Diffuse hyperplasia of thyroid due to Graves dz (85%)
  - Hyperfunctional multinodular goiter
  - Hyperfunctional adenoma

Multinodular goiter doesn't always produce hyperthyroidism. It can produce a euthyroid state or hypothyroidism.

Grave's disease is an autoimmune disease in which autoantibodies against the thyroid stimulating hormone receptor (TSHR) of the thyroid follicular cells ACTIVATE the receptor. This causes an increase in the production and secretion of T3 and T4 independent of TSH. In fact, the high levels T3 and T4 would downregulate TRH and TSH secretion. Thus, Grave's disease is noted for paradoxically high T3 and T4 with low TRH and TSH.

Long story short...
Grave's Disease:
T3 and T4: high
TRH: Low
TSH: Low

Hyperthyroidism's symptomology, especially increased basal metabolic rate, is due to elevated T3 and T4.

Clinical symptoms and lab diagnosis

- Increased basal metabolic rate
- Warm and flushed skin
- Heat intolerance, sweating
- Weight loss, increased apetite
- Cardiac manifestations (tachycardia, arrhythmias, heart failure)
- Ocular changes (thyroid ophthalmopathy)
- Decreased TSH; increased free T4 or T3
- Radioiodine uptake (etiology)

Most of the subsequent symptoms are due to the increase in basal metabolic rate and adrenergic stimulation (one of the initial treatments for Grave's is beta blockers)

highly characteristic of Graves

due to negative feedback

This helps differentiate between factitious hyperthyroidism, which is due to exogenous thyroid hormone medication and does not cause increase uptake of radioiodine for T3 and T4 synthesis, and true hyperthyroidism, which would cause increased uptake of radioiodine due to increase endogenous production of T3 and T4.

Hyperthyroidism is noted for very protuberant and wide eyes.

What are the concentrations of T3 and T4, TRH, and TSH in Grave's disease relative to physiologic levels?

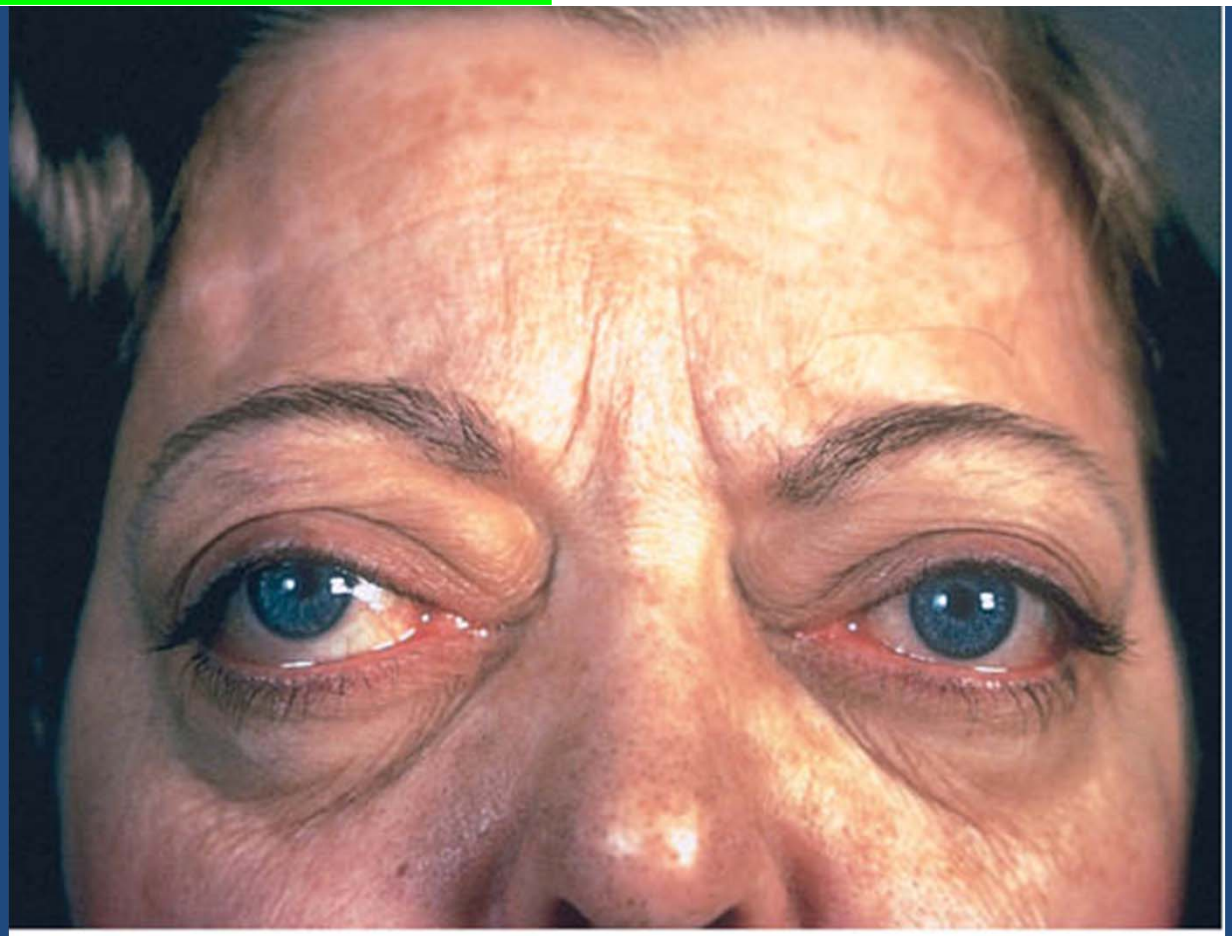
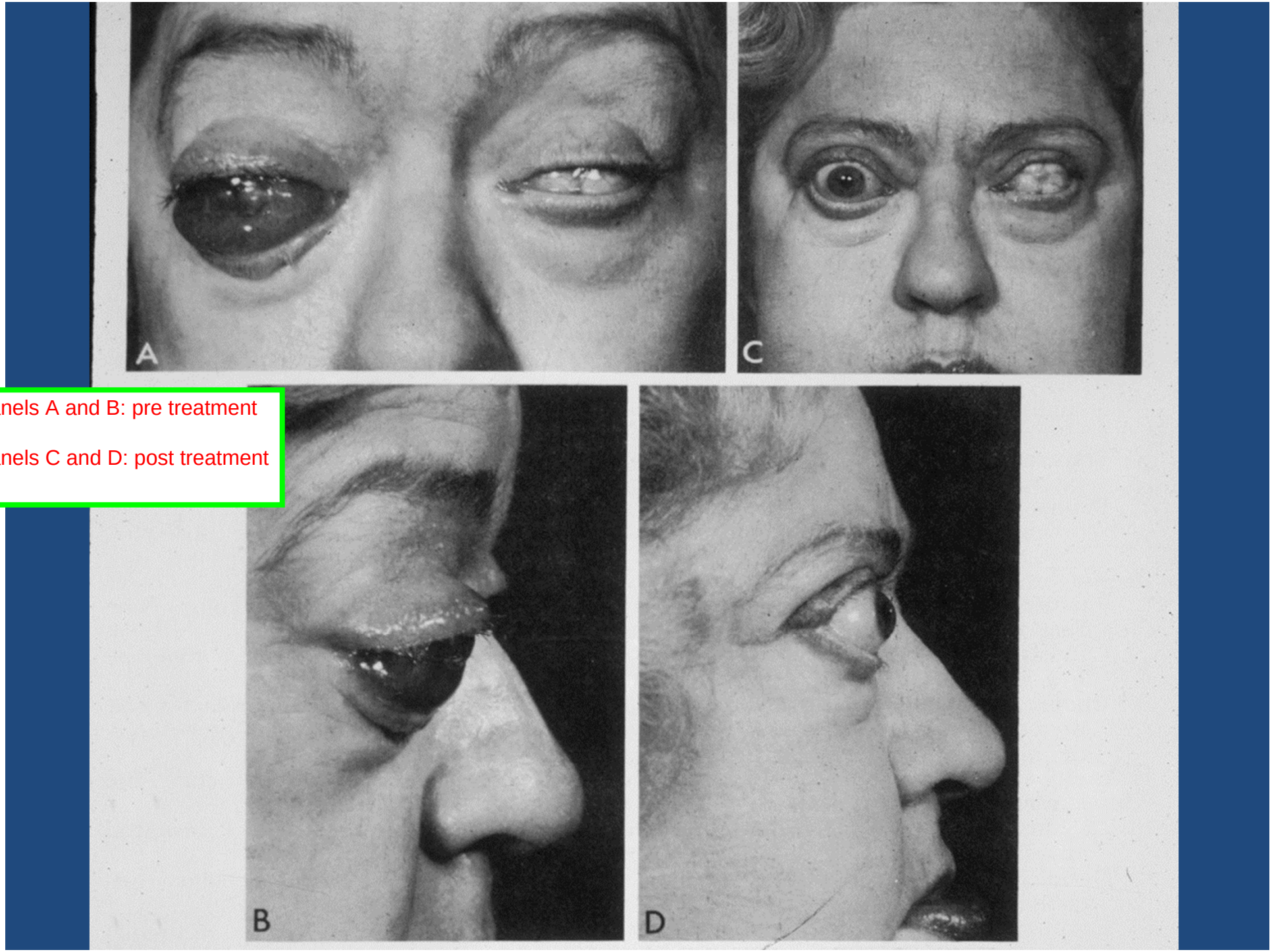


FIGURE 24–9 A person with hyperthyroidism. A wide-eyed, staring gaze, caused by overactivity of the sympathetic nervous system, is one of the features of this disorder. In Graves disease, one of the most important causes of hyperthyroidism, accumulation of loose connective tissue behind the eyeballs, also adds to the protuberant appearance of the eyes.

The increased basal metabolic rate and subsequent sympathetic overdrive causes the wide-eyed staring gaze. Remember, that sympathetic drive is fight-or-flight, in which you'd want your eyes to be wide open to get a handle on your surroundings.

Buildup of glycosaminoglcans (GAG) in retro-ocular muscles and connective tissue cause the protuberant eyeballs.

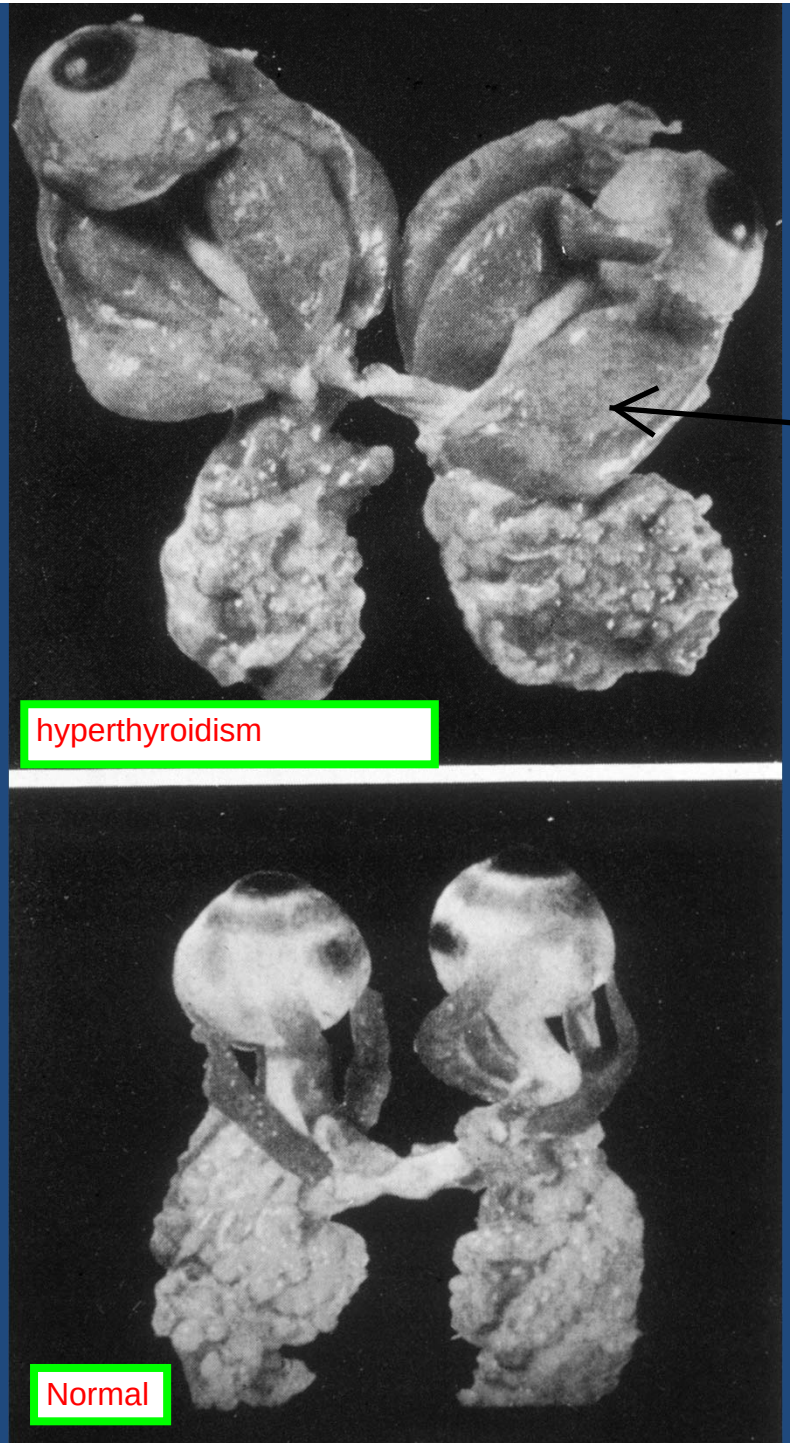
More ophthalmopathy due to hyperthyroidism.



Panels A and B: pre treatment

Panels C and D: post treatment

Dissected eye and retro-ocular muscles with ophthalmopathy due to hyperthyroidism.



Hypothyroidism: too little thyroid hormone

Hypothyroidism

- Decreased levels of thyroid hormone
- Common in the population (0.3%)
- F:M = 10:1
- Primary:
  - Autoimmune thyroiditis (Hashimoto)
  - Iodine deficiency
  - Drugs (lithium, etc)
  - Dyshormonogenetic goiter
- Secondary:
  - TSH or TRH deficiency

This is rare nowadays, but you see this in people far away from the ocean and with less access to iodine enriched salt.

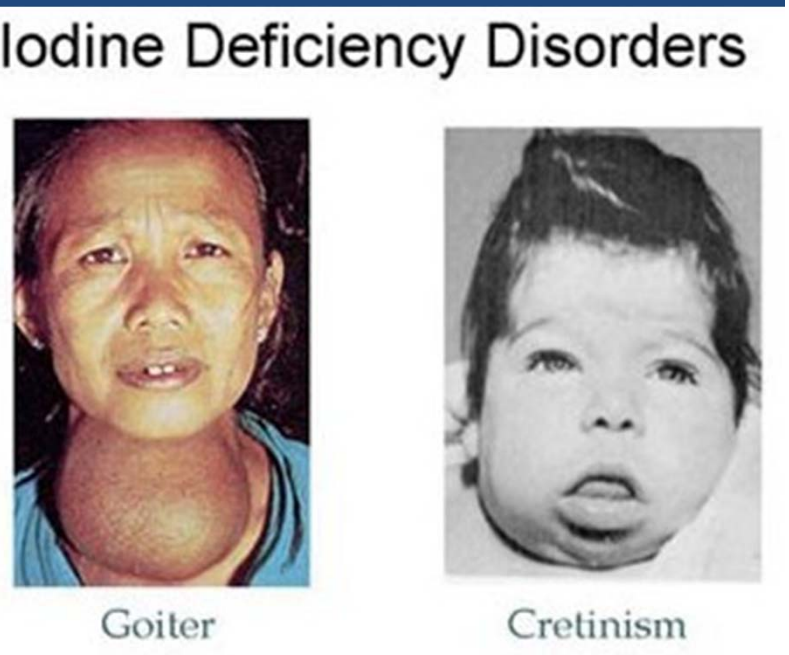
Presentations of hypothyroidism: Cretinism = children. Myxedema = older children and adults

- **Cretinism:**
  - Hypothyroidism that develops in early childhood
  - Impaired development of skeletal and CNS, severe **mental retardation,** short stature, coarse facial features, protruding tongue and umbilical hernia
- **Myxedema:**
  - Hypothyroidism that develops in **older child or adult**

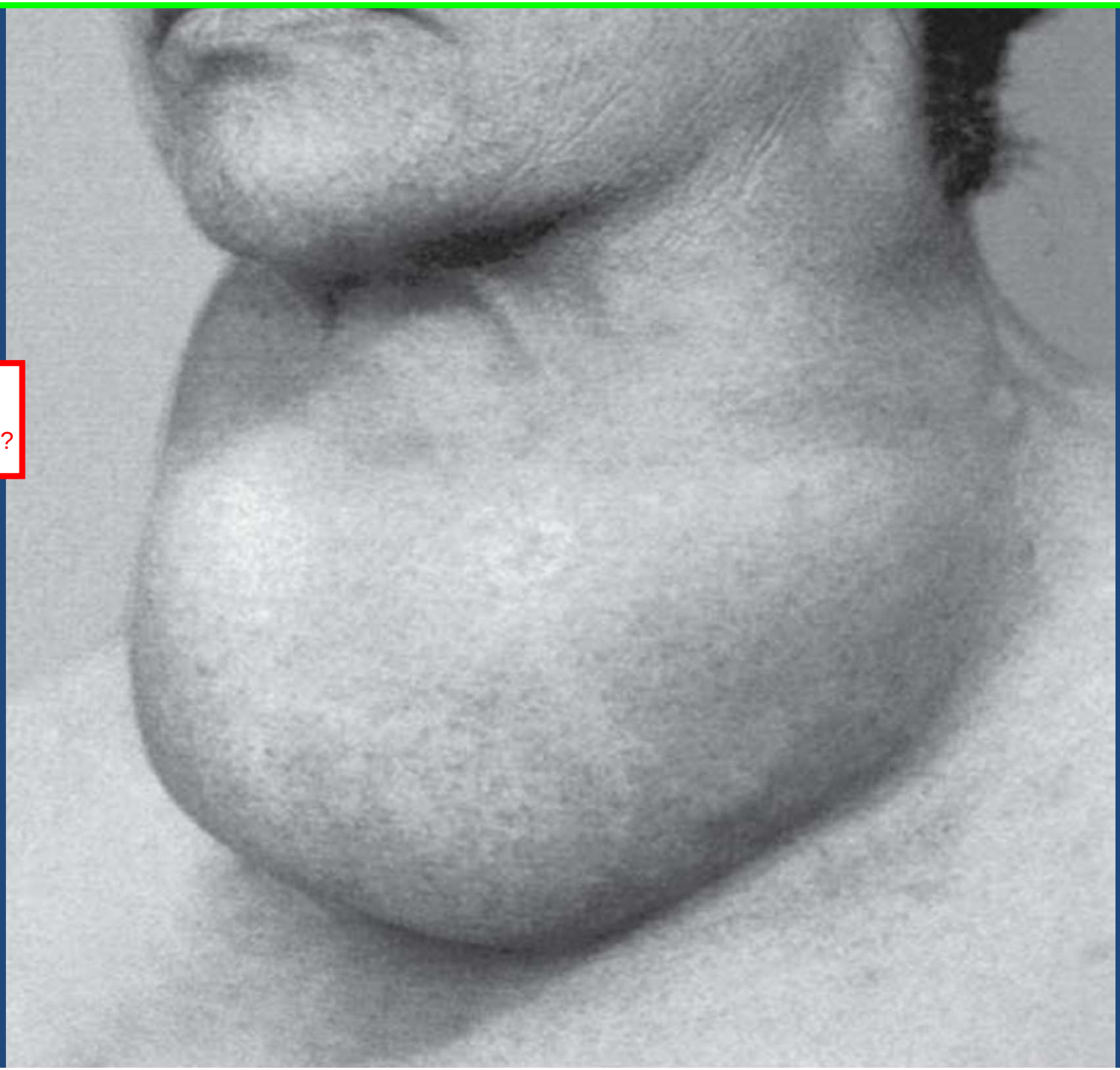
Reversibility is dependent on timing of treatment. she did not specify the timing.

a specific form of cutaneous and dermal edema due to deposition of connective tissue components like GAGs

NOTE: Pretibial myxedema is different and occurs in Grave's disease, which is a hyperthyroid disease.

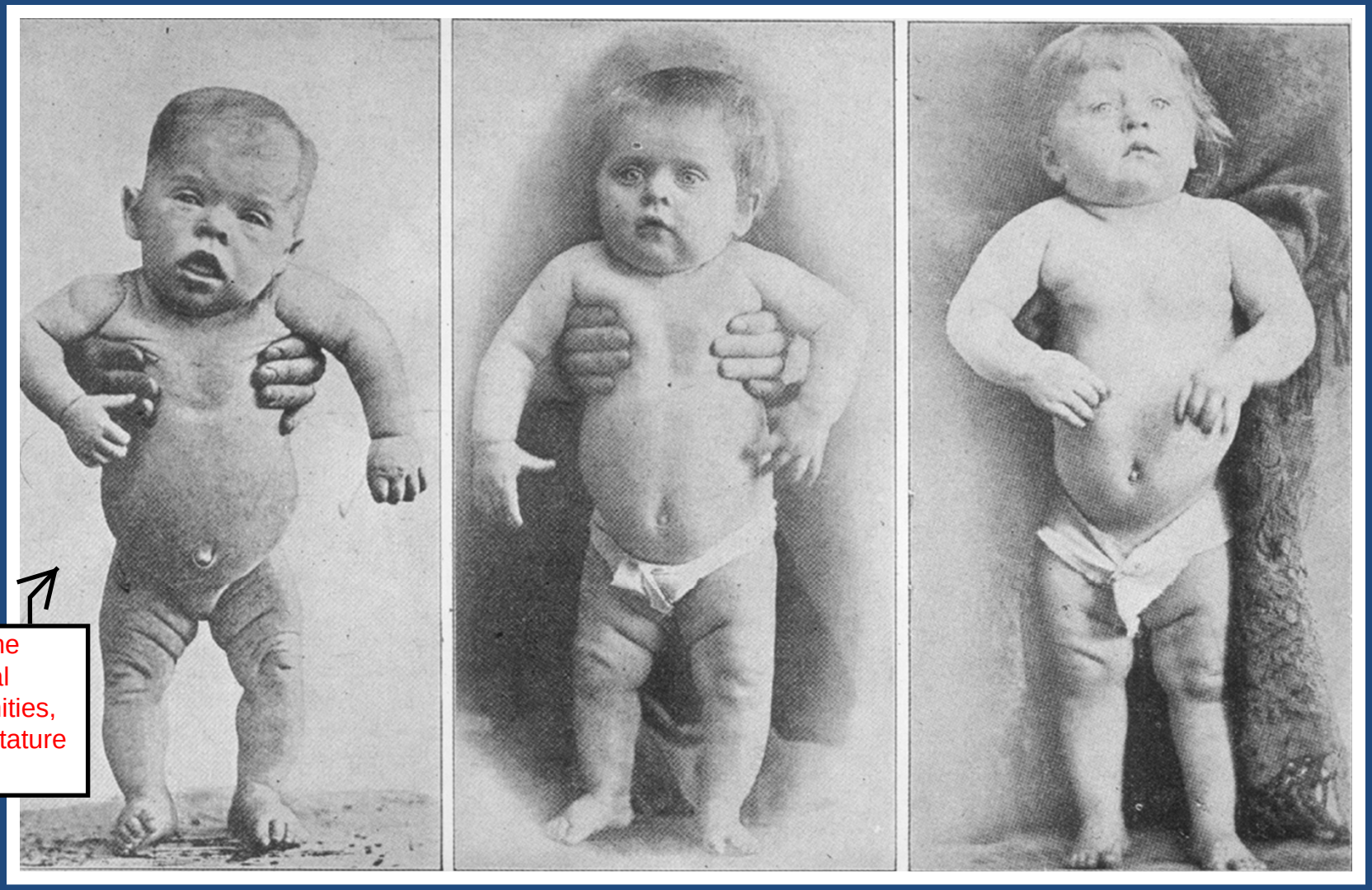


An extreme example of goiter, which is a swelling of the thyroid gland most commonly due to iodine deficiency. Goiter can be a presentation of both hypo- and hyperthyroidism.



What does hypothyroidism in children present as?

