Волгоградский государственный медицинский университет

Кафедра патологической анатомии

LECTURE. Diseases of endocrine system.

Endocrine Pathology

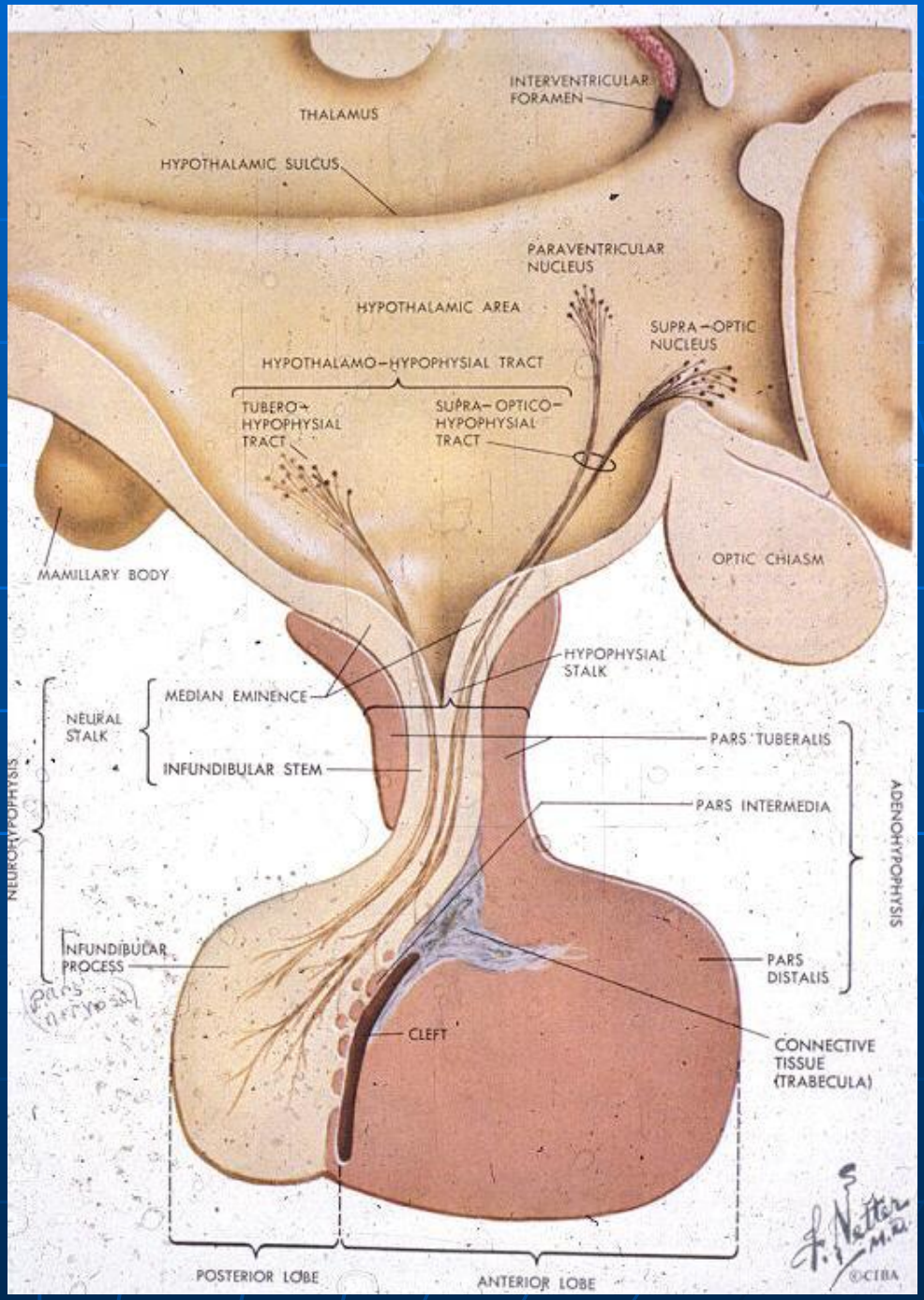
- Cell signaling system
- Surface receptors
  - cAMP and tyrosine kinase system
- Cytoplasmic receptors
  - Penetrate cell membrane
  - Gene activation -> transcription -> translation
- Intranuclear receptors
  - Gene activation -> transcription -> translation

Endocrine Pathology

- Too much hormone activity
- Too little hormone activity
  - Autoimmune destruction
  - Inflammatory destruction
  - Tumor or vascular destruction
- Space occupying lesions (tumors)
  - Malignant
  - Benign