Infantile hypothyroidism



Infantile hypothyroidism 17 months of age

6 months after thyroid extract therapy

One year after treatment

West. 1894. In Gould and Pyle, Anomalies and Curiosities of Medicine, 1896, p. 806

Hashimoto thyroiditis

helpful for diagnosis because other kinds of thyroiditis are painful

- Most common cause of hypothyroidism (normal iodine level areas)
- Autoimmune destruction of gland
- Painless symmetric enlargement of gland
- Older women are more affected (10:1 to 20:1 / F:M)
- Genetic predisposition
- Increased risk for other autoimmune disorders and B-cell non-Hodgkin lymphomas
- Pathogenesis: progressive depletion of thyroid epithelial cells and replacement by mononuclear cells.

From Robbins: different ways the gland can be destroyed. In any situation, the immune system is bashing your thyroid

Hashimoto thyroiditis

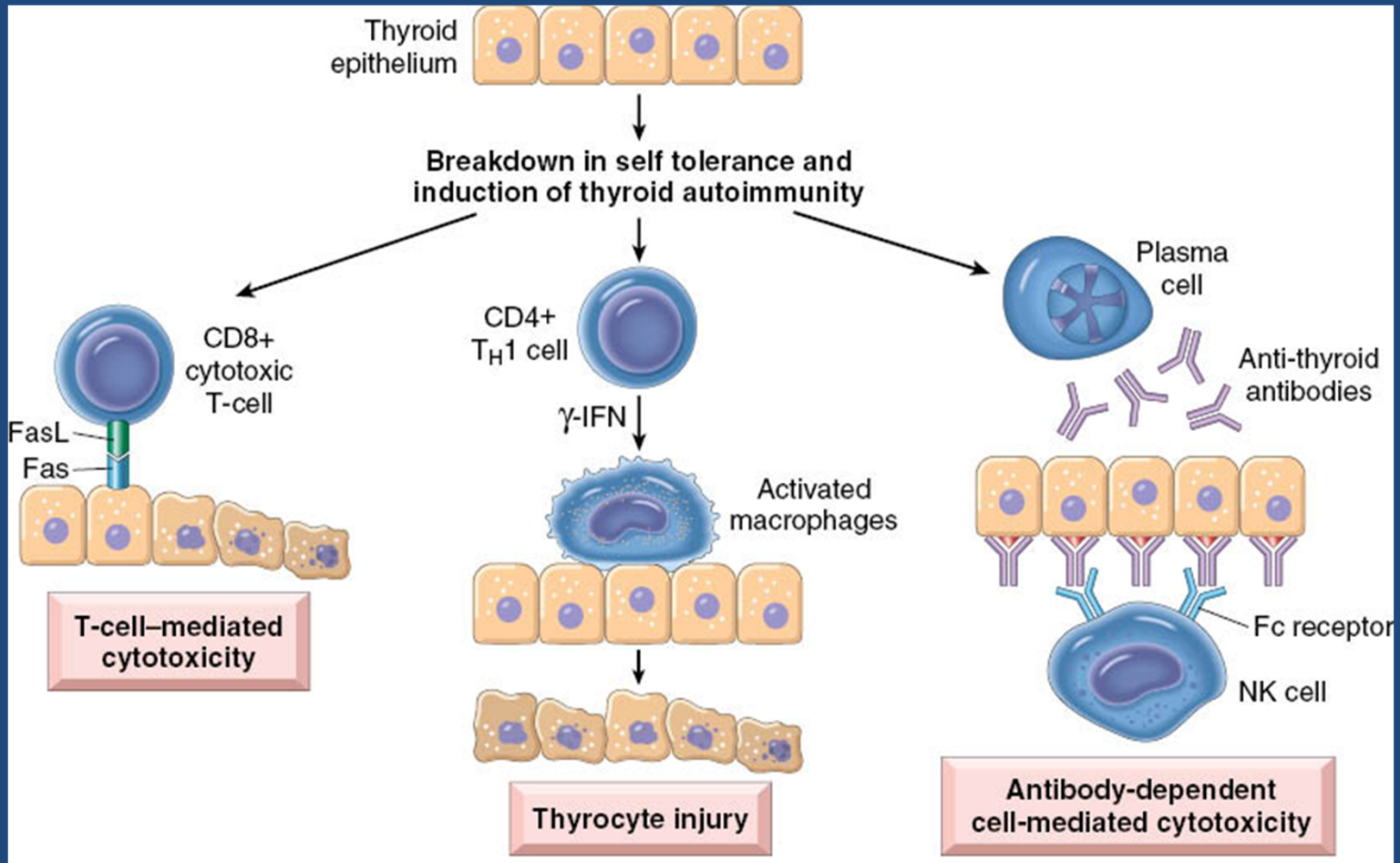
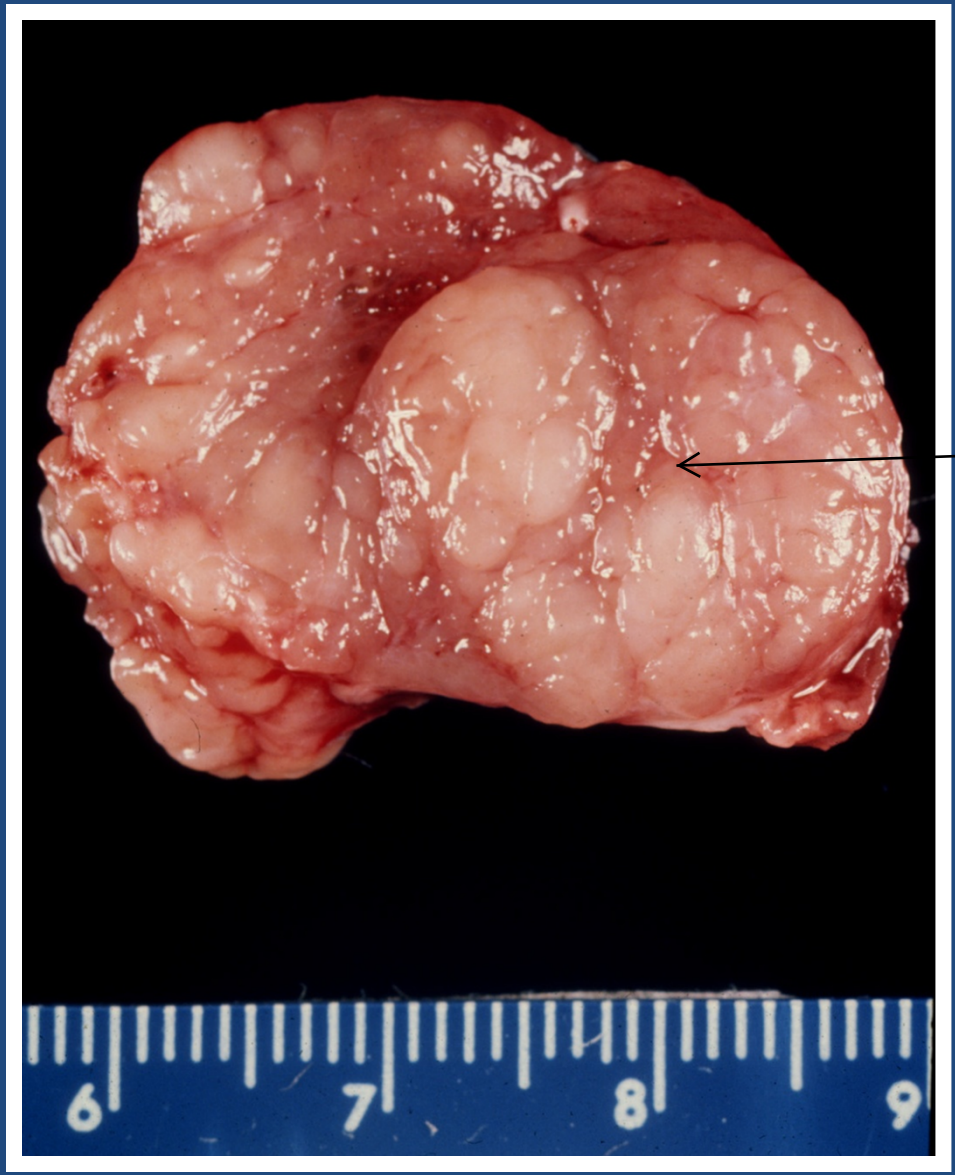


FIGURE 24–10 Pathogenesis of Hashimoto thyroiditis. Breakdown of peripheral tolerance to thyroid auto-antigens, results in progressive autoimmune destruction of thyrocytes by infiltrating cytotoxic T cells, locally released cytokines, or by antibody-dependent cytotoxicity.

Gross appearance of a thyroid with Hashimoto's thyroiditis.



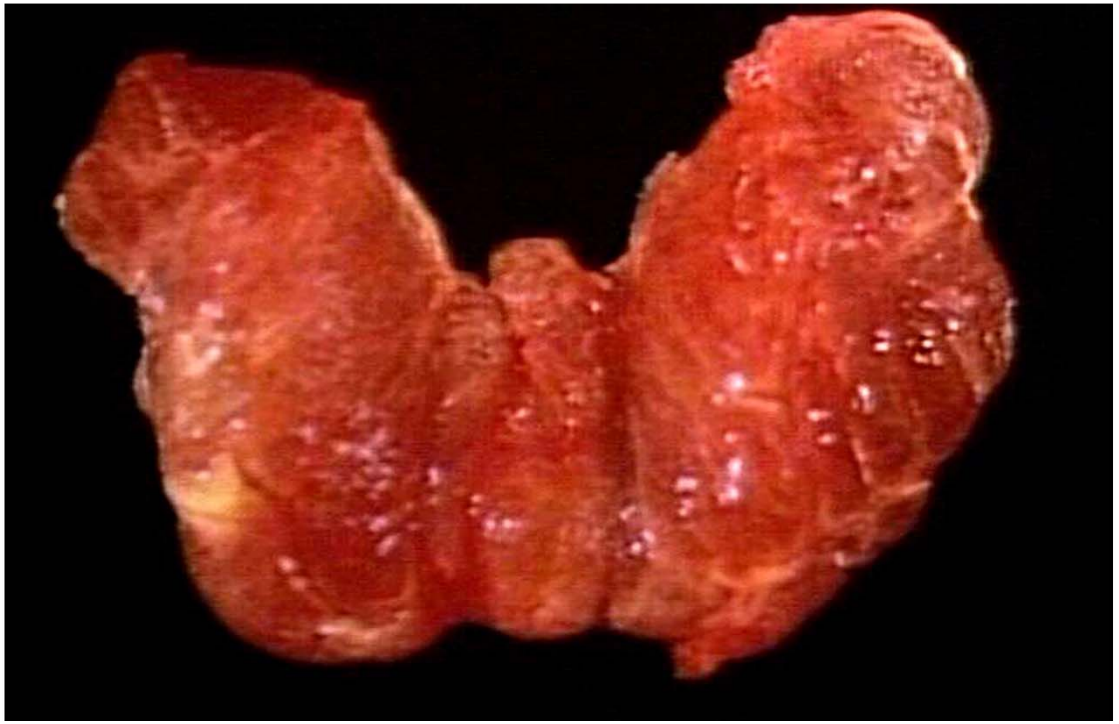
Very fleshy and whitish because it is completely infiltrated by mononuclear cells.

It actually looks like the cut surface of a lymph node, which makes sense given that there is infiltration by mononuclear inflammatory cells that are forming germinal centers.

Gross appearance of a thyroid with Hashimoto's thyroiditis (mimicks lymphoma)

Normal thyroid for reference.

Normal Thyroid



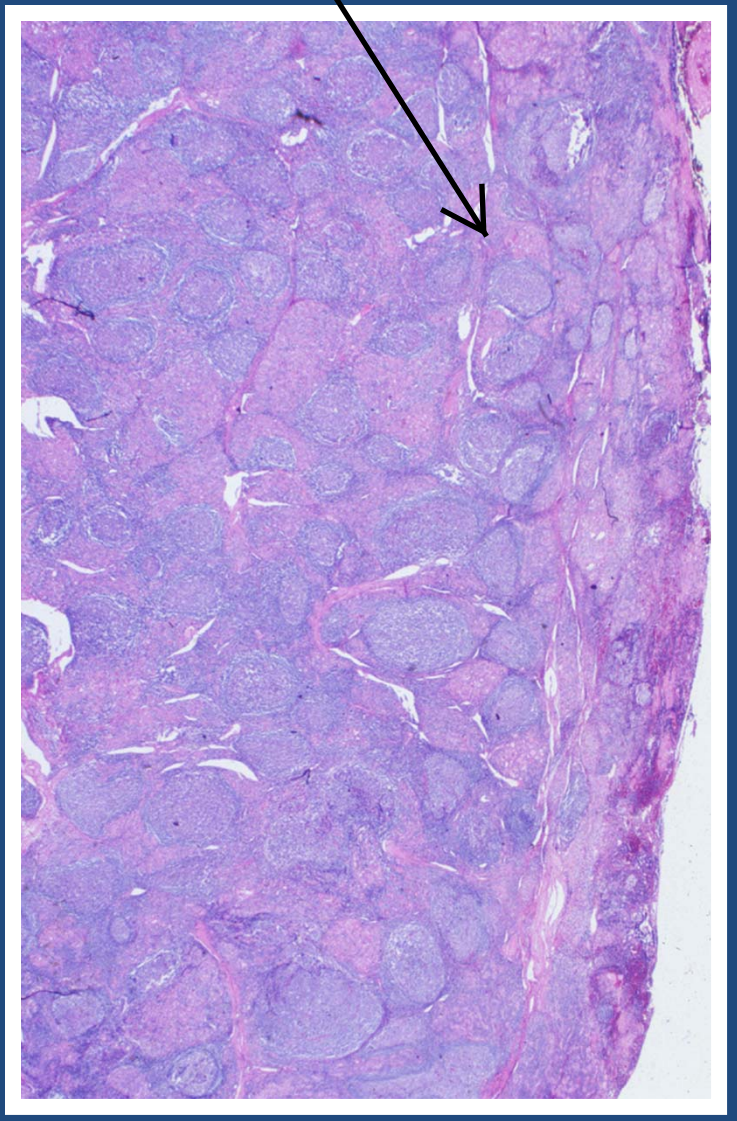
Note that the normal thyroid has a "fleshy, beefy" appearance.

microanatomy in Hashimoto's thyroiditis

Pathology

- Mononuclear inflammatory infiltrate
- Germinal centers
- Hurthle cells (epithelial cells with abundant eosinophilic, granular cytoplasm)

These three things are used to diagnose Hashimoto's.



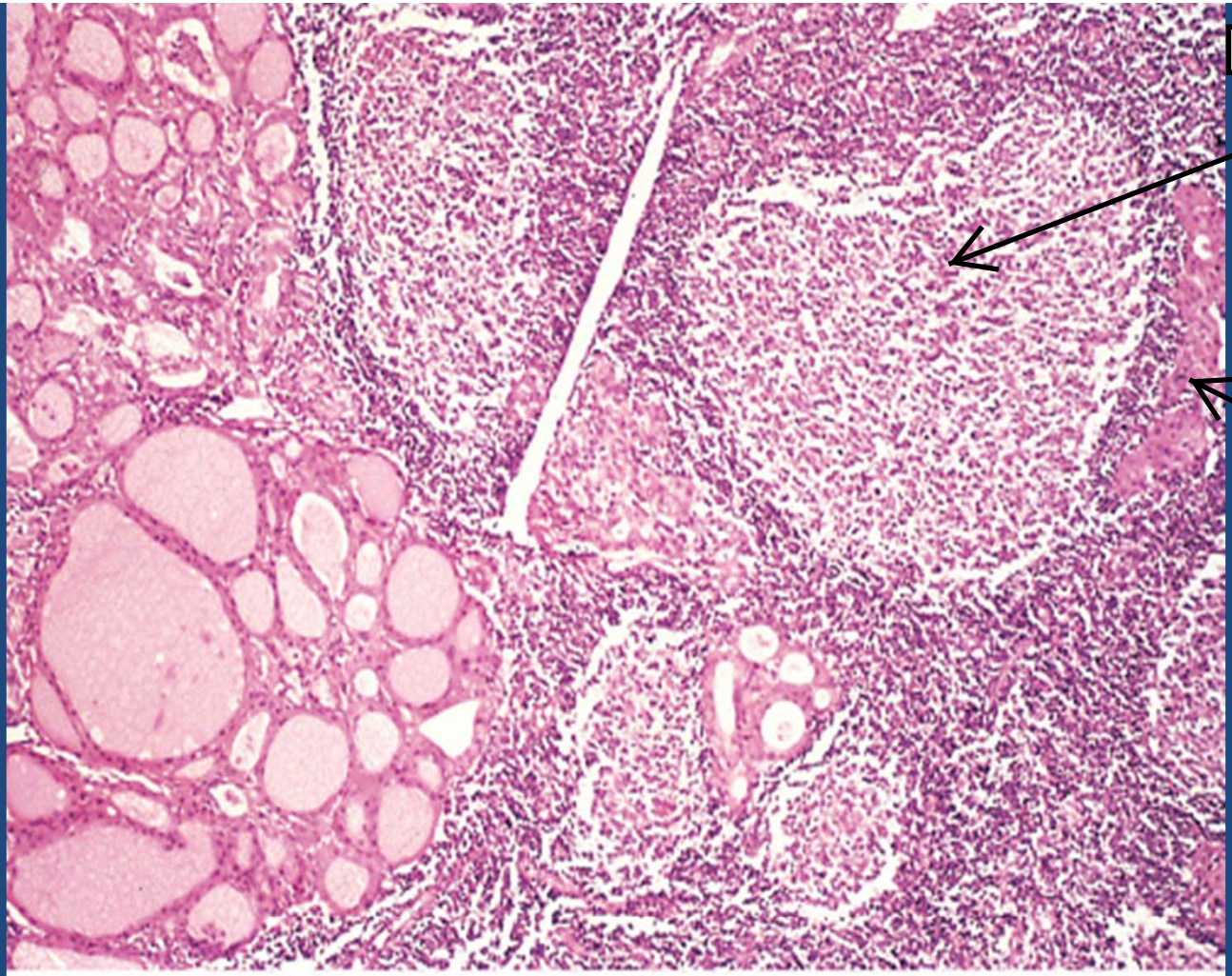


FIGURE 24–11 Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate with germinal centers. Residual thyroid follicles lined by deeply eosinophilic Hürthle cells are also seen.

De Quervain thyroiditis: a rare thyroiditis that elicits neck pain and goes through various stages leading to full recovery

Subacute (granulomatous) thyroiditis
De Quervain thyroiditis

- Much less frequent than HT
- F:M 3:1 to 5:1
- Post-viral inflammatory process (seasonal)
- Neck pain, fever
- Transient hyperthyroidism > transient hypothyroidism > full recovery
- Pathology:
- Follicles destroyed by neutrophilic microabscesses
- Multinucleate giant cells enclosing pools of colloid

different from Hashimoto's, which is painless

This differs from Hashimoto's which has no full recovery since the gland is destroyed and fibrosed.

A viral infection leads to an autoimmunity that attacks the thyroid gland. There is initial hyperthyroidism as the follicular cells are damaged, allowing colloid and thyroid hormones to enter the blood. Then, the pituitary downregulates TSH production through feedback, and the released colloid is depleted, leading to transient hypothyroidism. There is an eventual full recovery.

What three microscopic observations are used to diagnose Hashimoto's thyroiditis?

microanatomy of granulomatous (De Guervain's) thyroiditis

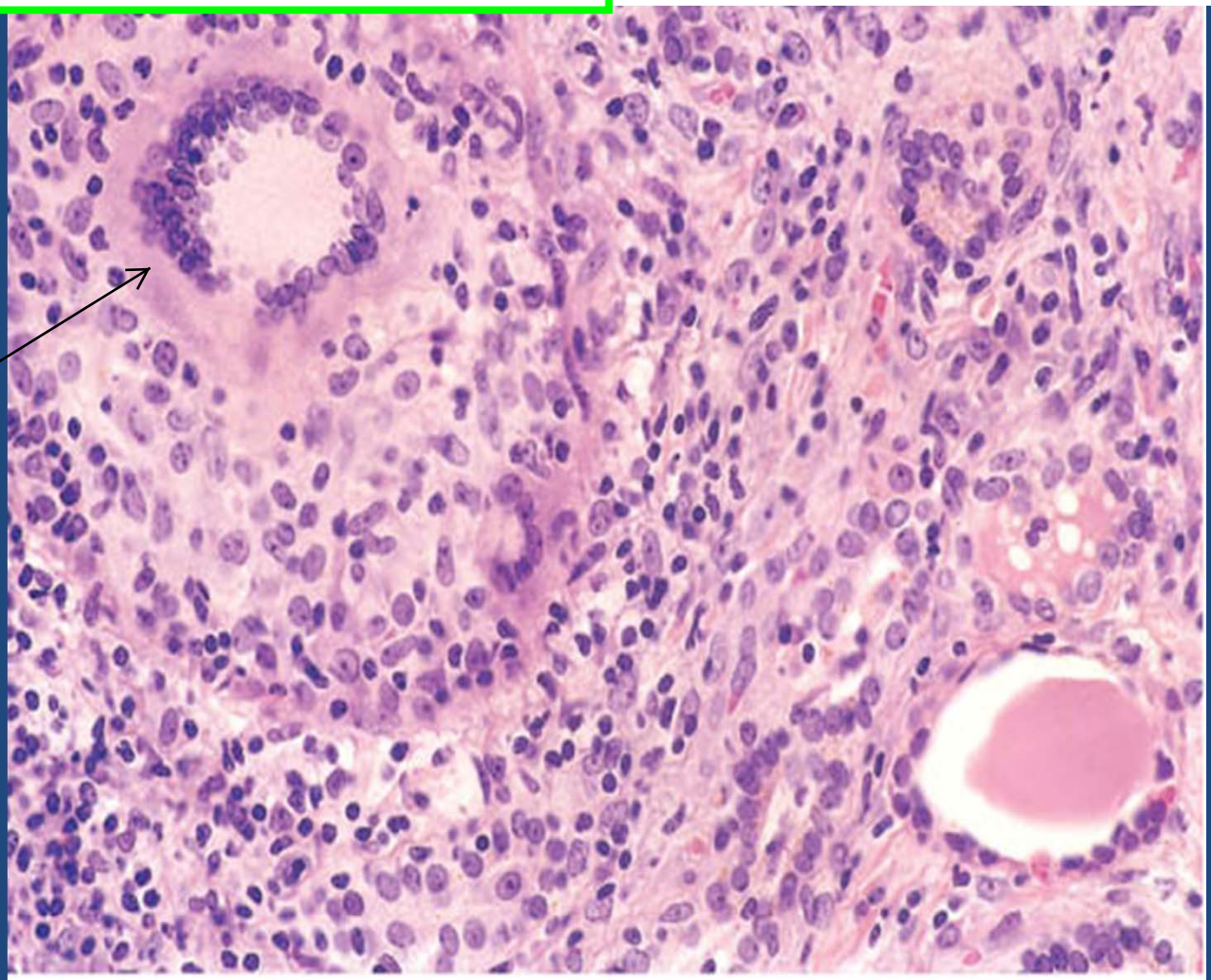


FIGURE 24–12 Granulomatous thyroiditis. The thyroid parenchyma contains a chronic inflammatory infiltrate with a multinucleate giant cell *(above left)* and a colloid follicle *(bottom right)*.

Yet another kind of thyroiditis

Subacute lymphocytic (painless) thyroiditis

- Uncommon cause of hypothyroidism
- Commonly “postpartum thyroiditis”
- Mild gland enlargement and hyperthyroidism
- Pathology:
- Lymphocytic infiltration and germinal centers
- No Hurthle cells or fibrosis

tends to be transient

It goes through the same transient hyperthyroidism by the same mechanism as in De Quervain's thyroiditis.

Details about Grave's Disease

Graves Disease

- Most common cause of endogenous hyperthyroidism
- Triad: hyperthyroidism; infiltrative ophthalmopathy (exophthalmos); localized, infiltrative dermopathy (pretibial myxedema)
- F:M > 7:1
- Genetic susceptibility (HLA-B8 and –DR3)
- Autoimmune disorder:
- Autoantibodies to TSH receptor:
- LATS (long-acting thyroid stimulator); IgG Ab
- Thyroid growth-stimulating Ig (TGI)
- TSH-binding inhibitor Igs (TBII)

85-90%

this is different from the myxedema associated with adult hypothyroidism

very high genetic susceptibility

Instead of destroying the gland like in Hashimoto's thyroiditis, the autoantibodies stimulate the TSH receptor. This causes the gland to grow and keep secreting thyroid hormones.

Memorize LATS! It is the IgG Ab that targets the TSH-R to cause the gland to grow and secrete thyroid hormones.

Gross appearance of a Grave's Disease thyroid

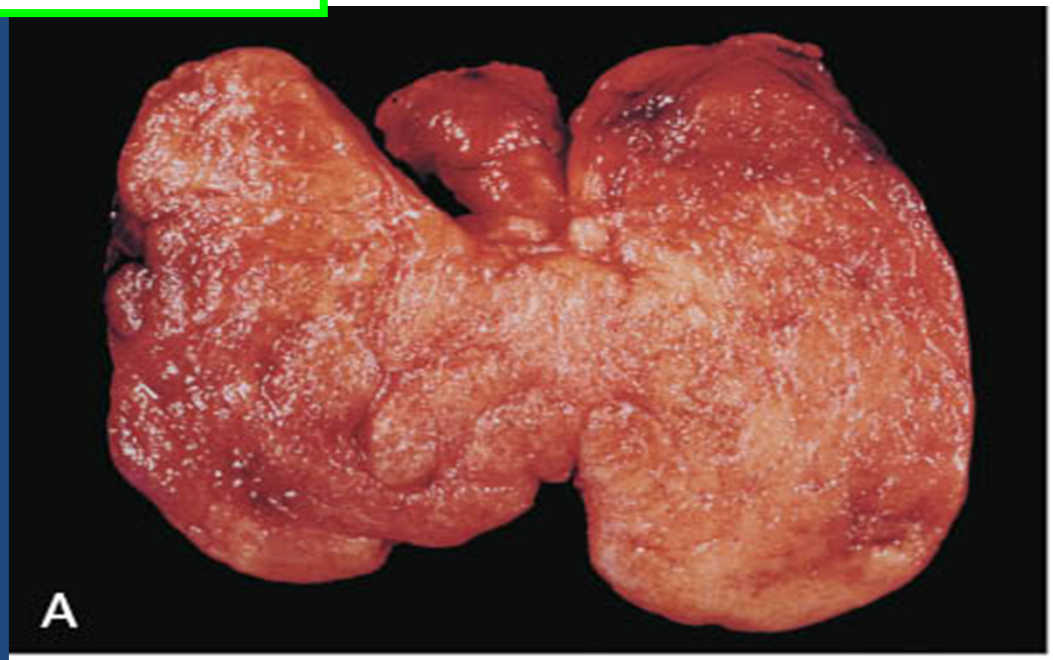


FIGURE 24–13A Graves disease. **A,** There is diffuse symmetric enlargement of the gland and a beefy deep red parenchyma. Compare with gross photograph of multinodular goiter in Figure 24–15. **B,** Diffusely hyperplastic thyroid in a case of Graves' disease. The follicles are lined by tall, columnar 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.

(Reproduced with permission from Lloyd RV et al. (eds): Atlas of Nontumor Pathology: Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002.)

Buzzwords to describe Grave's disease thyroid:
-symmetric enlargement
-beefy and deep red parenchyma

Microscopic description of thyroid in Grave's Disease

Graves Disease

Normal follicles would be nice and round.

- Symmetric enlargement of gland
- Diffuse hypertrophy and hyperplasia
- Crowded and tall follicular cells; small papillae
- Mononuclear infiltrates are common
- Scalloped colloid
- Elevated free T4 and T3; depressed TSH; increased RAIU

scalloped colloid = another buzzword to remember (see box in upper right hand corner for an explanation)

These refer to pseudopapillae since they lack the fibrovascular core that is characteristic of true papillae. Since papillary carcinomas contain real papillae, the presence of papillary structures place papillary carcinoma on your differential. Thus, it is important to distinguish between pseudopapillae and true papillae to distinguish between Grave's and papillary carcinoma.

Scalloped colloid refers to the round, white cicles on the edges of the colloid space. This indicates active uptake of stored colloid.

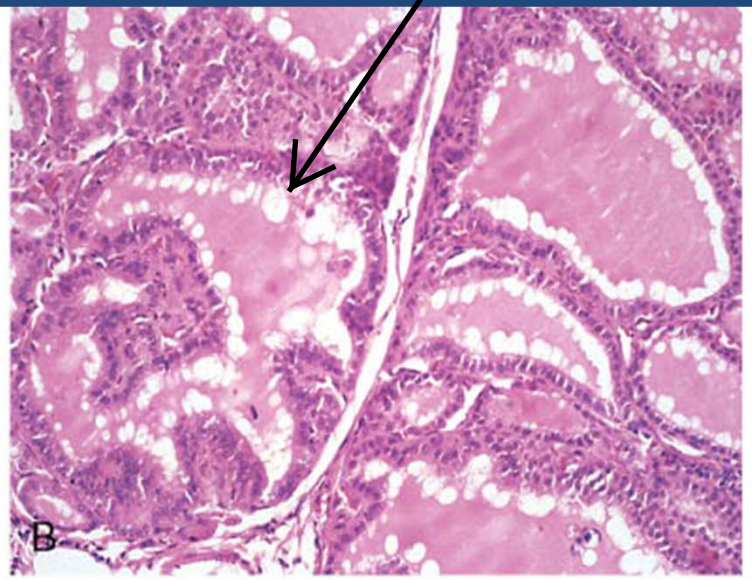
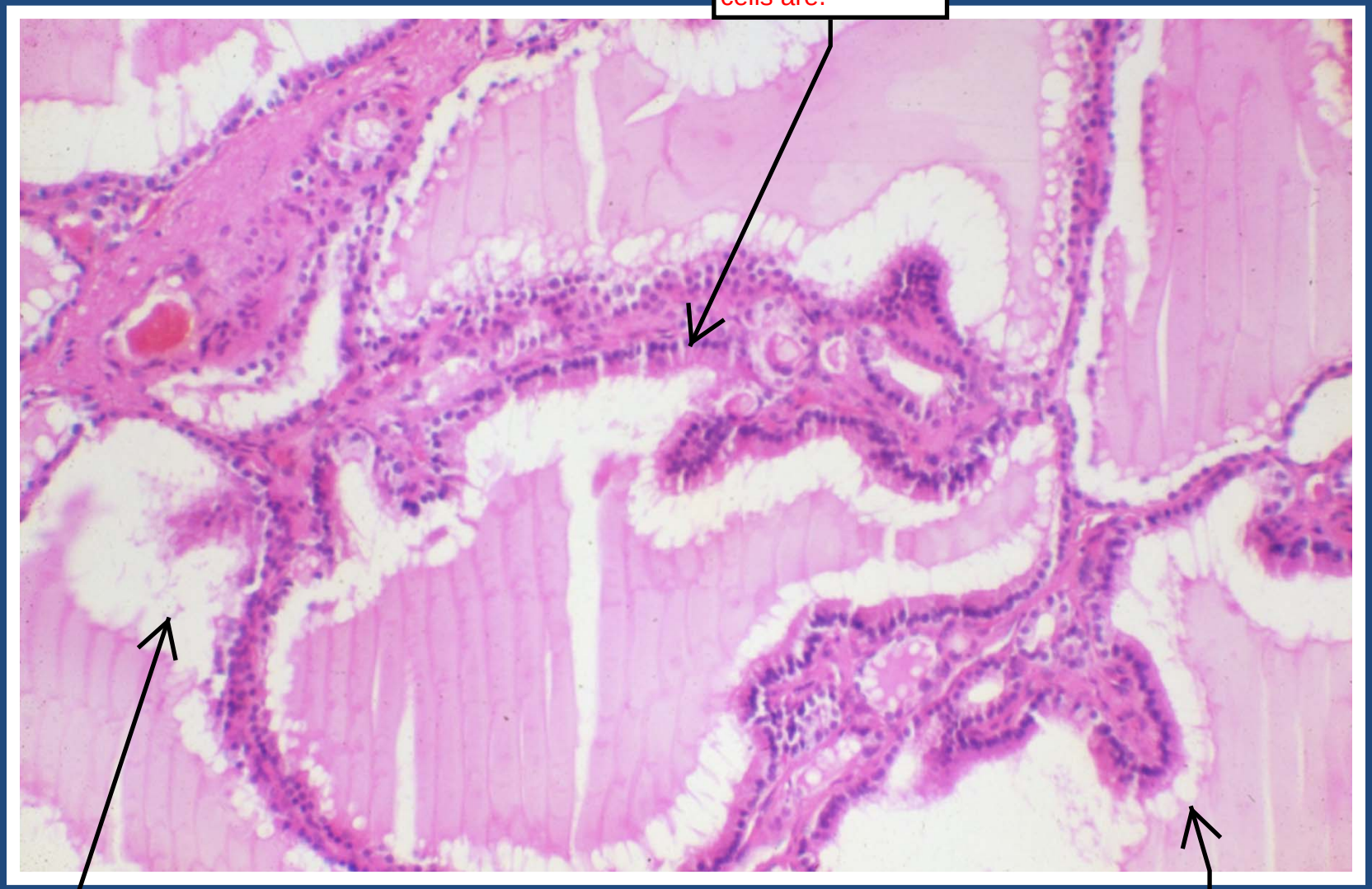


FIGURE 24–13B Graves disease. **A,** There is diffuse symmetric enlargement of the gland and a beefy deep red parenchyma. Compare with gross photograph of multinodular goiter in Figure 24–15. **B,** Diffusely hyperplastic thyroid in a case of Graves' disease. The follicles are lined by tall, columnar 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.

More histology of Grave's Disease



Pseudopapillae and scalloping in Graves' disease

Diffuse and Multinodular Goiters

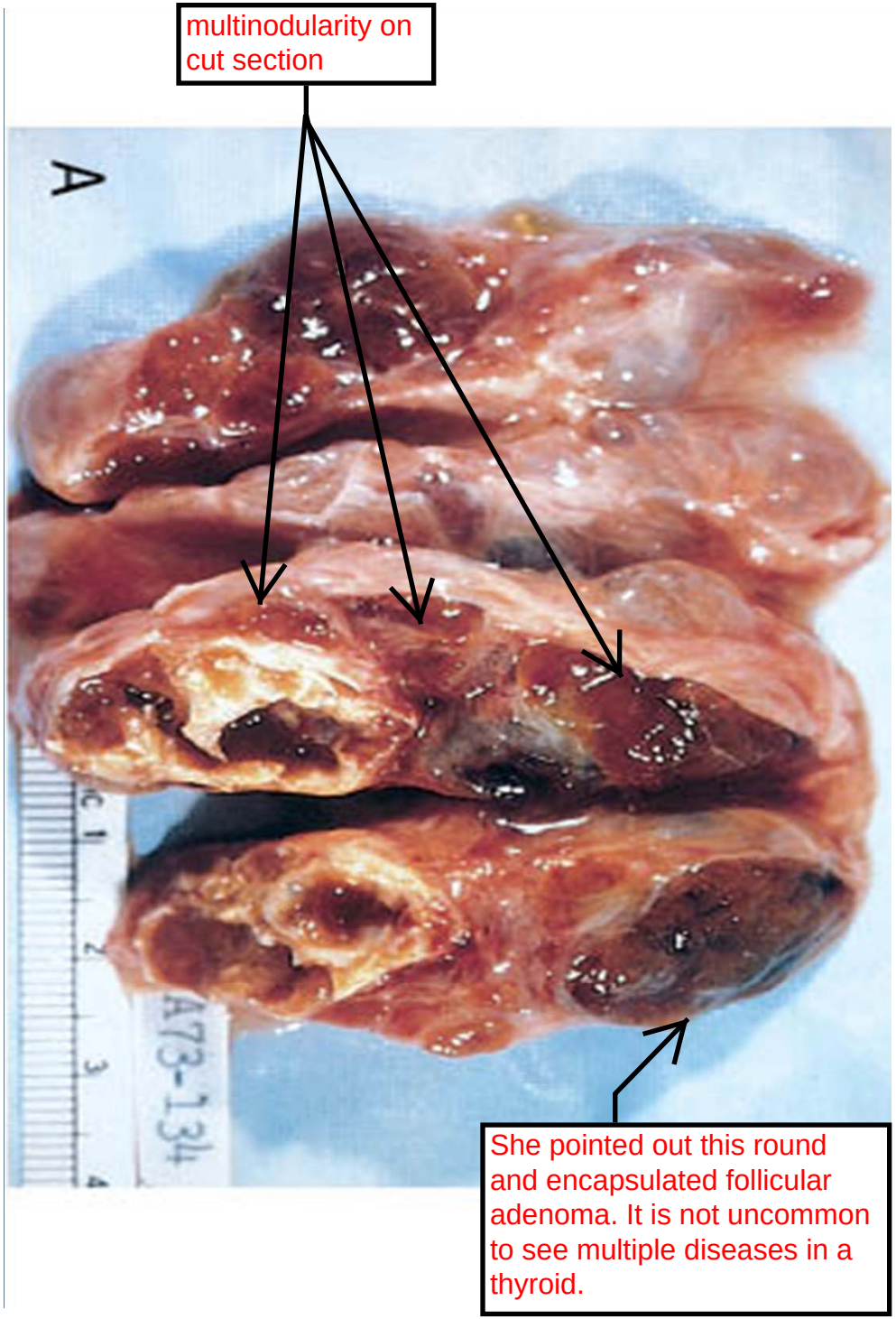
- Dietary iodine deficiency → impaired synthesis of thyroid hormone (goiter)
- Increased TSH → compensatory in gland functional mass → euthyroid state
- Diffuse nontoxic (simple) goiter
- Multinodular goiter

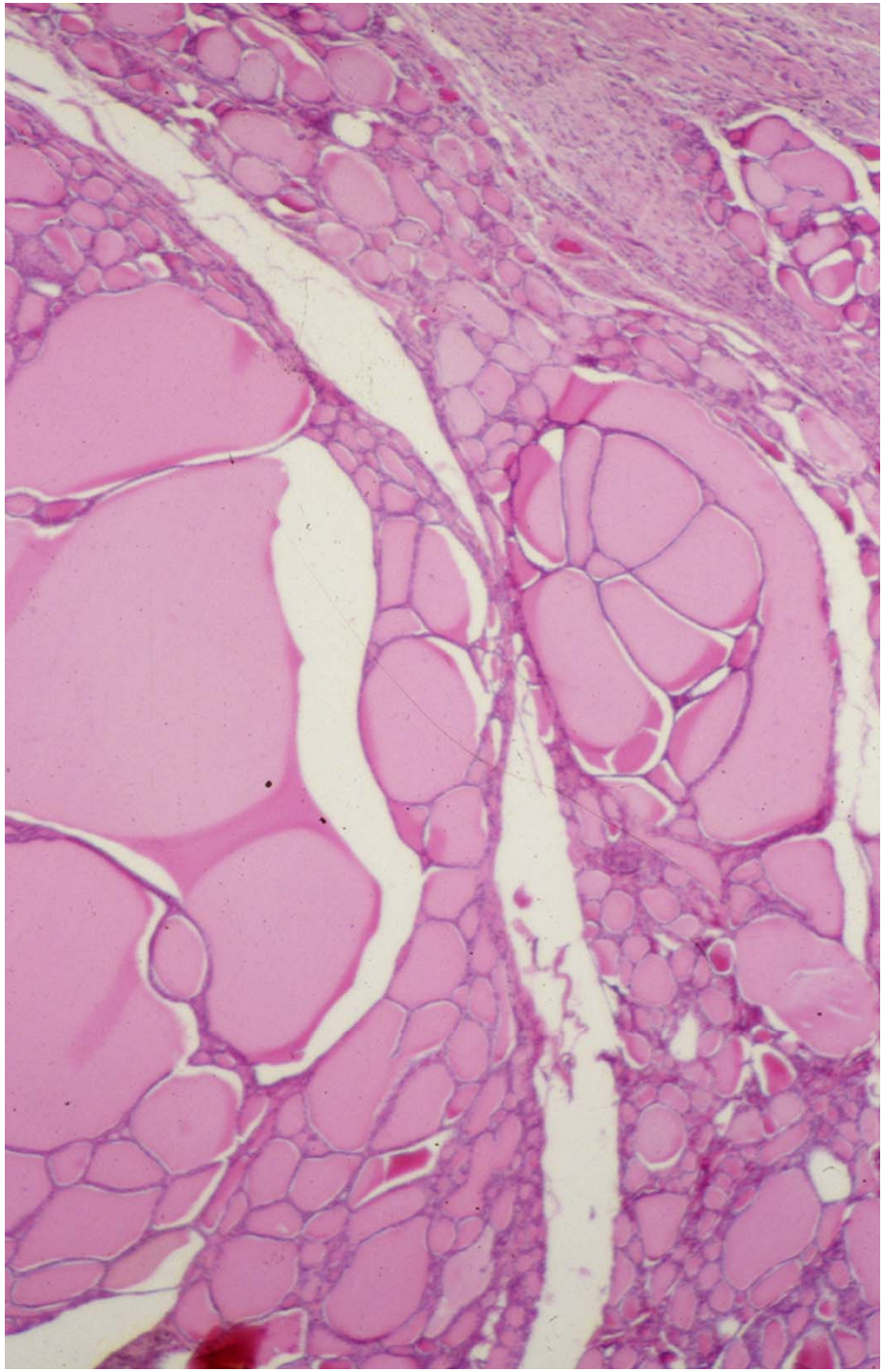
Iodine deficiency is the usual cause (90% according to Wiki).

To compensate for the impaired thyroid hormone synthesis, the pituitary pumps out more TSH via increased synthetic rate. This leads to a euthyroid state. If this compensation is in excess, you end up with hyperthyroidism due to hyperfunctional, multinodular goiters. If the compensation is insufficient, then you can end up with hypothyroidism. Thus, goiter can present as eu-, hypo-, or hyperthyroidism.

In Grave's disease, how do you describe the colloid?

Gross appearance of a multinodular goiter.





Thyroid neoplasms

"cold" means nonfunctional

- Follicular adenomas (well-encapsulated; cold nodules; sometimes “toxic”)
  - 20% have point mutations in RAS
- Carcinomas:
- 1.5% of all cancers

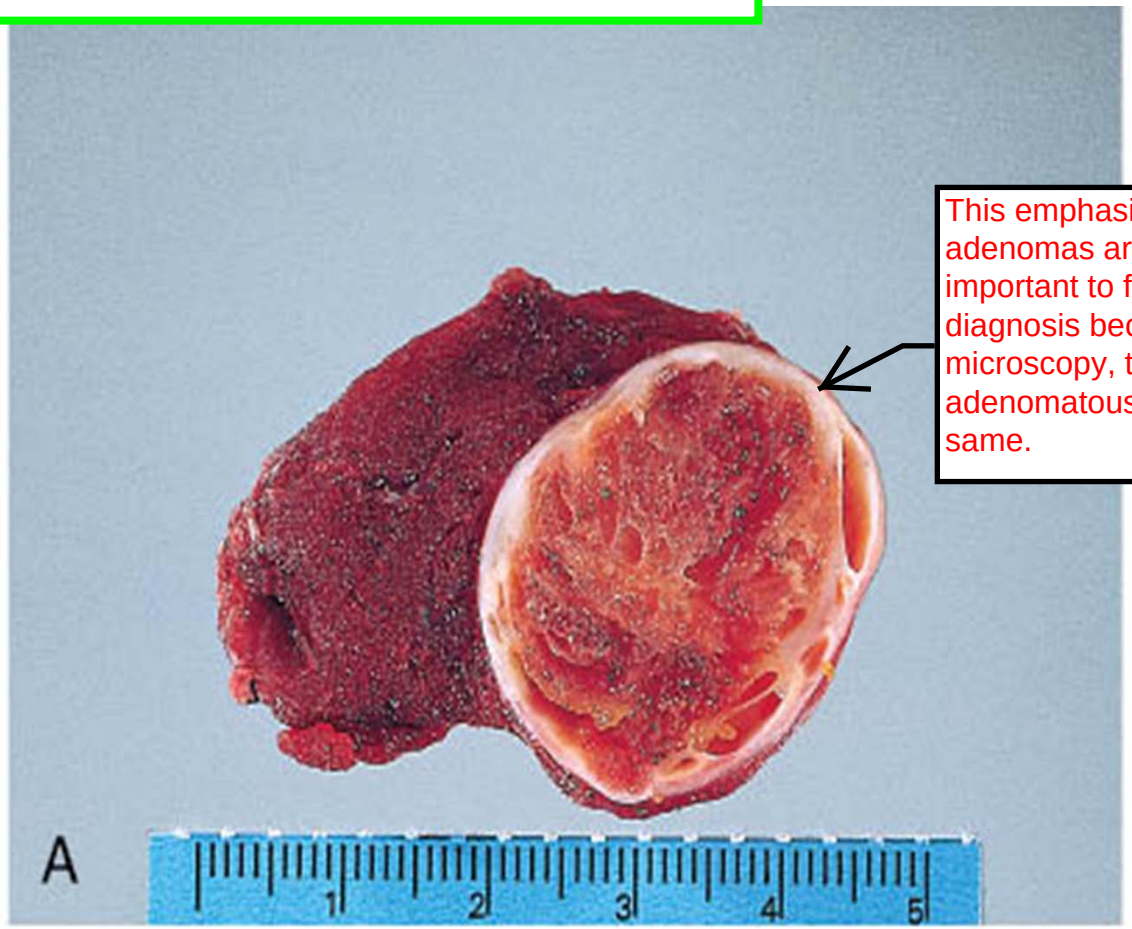
pretty common

- Female predominance
- Papillary (75-85%)

Luckily, the papillary carcinomas have a good prognosis

- Follicular (10-20%)
- Medullary (5%)
- Anaplastic (<5%)

Gross appearance of a follicular adenoma with its characteristic capsule.



This emphasizes that follicular adenomas are encapsulated. It is important to find the capsule for diagnosis because under microscopy, the normal follicles and adenomatous follicles look the same.

FIGURE 24–16A Follicular adenoma of the thyroid. **A,** A solitary, well-circumscribed nodule is seen. **B,** The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.

Microscopic picture of the middle of a follicular adenoma.

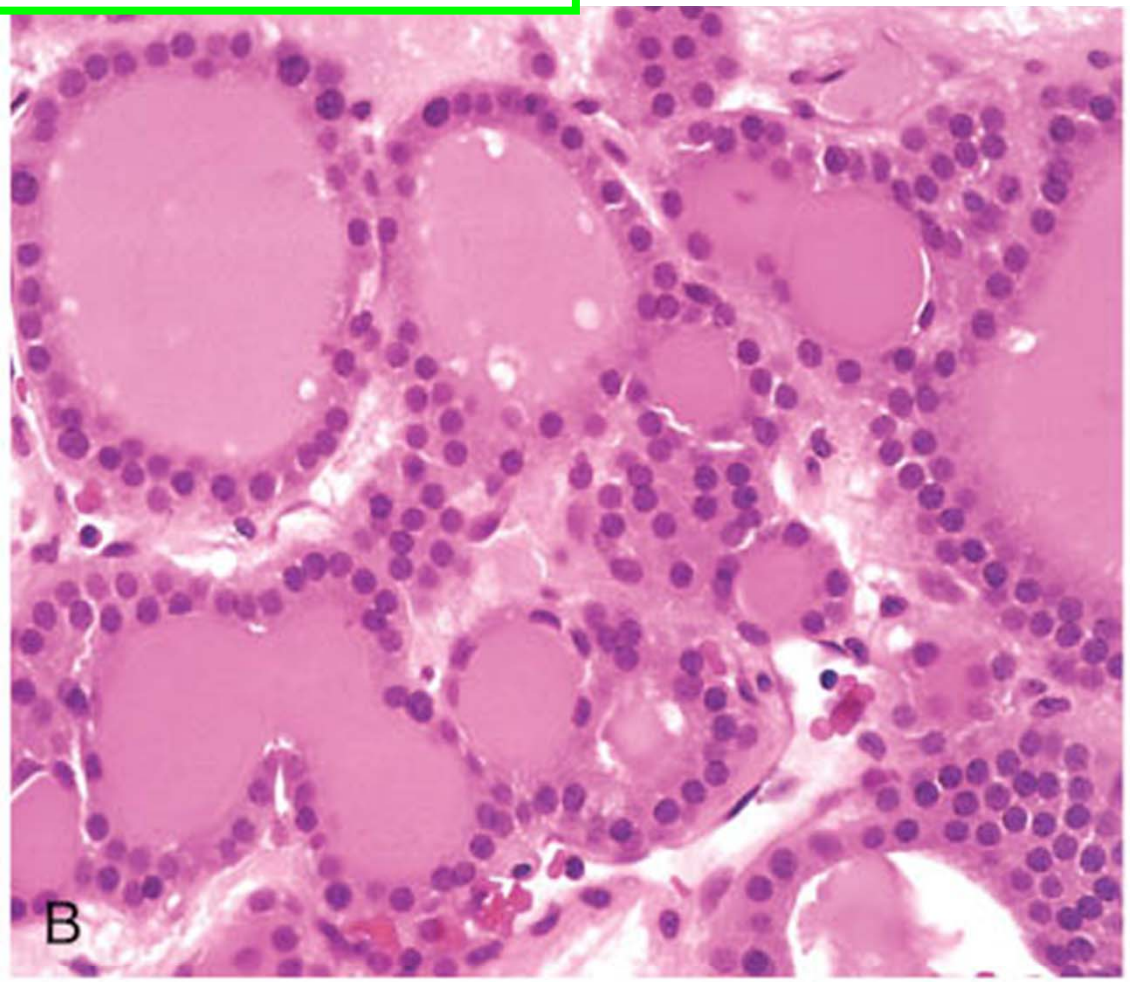


FIGURE 24–16B Follicular adenoma of the thyroid. **A,** A solitary, well-circumscribed nodule is seen. **B,** The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.

Without the capsule, you cannot determine if this picture came from normal thyroid or the middle of an adenoma (unless you look at the image label...that's usually a good clue).

Follicular carcinoma

- About half harbor RAS mutations
- NRAS is the most common
- PAX8-PPARγ1 fusion
- 2nd most common
- Female predominance; older age
- Increased incidence in areas of iodine deficiency
- Cold nodules
- Tendency for vascular invasion (not lymphatic)

specifically, the second most common thyroid neoplasm

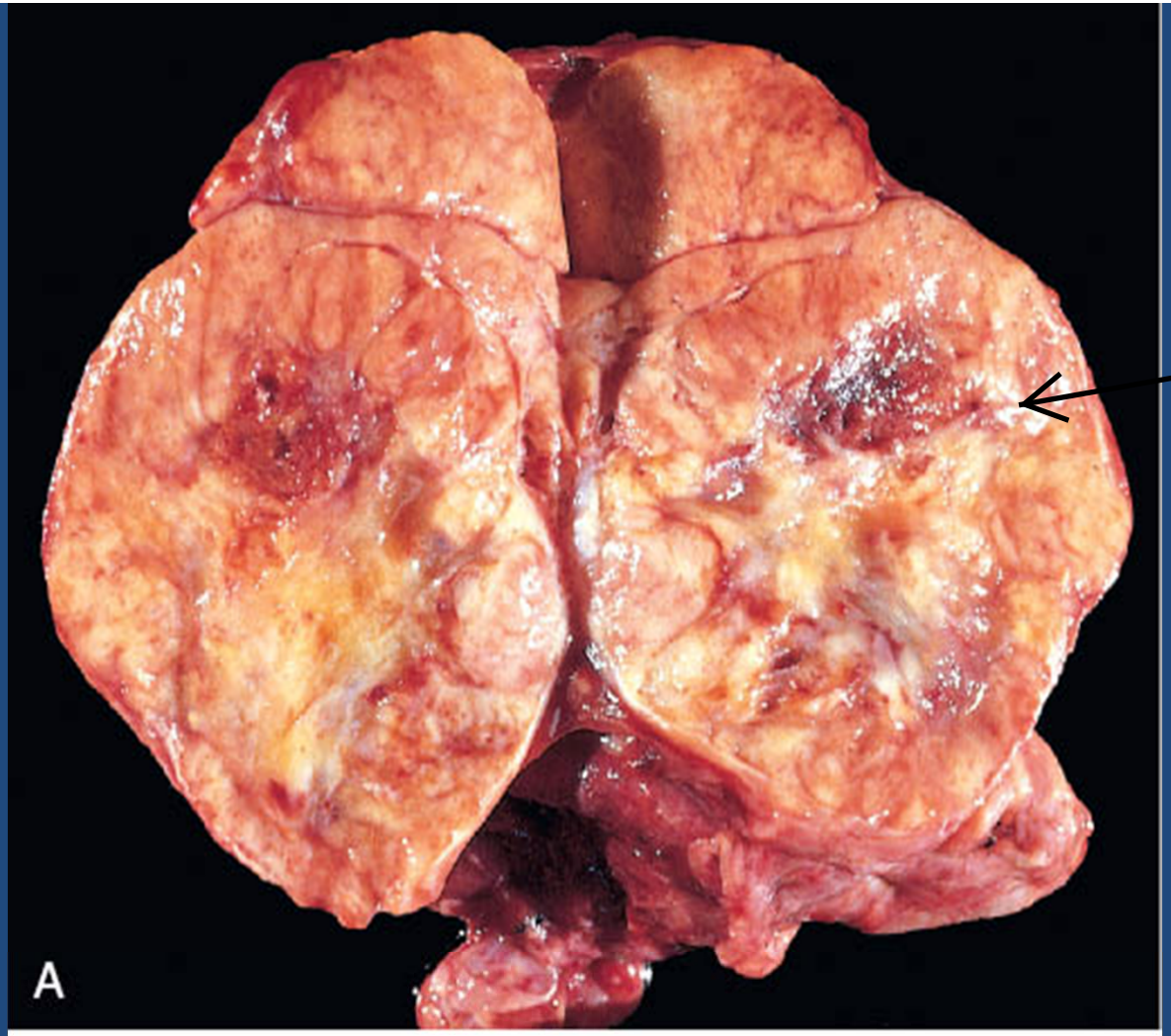


FIGURE 24–20A Follicular carcinoma. **A,** Cut surface of a follicular carcinoma with substantial replacement of the lobe of the thyroid. The tumor has a light-tan appearance and contains small foci of hemorrhage. **B,** A few of the glandular lumens contain recognizable colloid.

If you manage to get a gross specimen early in the pathogenesis of follicular carcinoma, you can see the capsule getting invaded and disrupted. The capsule is again very important to look at for diagnosis since the follicles in the middle of the neoplasm looks just like normal thyroid or follicular adenoma. Slide 51 shows how to differentiate thyroid adenoma from thyroid carcinoma on the basis of the capsule.

Microanatomy of a follicular carcinoma. It is bland looking in that it looks like a normal thyroid or follicular adenoma without the capsule in view.

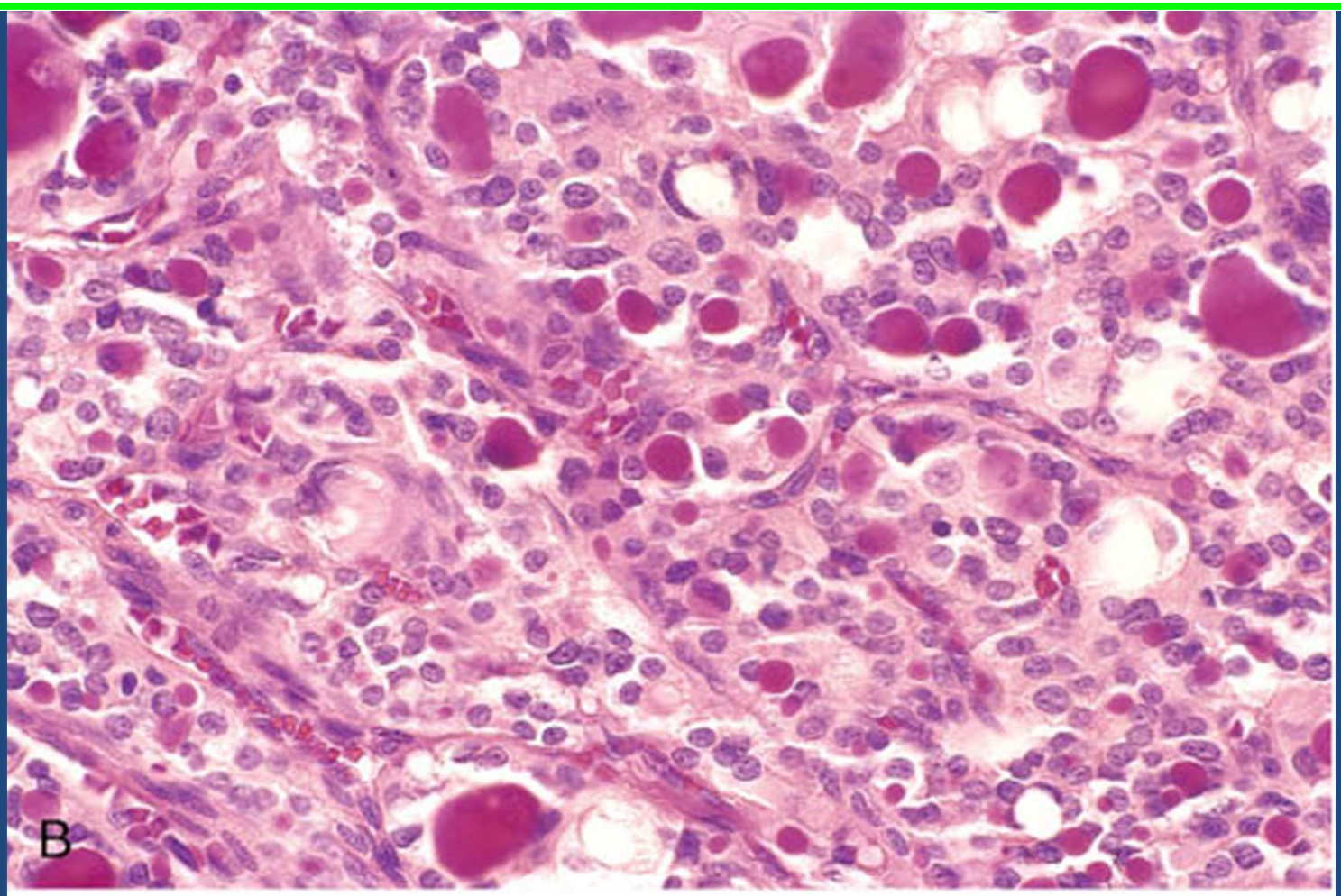


FIGURE 24–20B Follicular carcinoma. **A,** Cut surface of a follicular carcinoma with substantial replacement of the lobe of the thyroid. The tumor has a light-tan appearance and contains small foci of hemorrhage. **B,** A few of the glandular lumens contain recognizable colloid.

Capsular differences between follicular adenoma and follicular carcinoma.

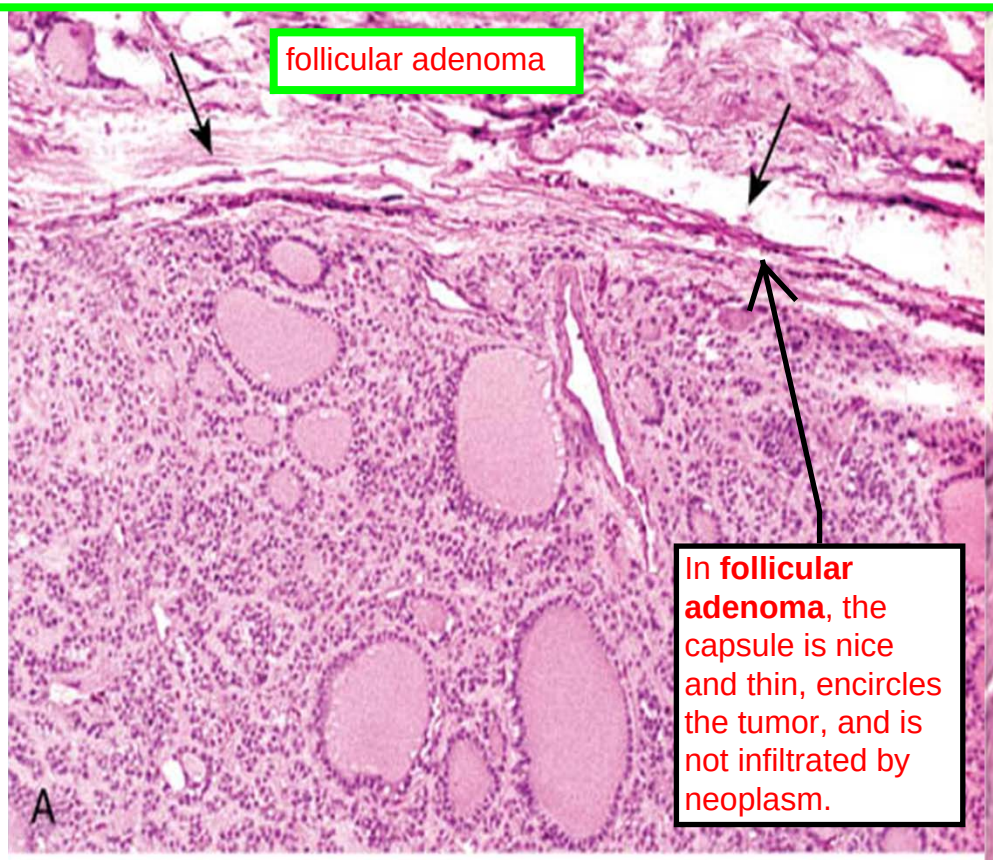
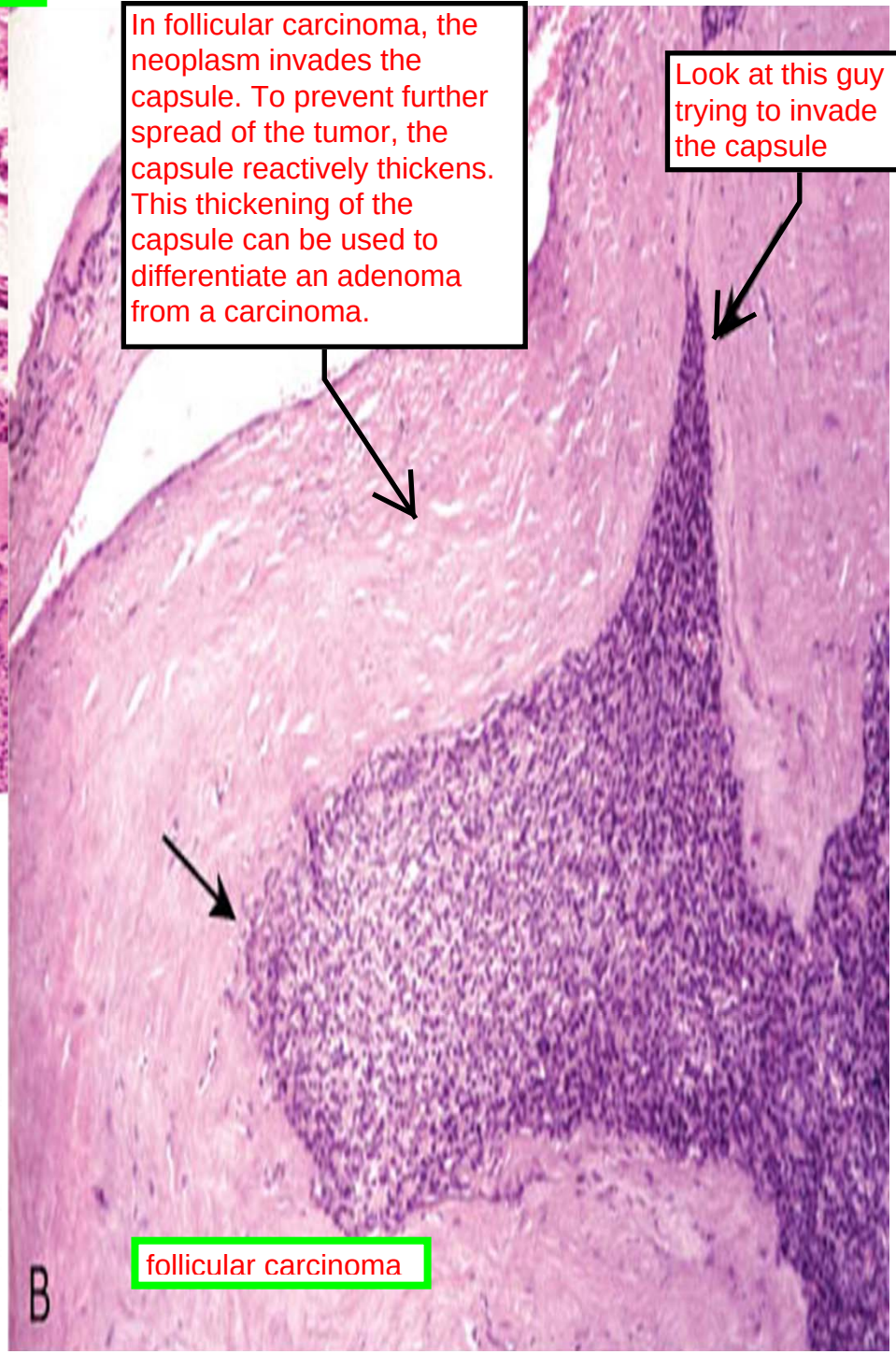


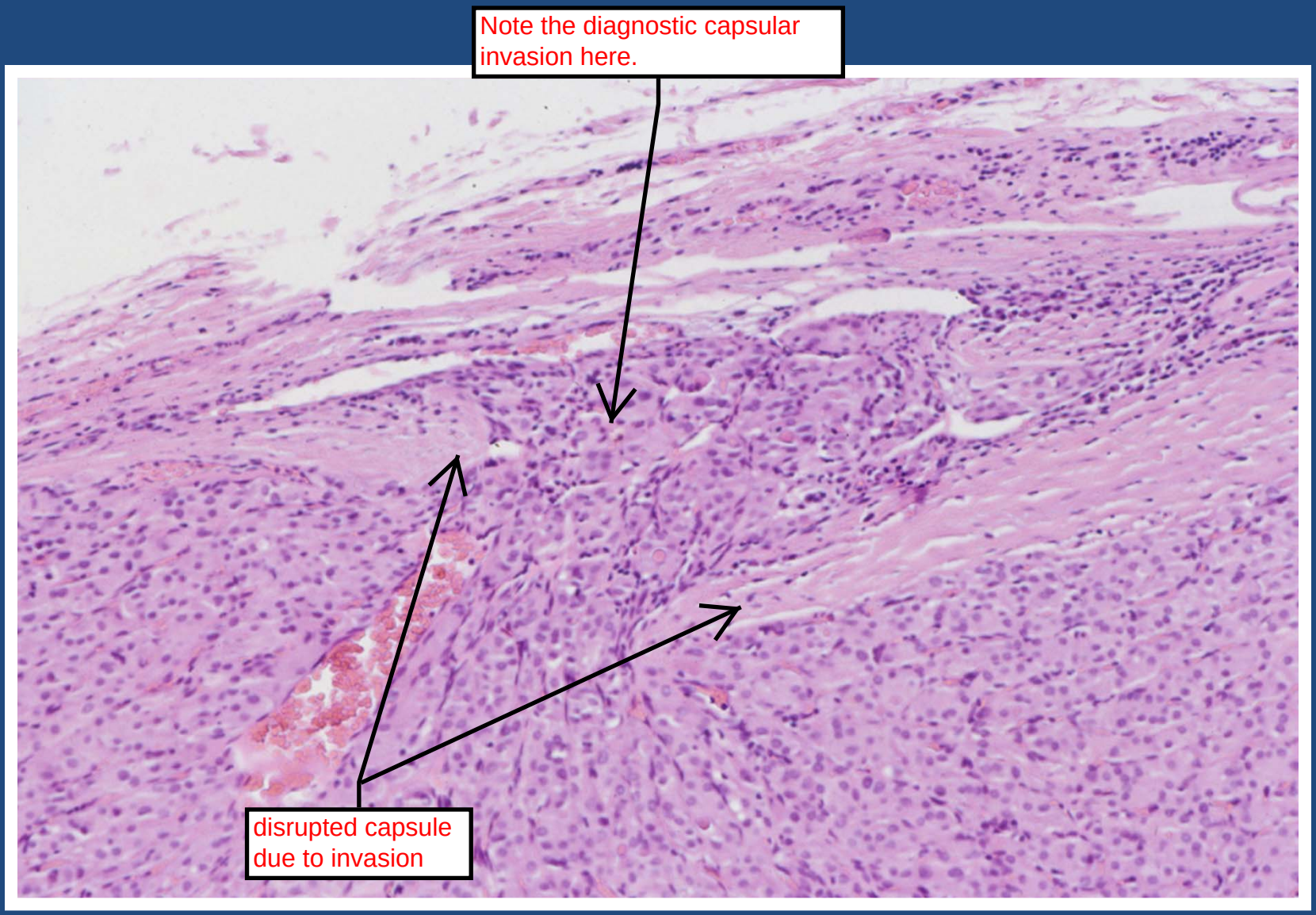
FIGURE 24–21A Capsular integrity in follicular neoplasms. In adenomas **(A)**, a fibrous capsule, usually thin but occasionally more prominent, circumferentially surrounds the neoplastic follicles and no capsular invasion is seen *(arrows);* compressed normal thyroid parenchyma is usually present external to the capsule *(top of the panel)*. In contrast, follicular carcinomas demonstrate capsular invasion (**B,** *arrows*) that may be minimal, as in this case, or widespread. The presence of vascular invasion is another feature of follicular carcinomas.

In follicular carcinoma, the neoplasm invades the capsule. To prevent further spread of the tumor, the capsule reactively thickens. This thickening of the capsule can be used to differentiate an adenoma from a carcinoma.

Look at this guy trying to invade the capsule

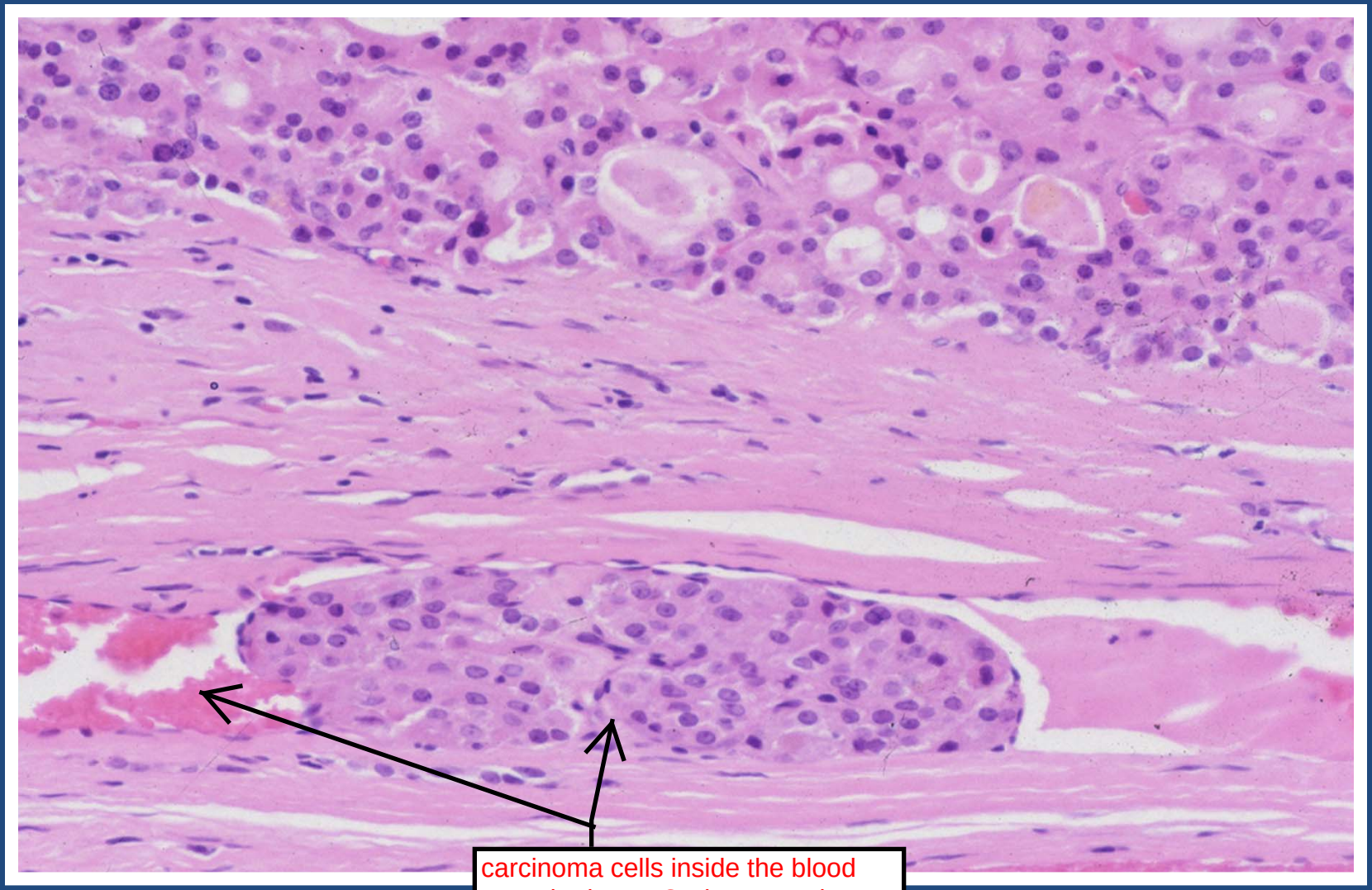


Capsular invasion is diagnostic of follicular carcinoma.



Capsular invasion in follicular carcinoma.

Vascular invasion is another diagnostic feature of a carcinoma versus an adenoma.



Vascular invasion is one of the features that separate a benign adenoma from a carcinoma

Cytology is important in the diagnosis of papillary carcinoma because many of its distinguishing features are nuclear.

Papillary carcinoma

- Rearrangement of tyrosine kinase receptors RET or NTRK1
- ret/PTC fusion gene (1/5); children and background of radiation
- Mutations in the BRAF oncogene (1/3 to 1/2)
- RAS mutations
- Most common thyroid cancer; excellent prognosis
- Morphology: papillae, optically clear nuclei (ground glass or "Orphan Annie" eye), nuclear pseudo-inclusions, intranuclear grooves, psammoma bodies

The nuclei are so convoluted that the cytoplasm interlaces itself into these convolutions such that it looks like there inclusions within the nuclei.

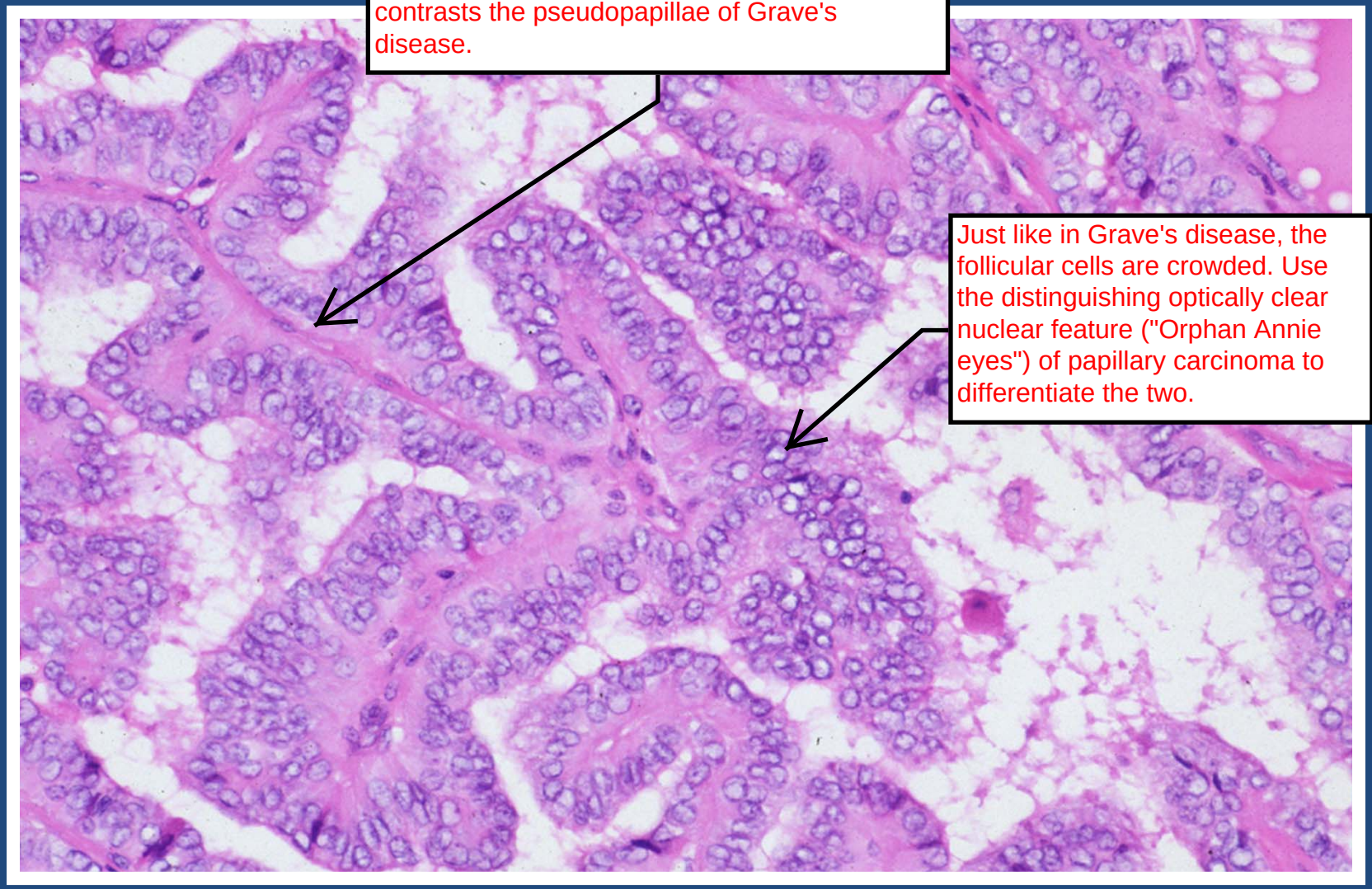
In what brain tumor would you see psammoma bodies?

Lots of variants of papillary carcinomas exist. Pathologists to the rescue!

Papillary carcinoma

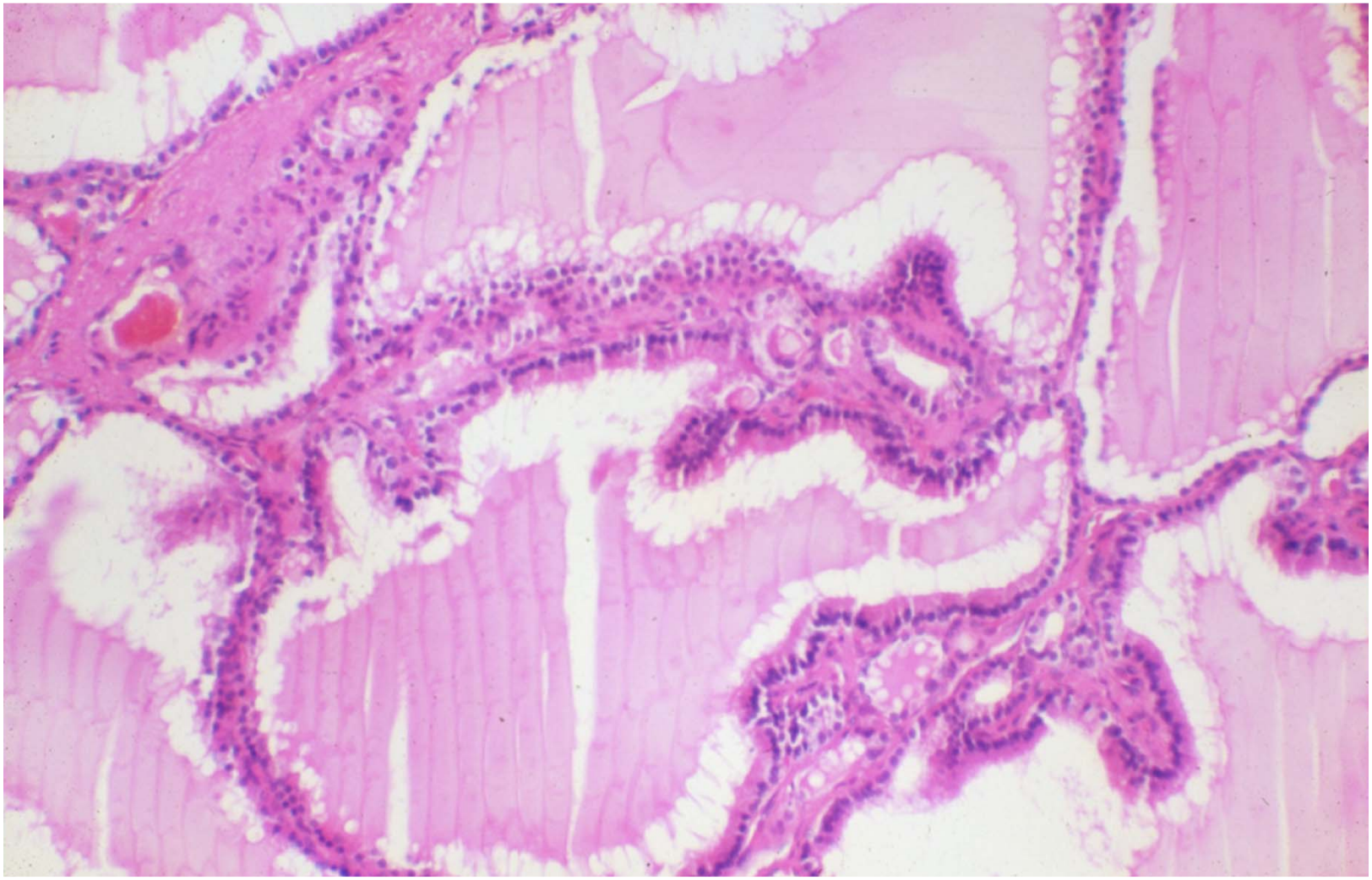
- Types:
- Encapsulated variant
- Follicular variant
- Tall cell variant
- Diffuse sclerosing variant
- Hyalinizing trabecular tumors

Histology of papillary carcinoma. The nuclear and papillary features can help you distinguish it from Grave's disease.



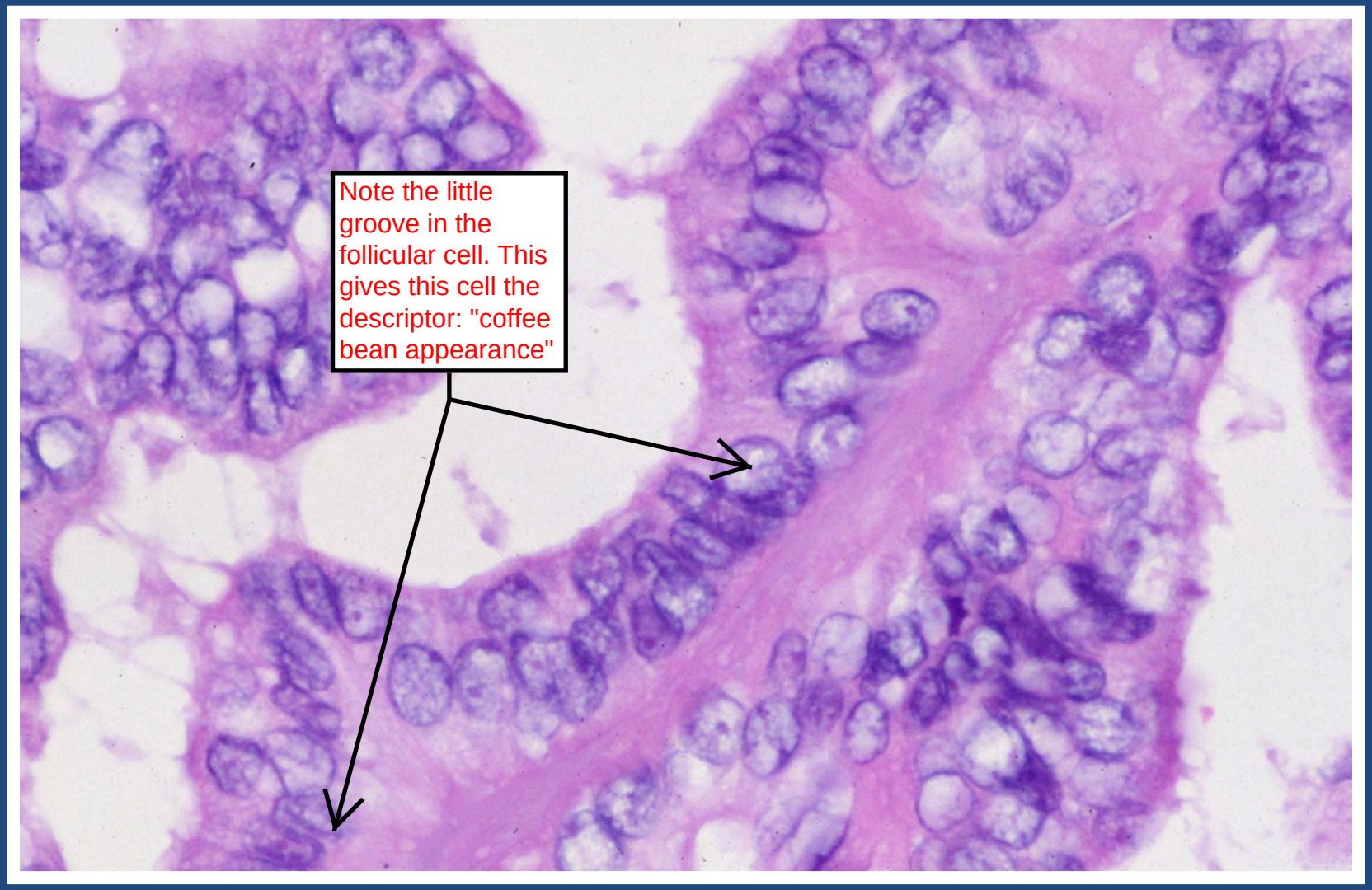
True Papillae in Papillary Carcinoma of the Thyroid. Note the crowded nuclei with optically clear nuclei (so-called Orphan-Annie eyes)

This is a reminder of what Grave's disease looks like under microscopy.



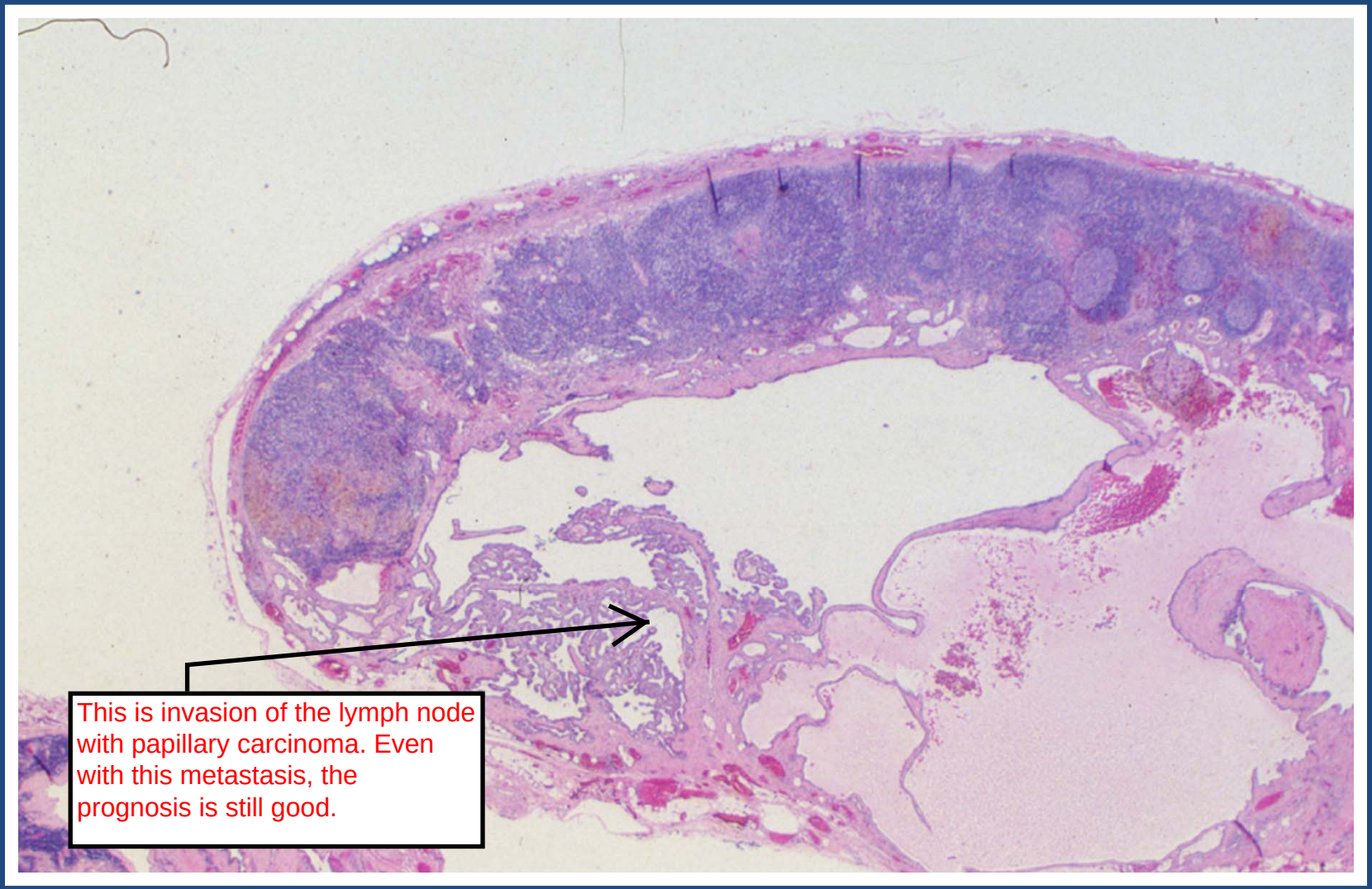
Pseudo Papillae of hyperthyroidism

Another picture of papillary carcinoma under microscope. You can see the coffee-bean appearance of certain follicular cells really well on this slide.



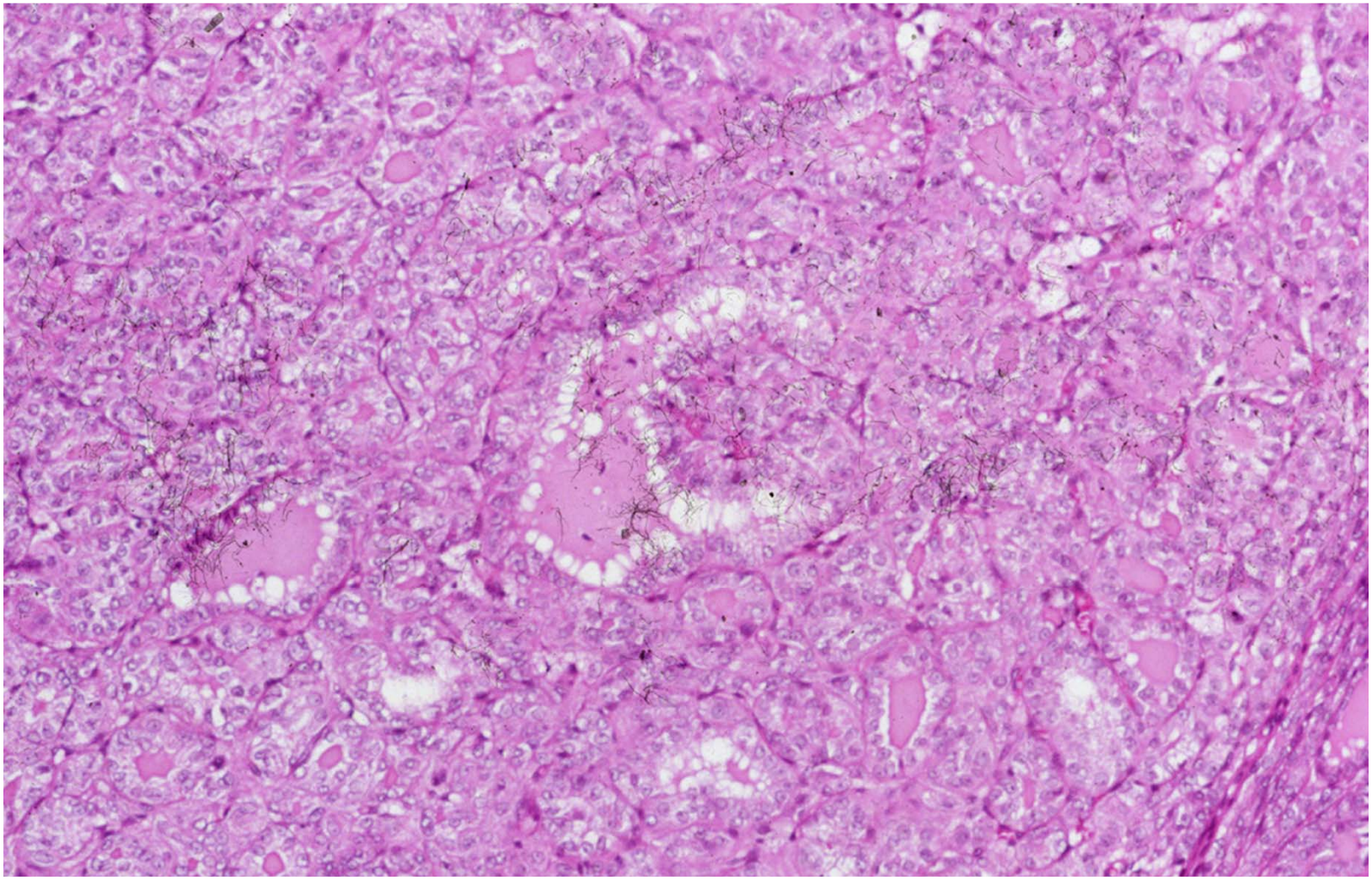
Crowded, optically clear nuclei in papillary carcinoma of the thyroid

Lymph node metastasis of papillary carcinoma



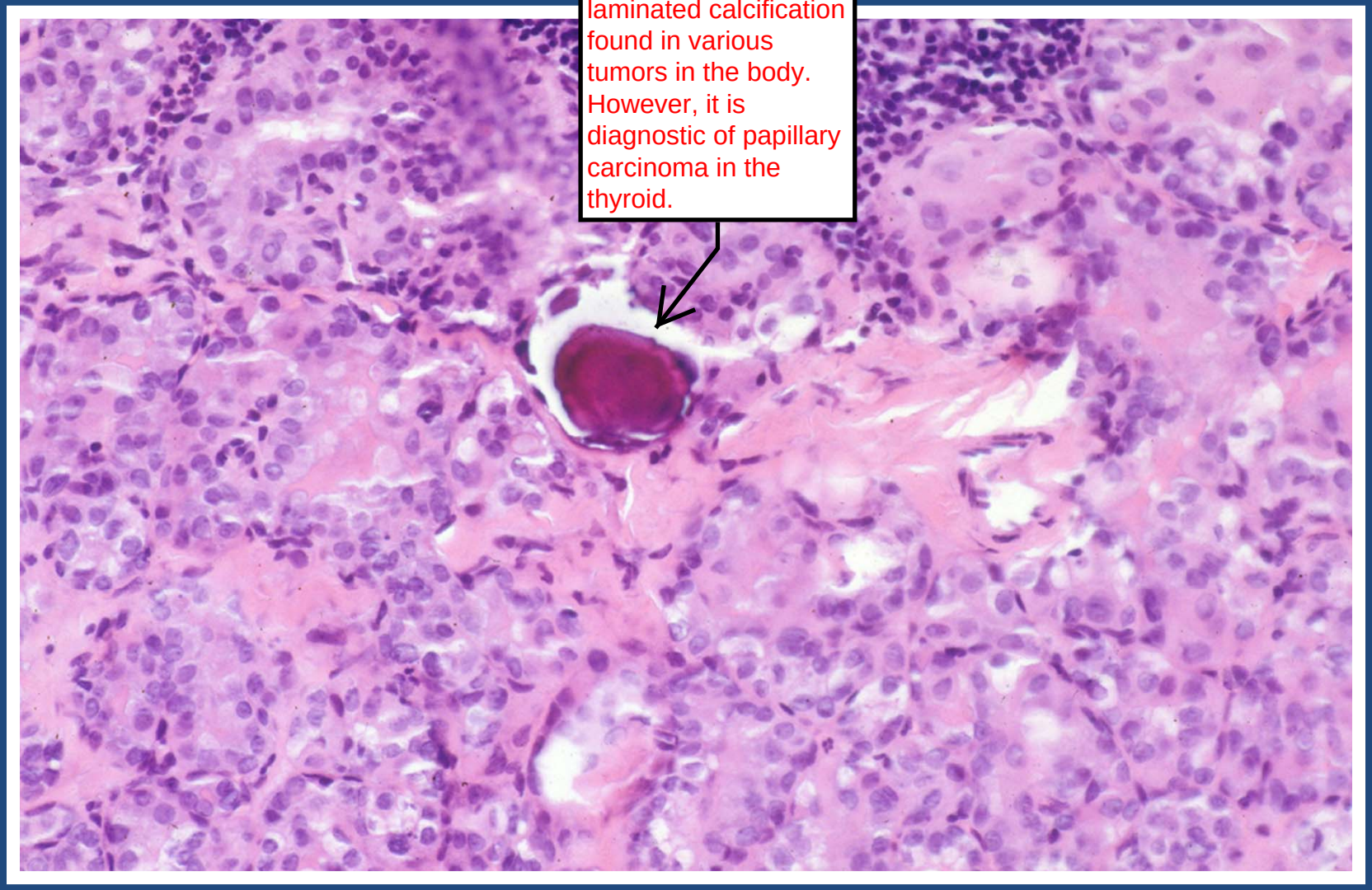
Metastatic papillary carcinoma in a lymph node

She skipped this slide.



Follicular variant of papillary carcinoma of the thyroid, There is one abortive papilla in the center of the picture.

Psammoma body in papillary carcinoma



Psammoma body in follicular variant of papillary carcinoma

Medullary Carcinoma

- Parafollicular C cells (neuroendocrine neoplasm) → calcitonin secretion
- Sporadic: 80% of cases
- Familial forms: MEN-2 (RET protooncogene point mutation)
- Solitary of multiple nodules
- Polygonal or spindle-shaped cells
- Nests, trabeculae or follicles
- Amyloid deposits

Gross appearances don't really help you diagnose medullary carcinoma.

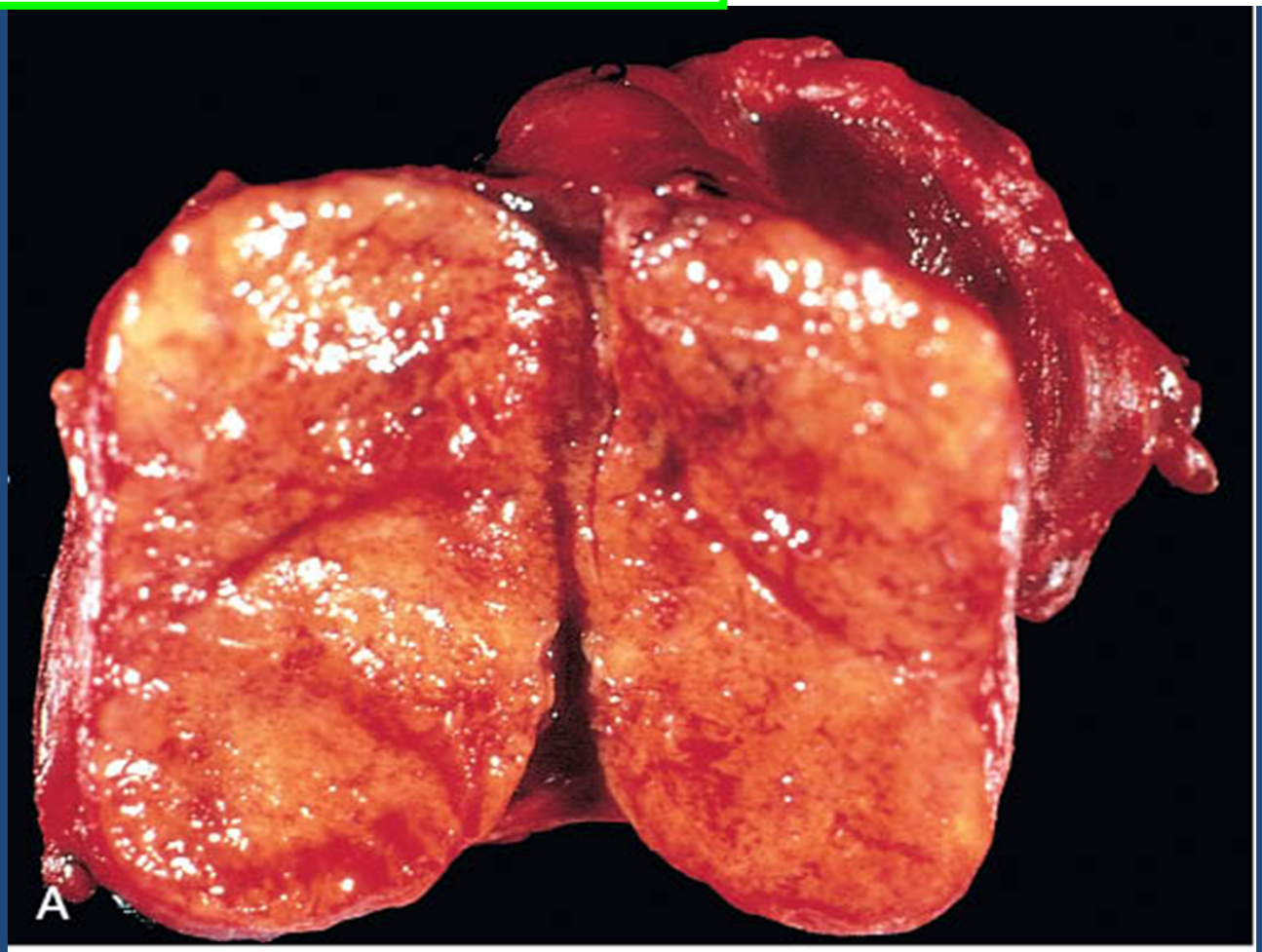
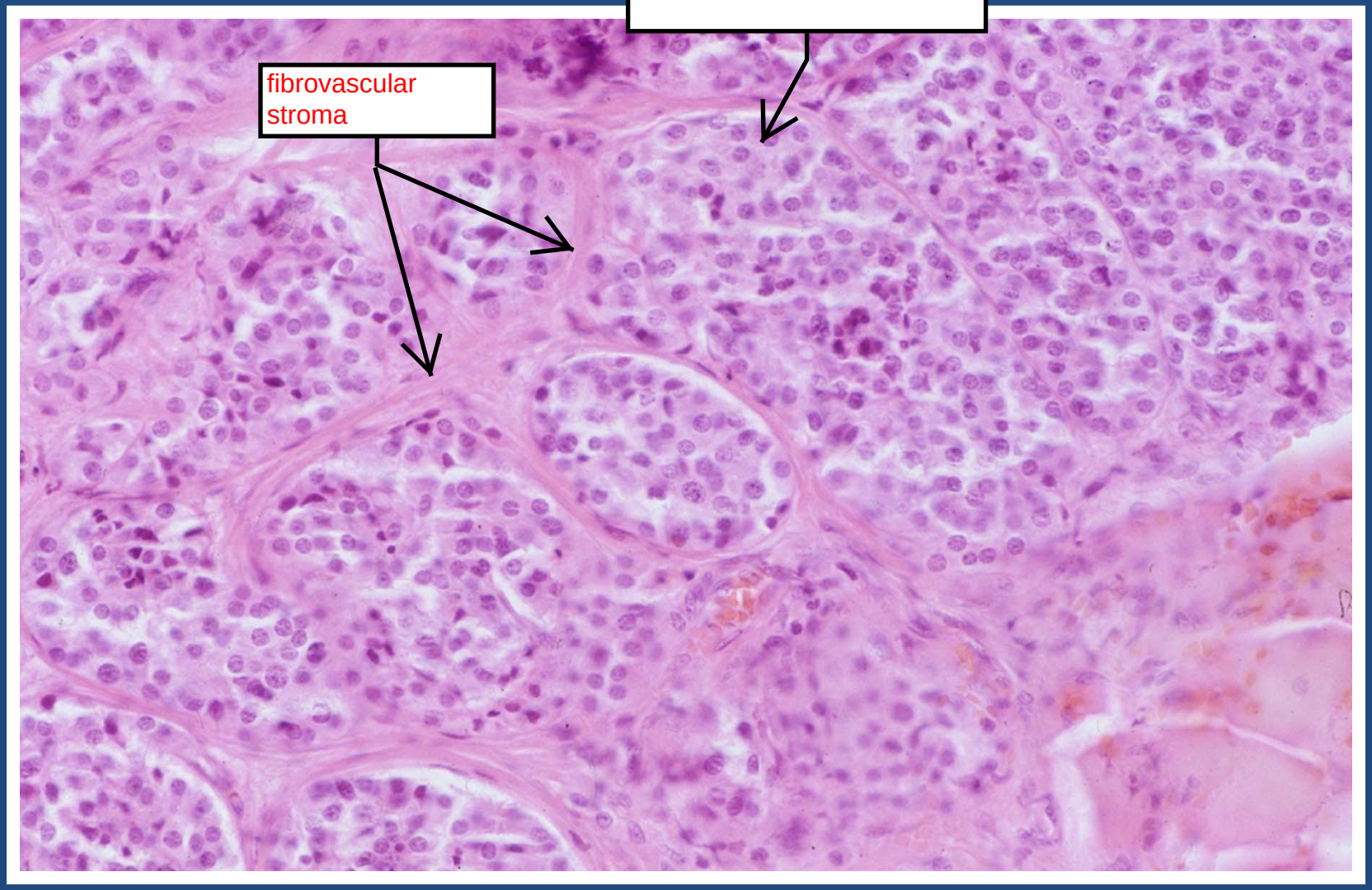


FIGURE 24–22A Medullary carcinoma of thyroid. **A,** These tumors typically show a solid pattern of growth and do not have connective tissue capsules. **B,** Histology demonstrates abundant deposition of amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells.

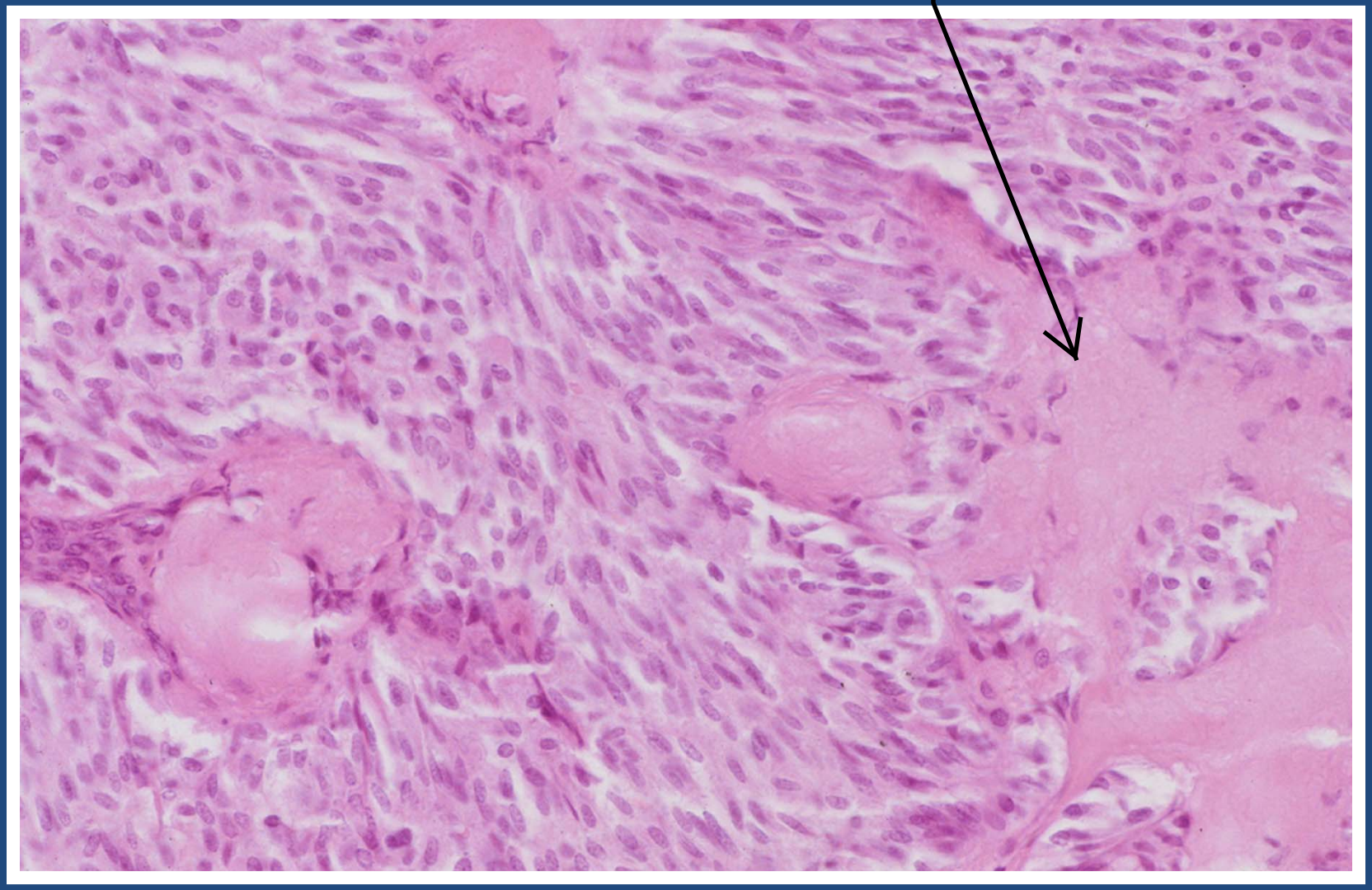
(Courtesy of Dr. Joseph Corson, Brigham and Women's Hospital, Boston, MA.)

This slide emphasizes the cell nests surrounded by fibrovascular stroma characteristic of medullary thyroid carcinomas.



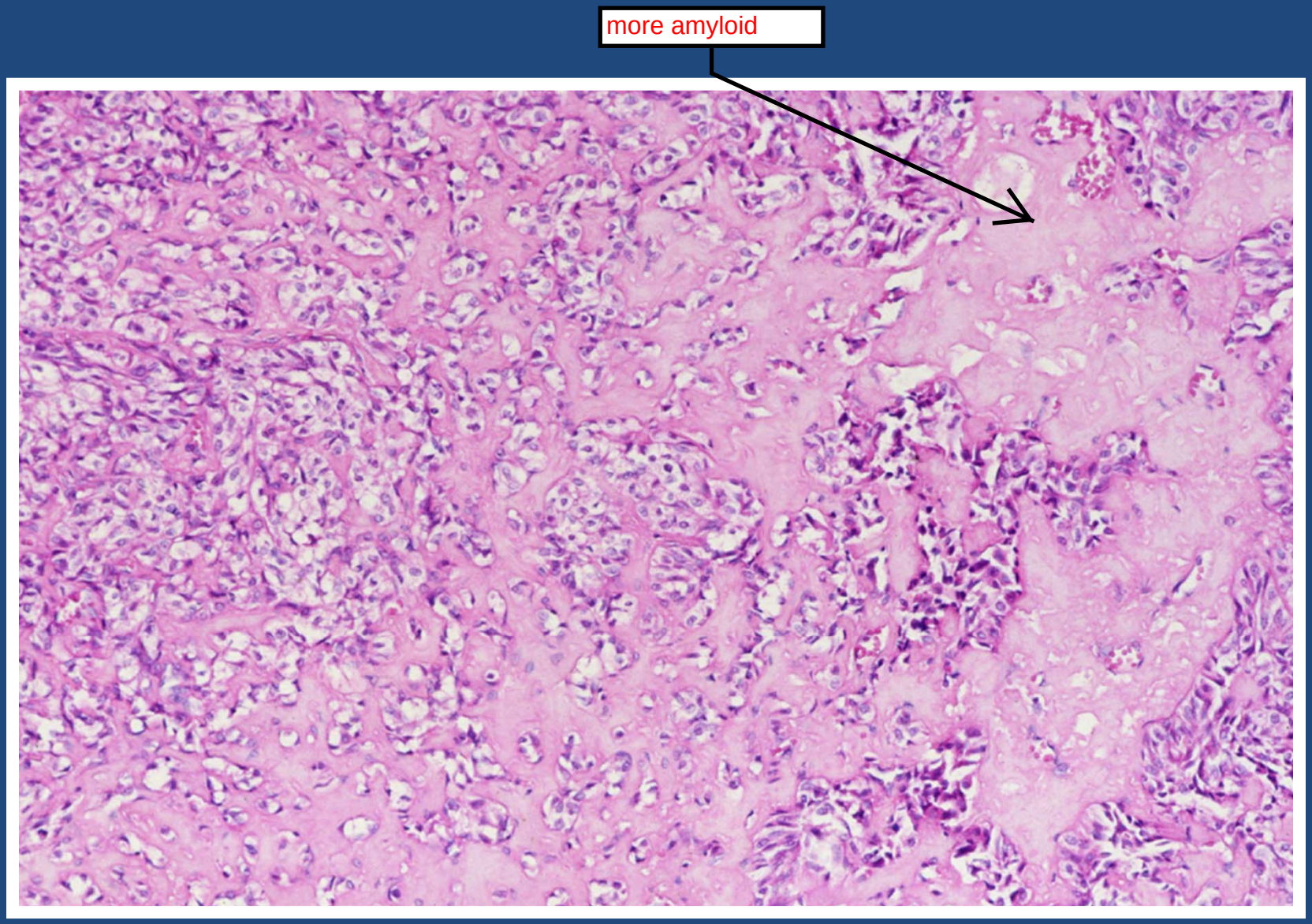
Nests of cells surrounded by fibrovascular stroma is characteristic of neuroendocrine tumors

This slide emphasizes the amyloid deposits characteristic of medullary thyroid carcinomas.



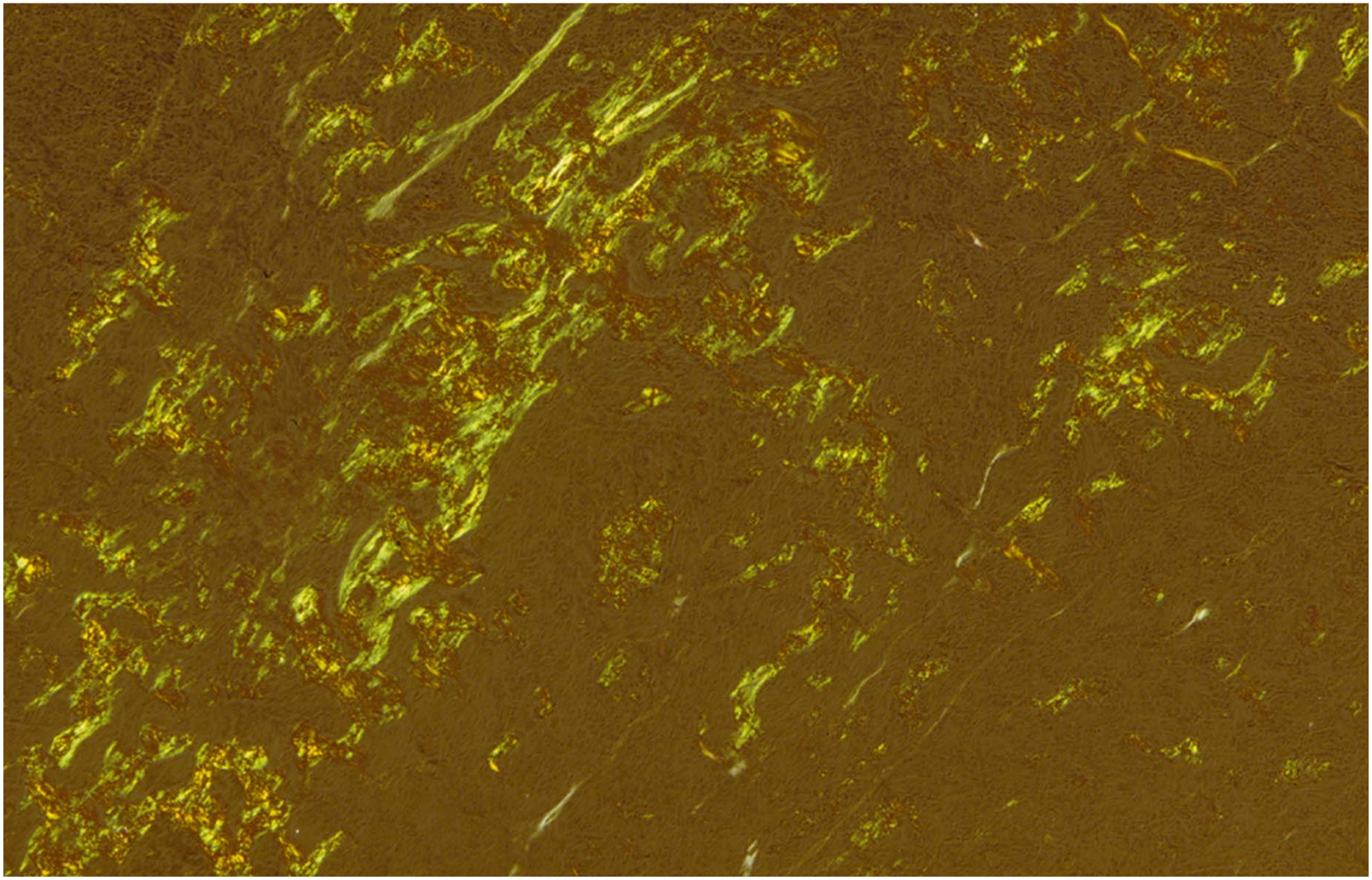
Spindle cell pattern and hyaline material

This slide emphasizes the amyloid deposits characteristic of medullary thyroid carcinomas.



Hyaline deposits crowd the tumor cells

Apple-green color with Congo red stain and polarization = amyloid. Again, another slide emphasizing that medullary thyroid carcinomas have amyloid deposits.



"Apple green" staining with Congo red stain and polarization demonstrates the hyaline deposits to be amyloid

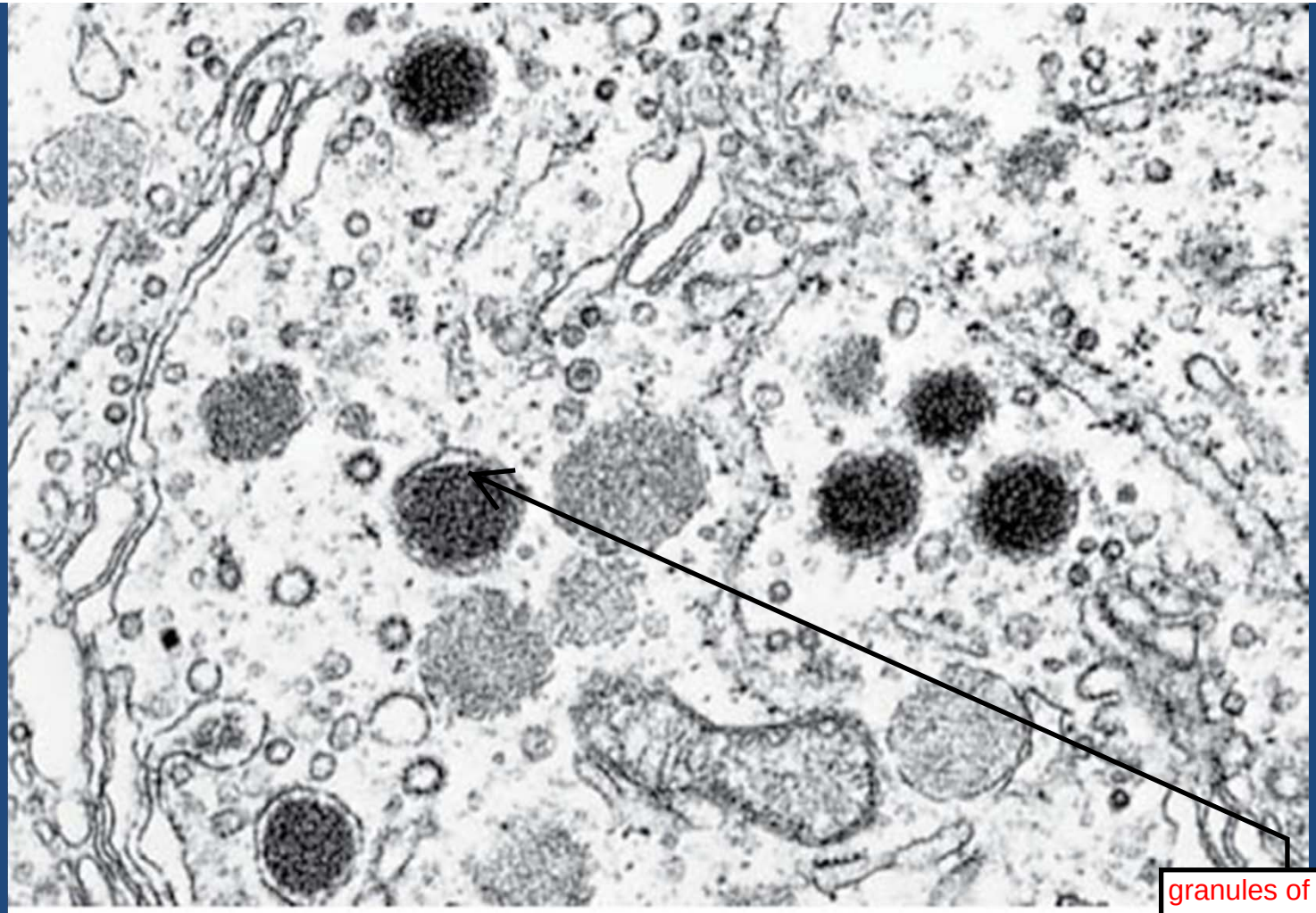


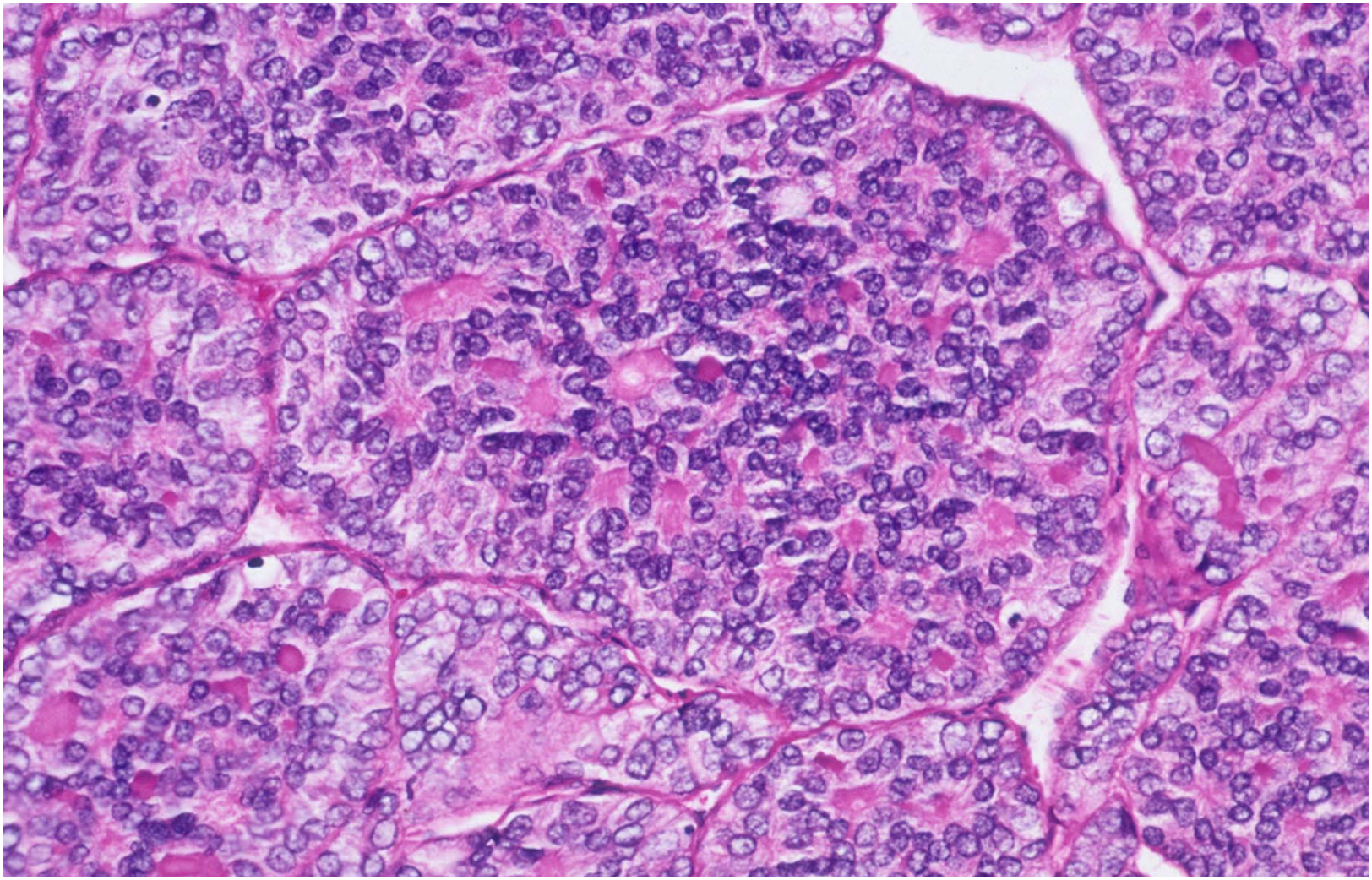
FIGURE 24–23 Electron micrograph of medullary thyroid carcinoma. These cells contain membrane-bound secretory granules that are the sites of storage of calcitonin and other peptides.

She skipped this. It isn't in Robbins. Just know that it has a bad prognosis.

Poorly-Differentiated Carcinoma

- 5-10% of thyroid carcinomas
- Definition is unsettled.
  - 1. Morphology is similar to medullary carcinoma but without amyloid or calcitonin
  - 2. Necrosis and more than 5 mitoses/hpf
- Less than 50% 5 year survival

She skipped this. It isn't in Robbins. Just know that it has a bad prognosis.



"Poorly-differentiated" or "insular" carcinoma

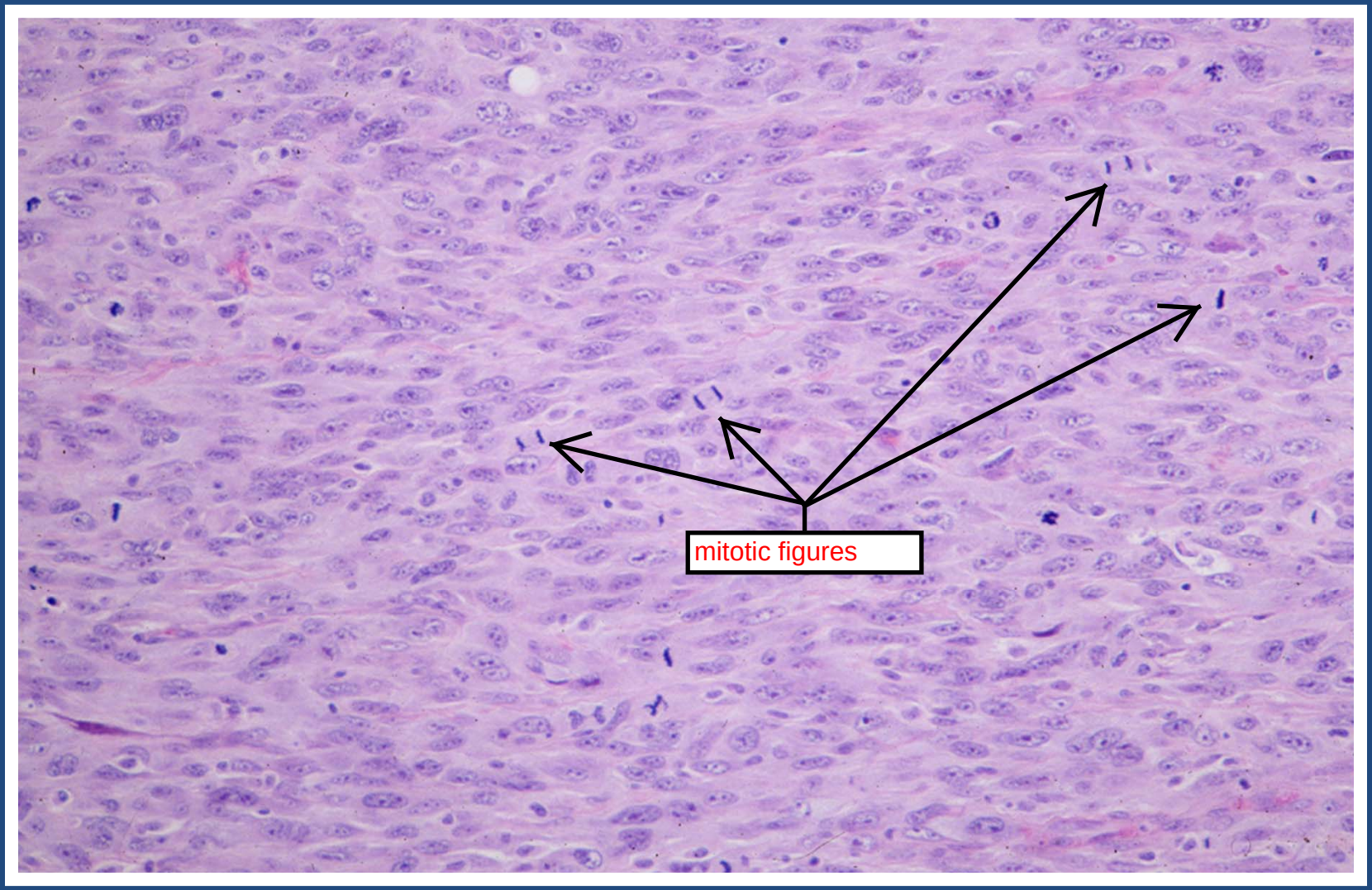
Anaplastic carcinoma: an aggressive, lethal cancer of the old.

Anaplastic carcinoma

- Highly aggressive, lethal tumors
- Inactivating point mutations of p53 tumor suppressor gene
- Older patients (65 yo)
- Hx: multinodular goiter, differentiated carcinoma
- Morphology: anaplastic cells (pleomorphic, giant cells, spindle cells, small cells)

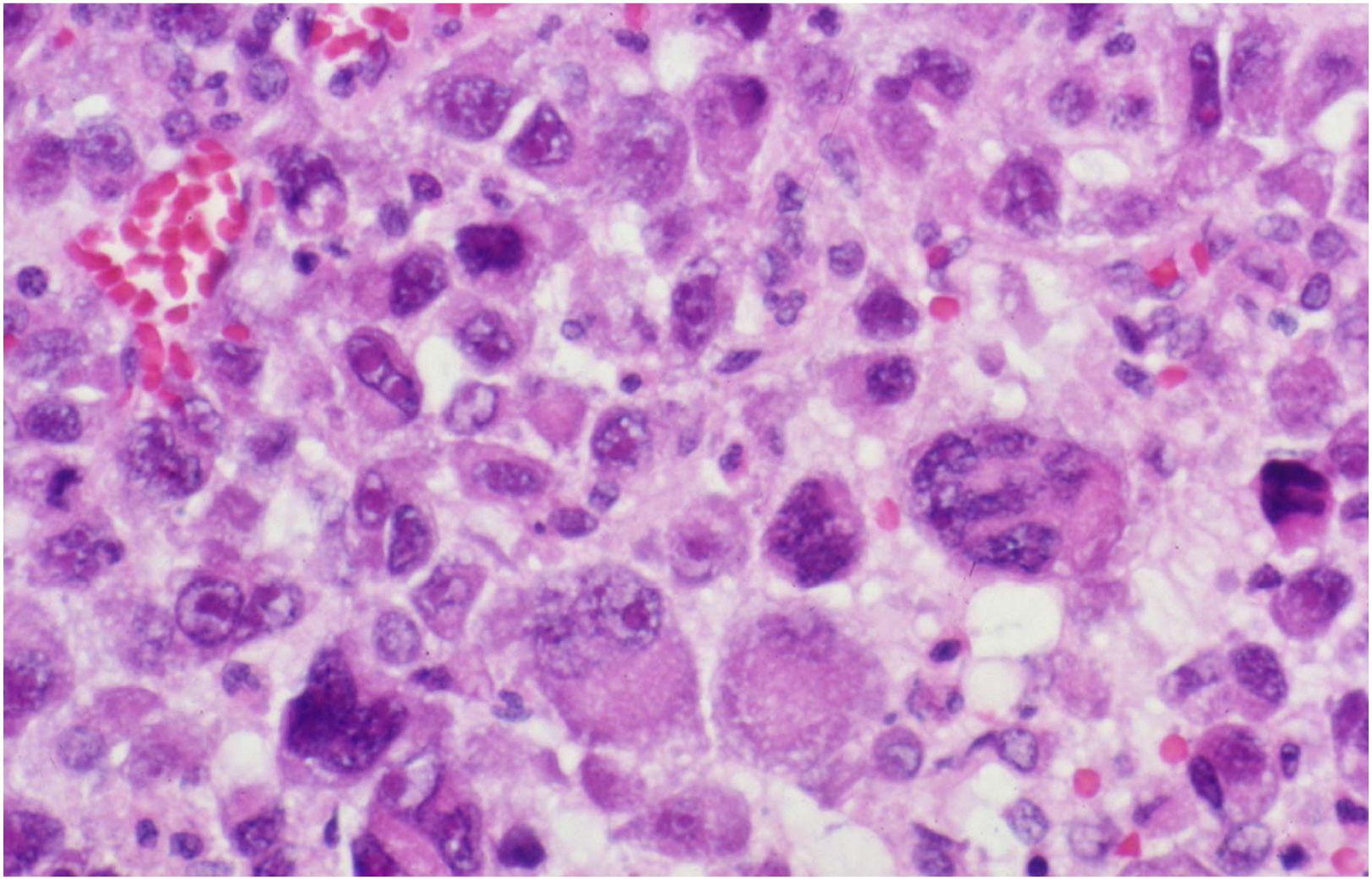
The formerly differentiated carcinoma could have progressed due to accumulation of more mutations, leading to anaplastic carcinoma.

Microscopic observation of anaplastic carcinoma reveals many pleomorphic cells and many mitotic figures.



Spindle cell anaplastic carcinoma

Note the bizarre pleomorphism in anaplastic carcinoma.



Bizarre cells in anaplastic carcinoma of the thyroid

She breezed past this saying we could look at it on our own. The diagram just shows what molecular disruptions in follicular cell pathways can lead to a particular thyroid cancer.

Schematic picture of molecular alterations seen in thyroid carcinomas

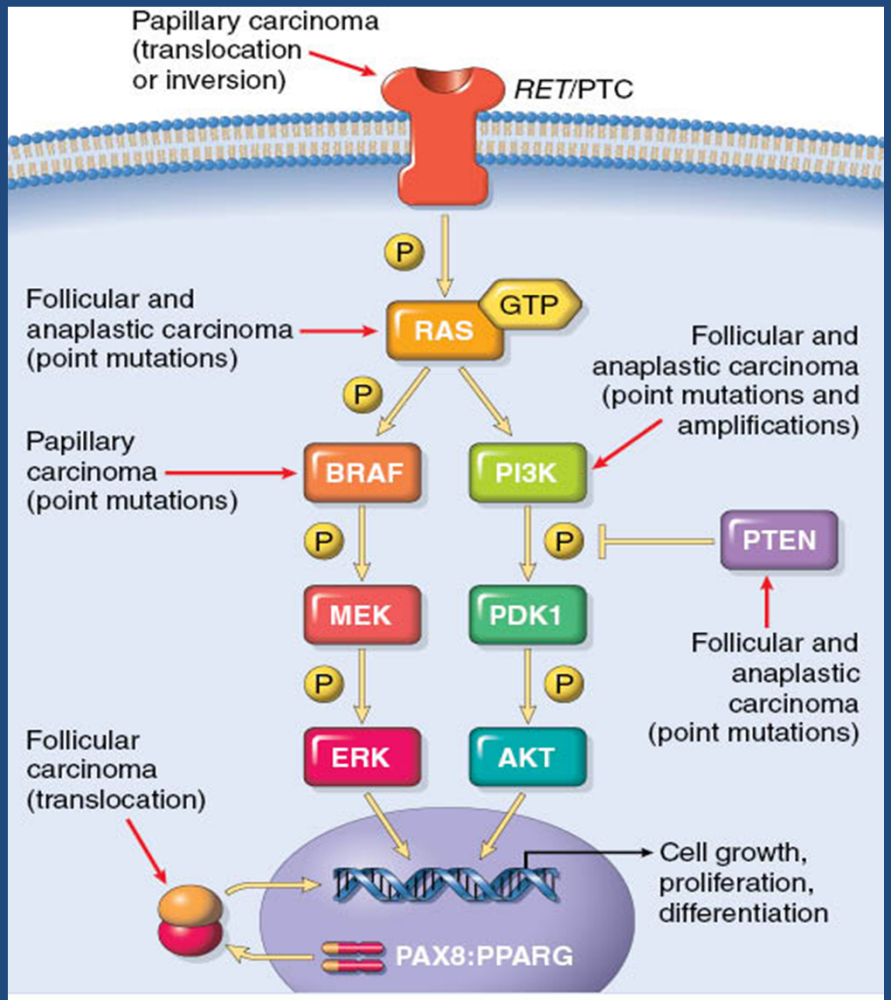


FIGURE 24–18 Genetic alterations in follicular cell–derived malignancies of the thyroid gland.

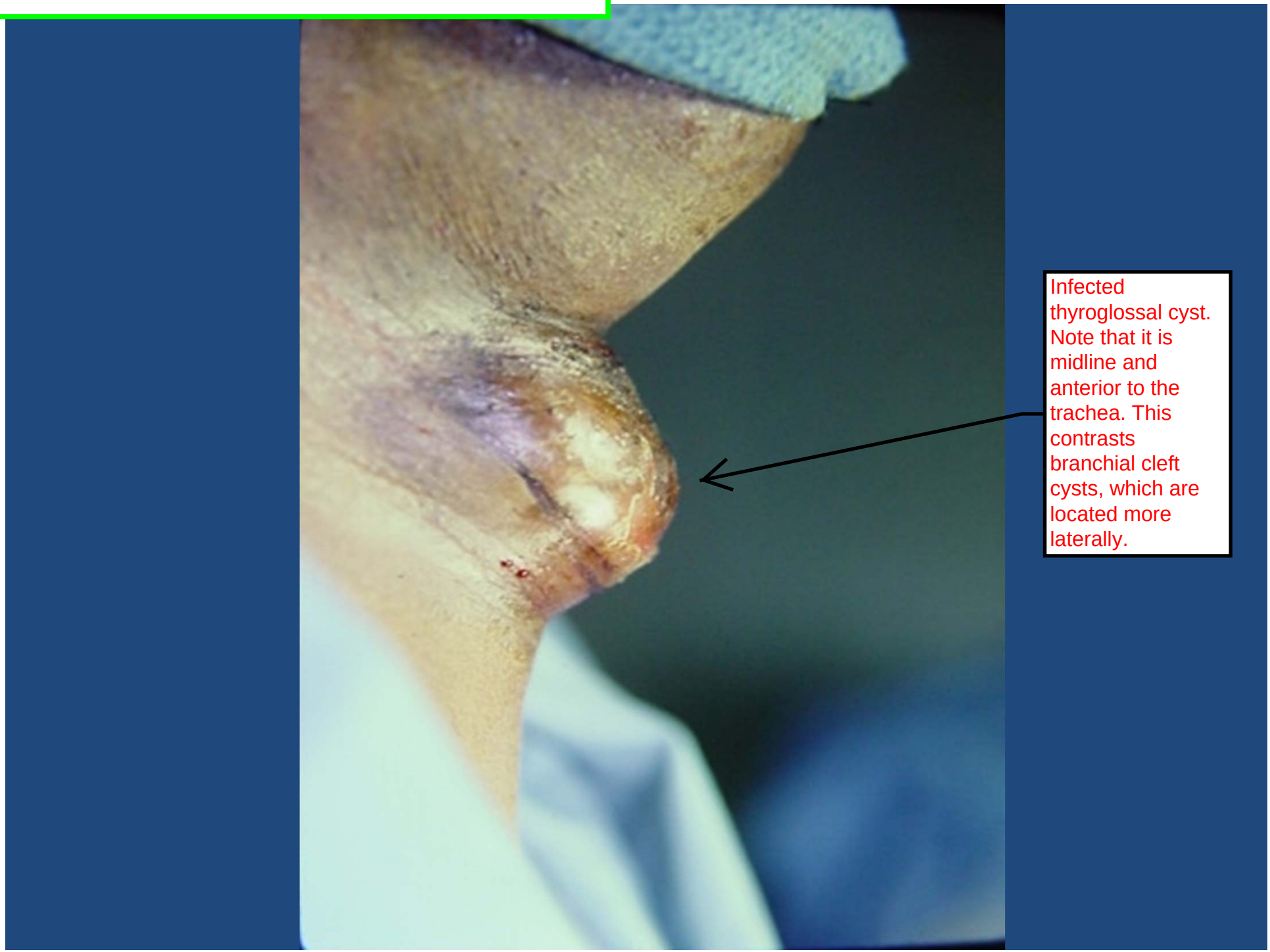
Congenital anomalies

- Thyroglossal duct or cyst:
- Most common clinically significant congenital anomaly of thyroid
- Mucinous, clear fluids may collect (spherical masses)
- Midline of neck (anterior to trachea)
- Higher lesions: stratified squamous epithelium
- Lower lesions: thyroidal acinar epithelium
- Can give rise to cancer

The lining of the cyst depends on its location

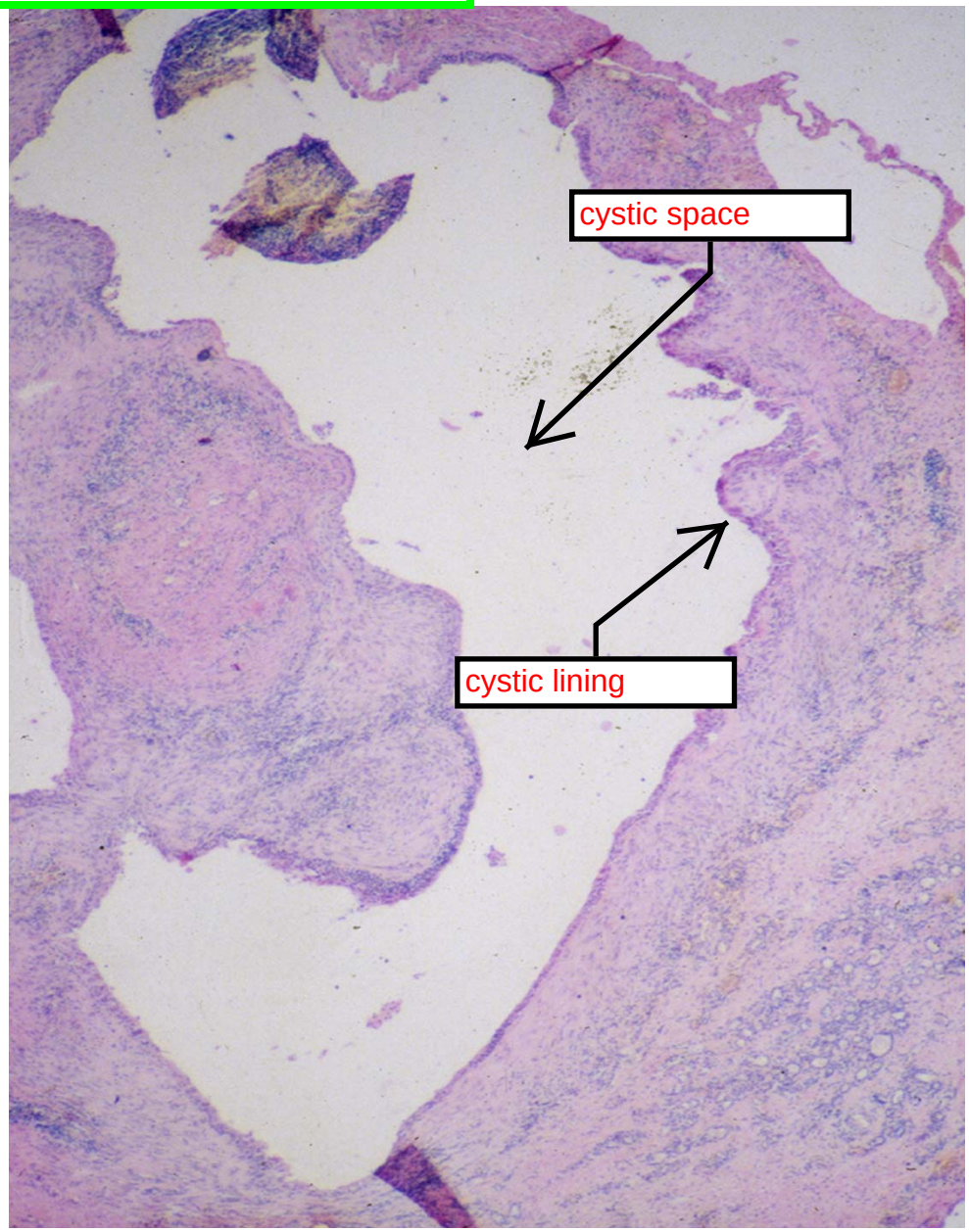
Embryology connection: The thyroid initially develops in the fetal oropharynx and descends through the tongue (hence, thyroGLOSSAL duct) and neck to reach its final position. Along its migratory path, it forms a duct that normally atrophies and closes. When this duct fails to close, a persistent duct or cyst can form.

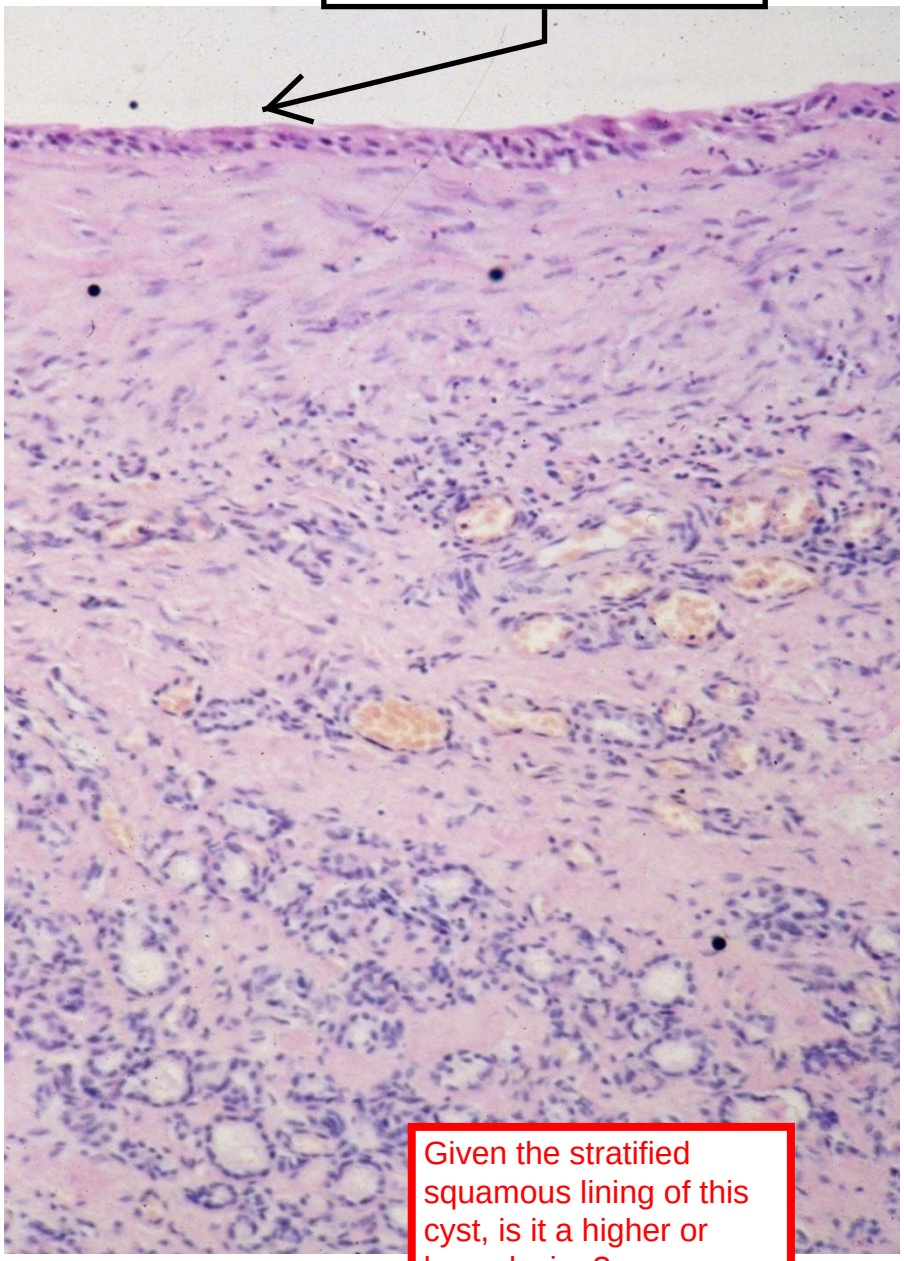
Thyroglossal cyst



Infected thyroglossal cyst. Note that it is midline and anterior to the trachea. This contrasts branchial cleft cysts, which are located more laterally.

Histology of a thyroglossal cyst.



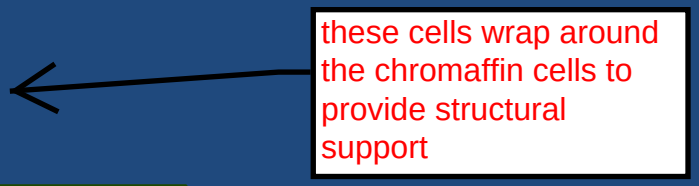


Given the stratified squamous lining of this cyst, is it a higher or lower lesion?

Thyroglossal duct

Adrenal medulla

- Distinct from adrenal cortex
- Neural crest (neuroendocrine or *chromaffin* cells)
- Sustentacular cells



- Produce catecholamines (epinephrine and norepinephrine)
- Adrenal medulla: part of paraganglion system

She just read the slide

Pheochromocytoma

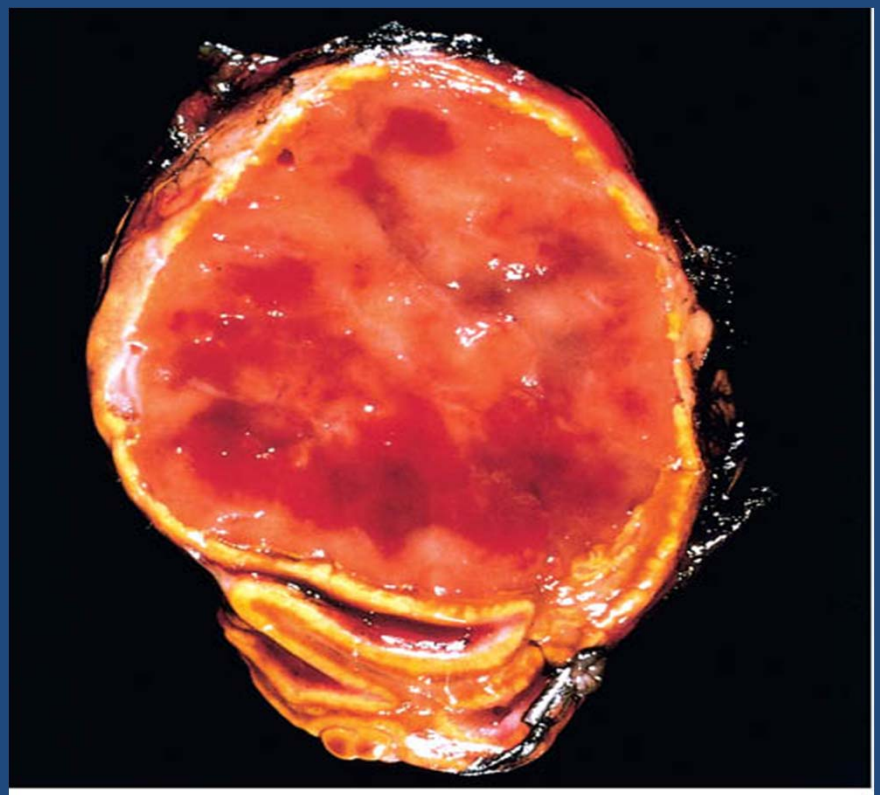
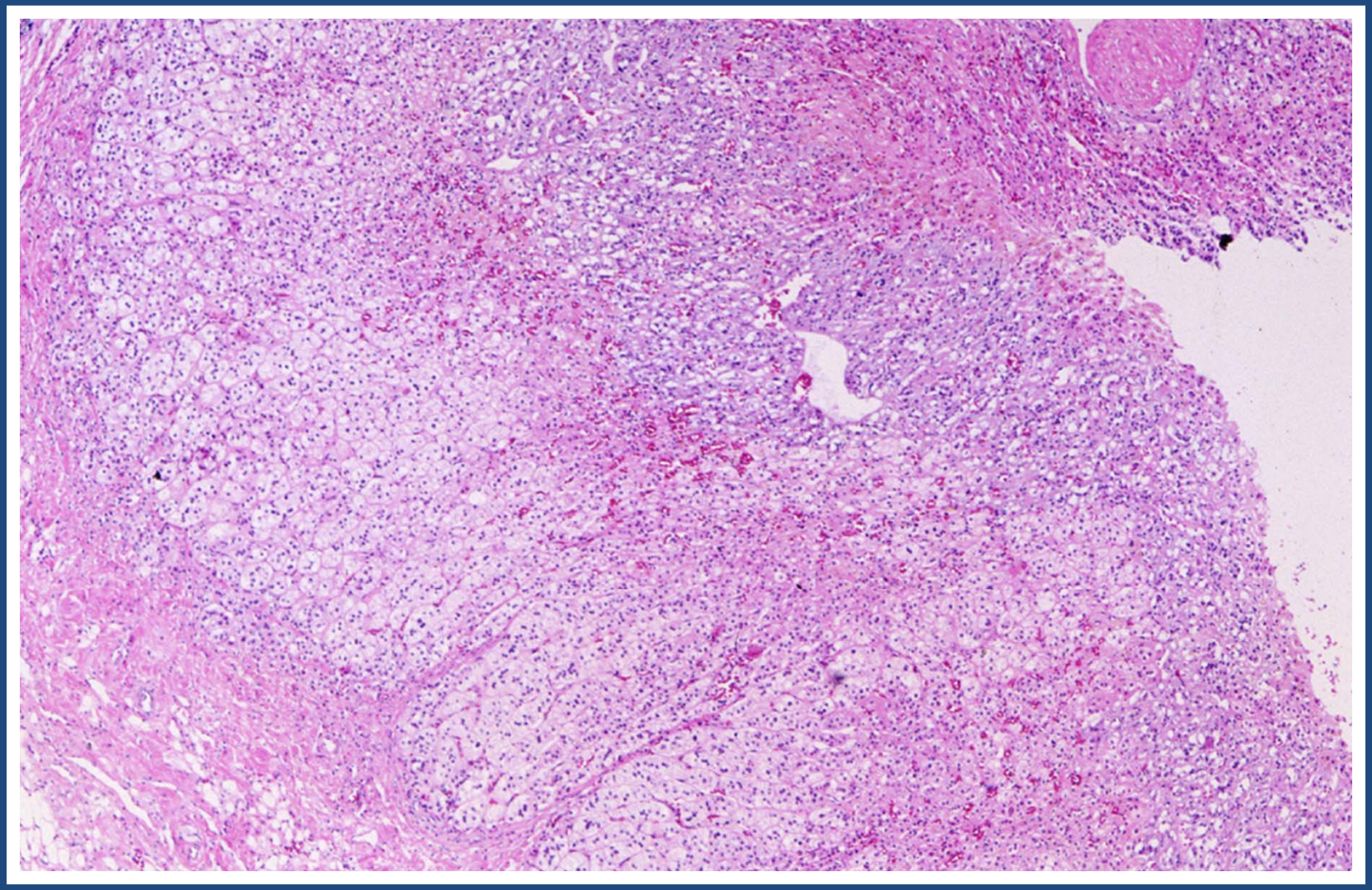


FIGURE 24–53 Pheochromocytoma. The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma-shaped residual adrenal is seen below.

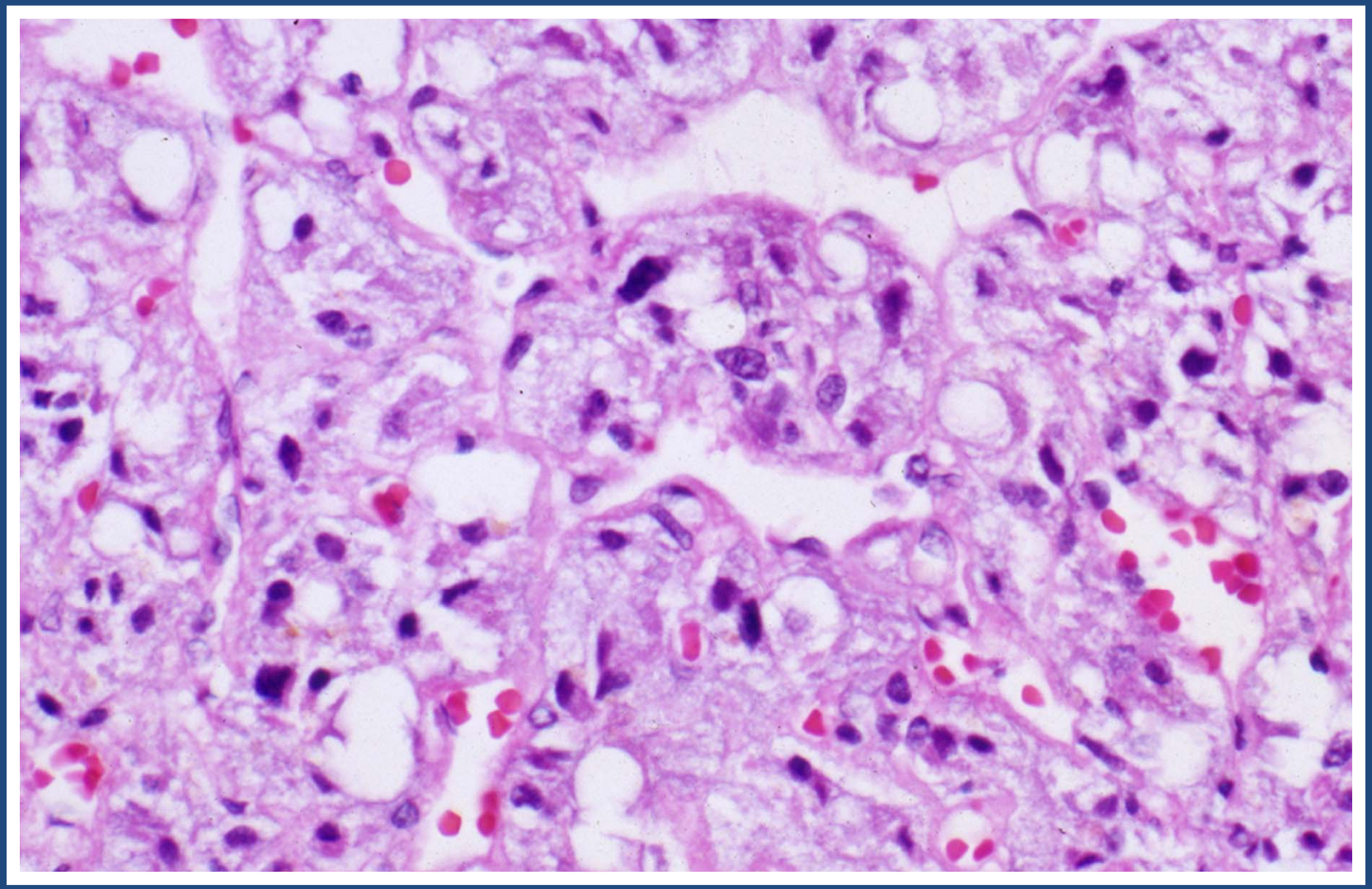
(Courtesy of Dr. Jerrold R. Turner, Department of Pathology, University of Chicago Hospitals, Chicago, IL.)

- Neoplasms composed of *chromaffin* cells
- Release cathecolamines
- Surgically correctable HTN
- Rule of "10s"
- 10% are extra-adrenal (paragangliomas), bilateral, malignant and not associated with HTN
- 25%→ germline SDHB mutation
- Dx: Urinary free catecholamines, vanillylmandelic acid, metanephrines

10% each

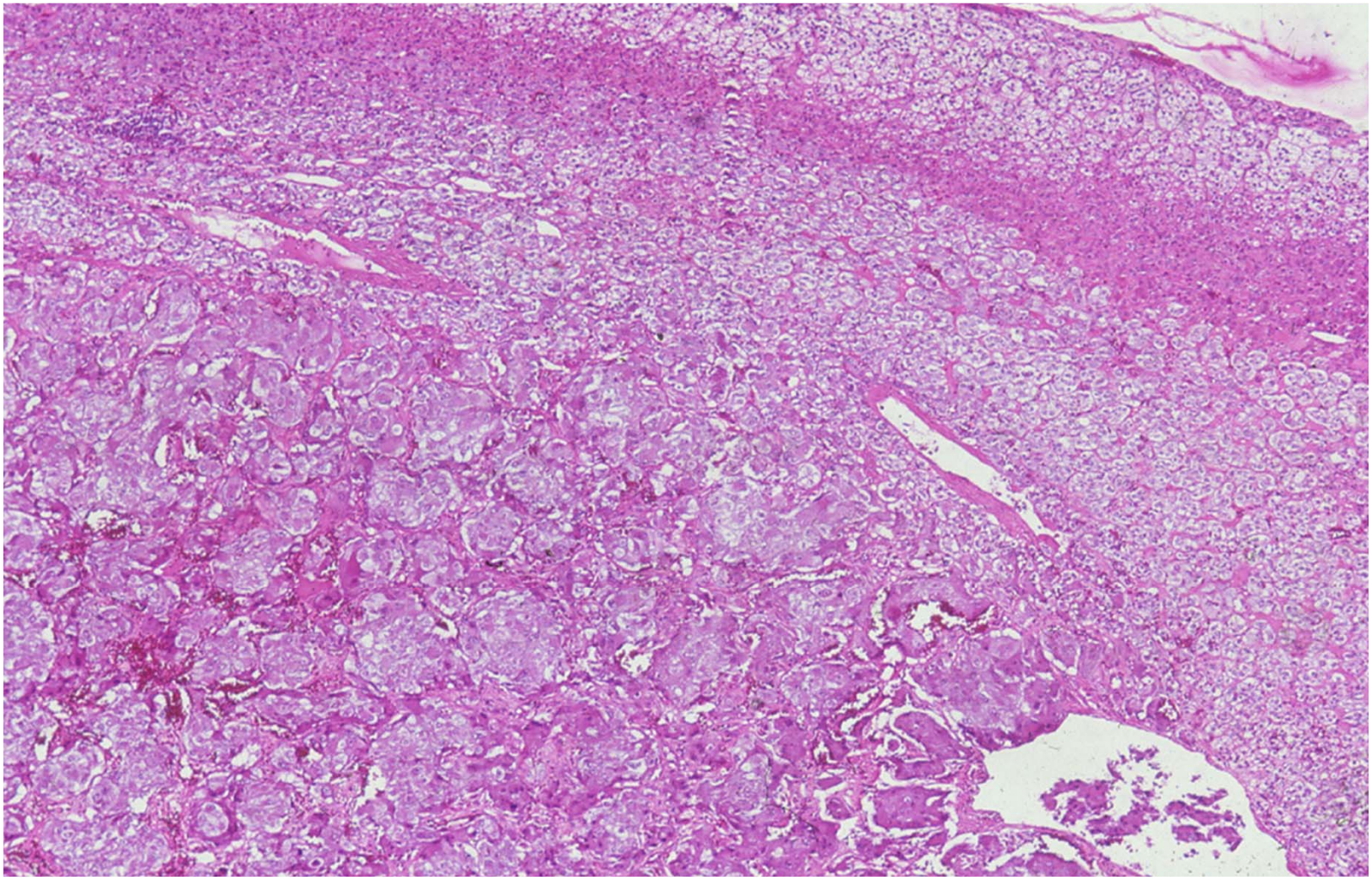


Normal Adrenal

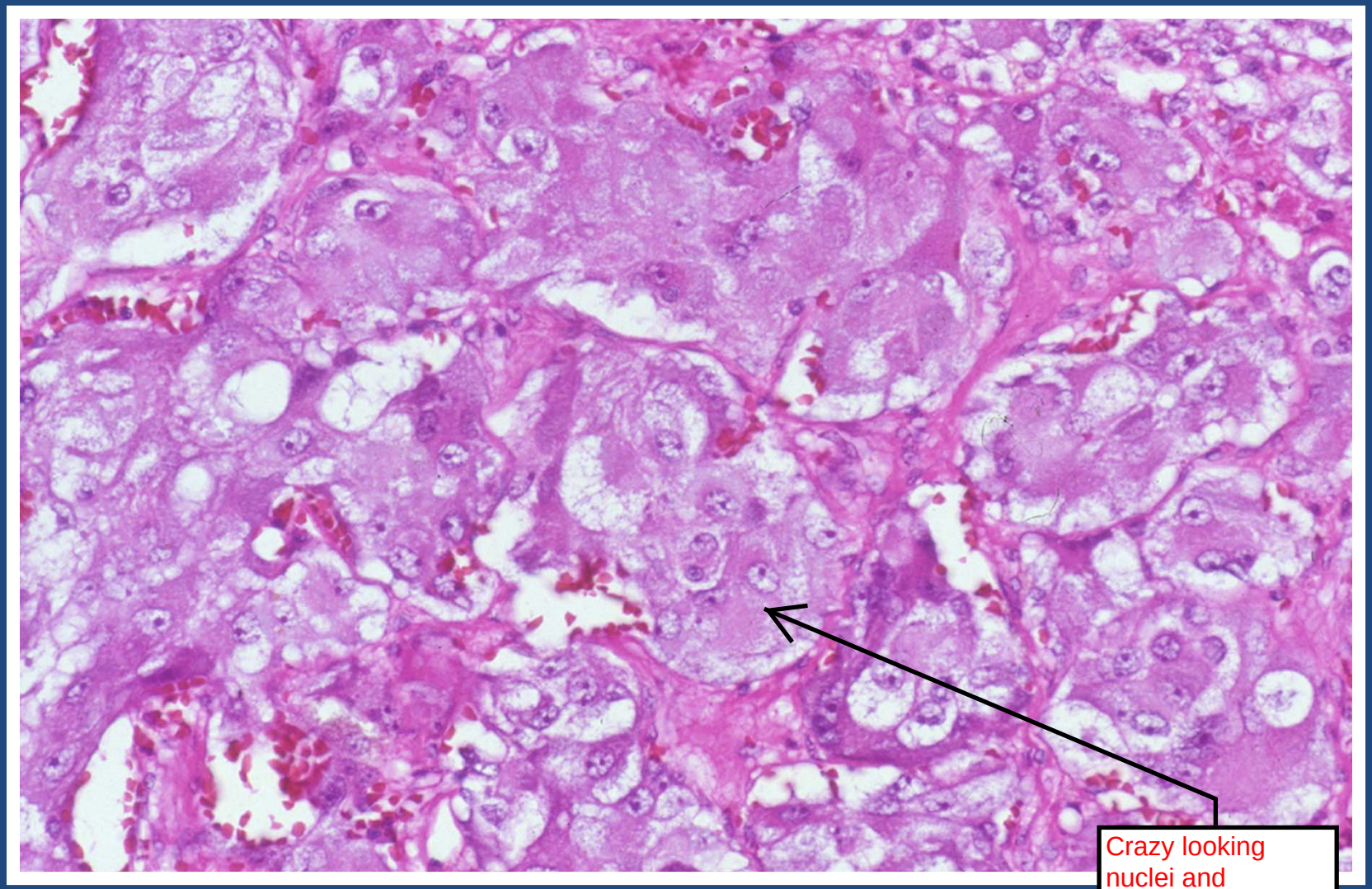


Normal medullary cells. Note vascularity and trabecular arrangement of cells.

On low power, you can tell that in pheochromocytoma, the slide looks more eosinophilic than the normal medulla shown two slides ago.



Adrenal medulla with pheochromocytoma



Pheochromocytoma. Bizarre cells

Multiple Endocrine Neoplasia syndromes (MEN syndromes)

- Genetically inherited disorders with associated proliferations (hyperplasias, adenomas, carcinomas)
- MEN 1 (Wermer syndrome) or "3Ps"
- Rare; germline mutation of MEN1 TSG (menin)
- Primary hyperparathyroidism (hyperplasia or adenoma)
- Endocrine neoplasm of pancreas
- Pituitary adenomas (prolactinoma)

Pituitary: adenomas
Parathyroid: primary hyperthyroidism
Pancreas: Islet cell tumors

islet cell tumors

Menin is a tumor suppressor gene product of MEN1. Thus, loss-of-function mutation of this gene would predispose one to cancer.

hyperplasia or adenoma

- MEN 2
- MEN 2A (Sipple syndrome)
- Germline mutation of RET protooncogene
- Pheochromocytoma
- Medullary Carcinoma of thyroid
- Parathyroid hyperplasia
- MEN 2B
- Medullary Carcinoma of thryoid
- Pheochromocytoma
- Mucosal neuromas or ganglioneuromas
- Marfanoid habitus

shared; then remember what is different to differentiate between MEN2A and MEN2B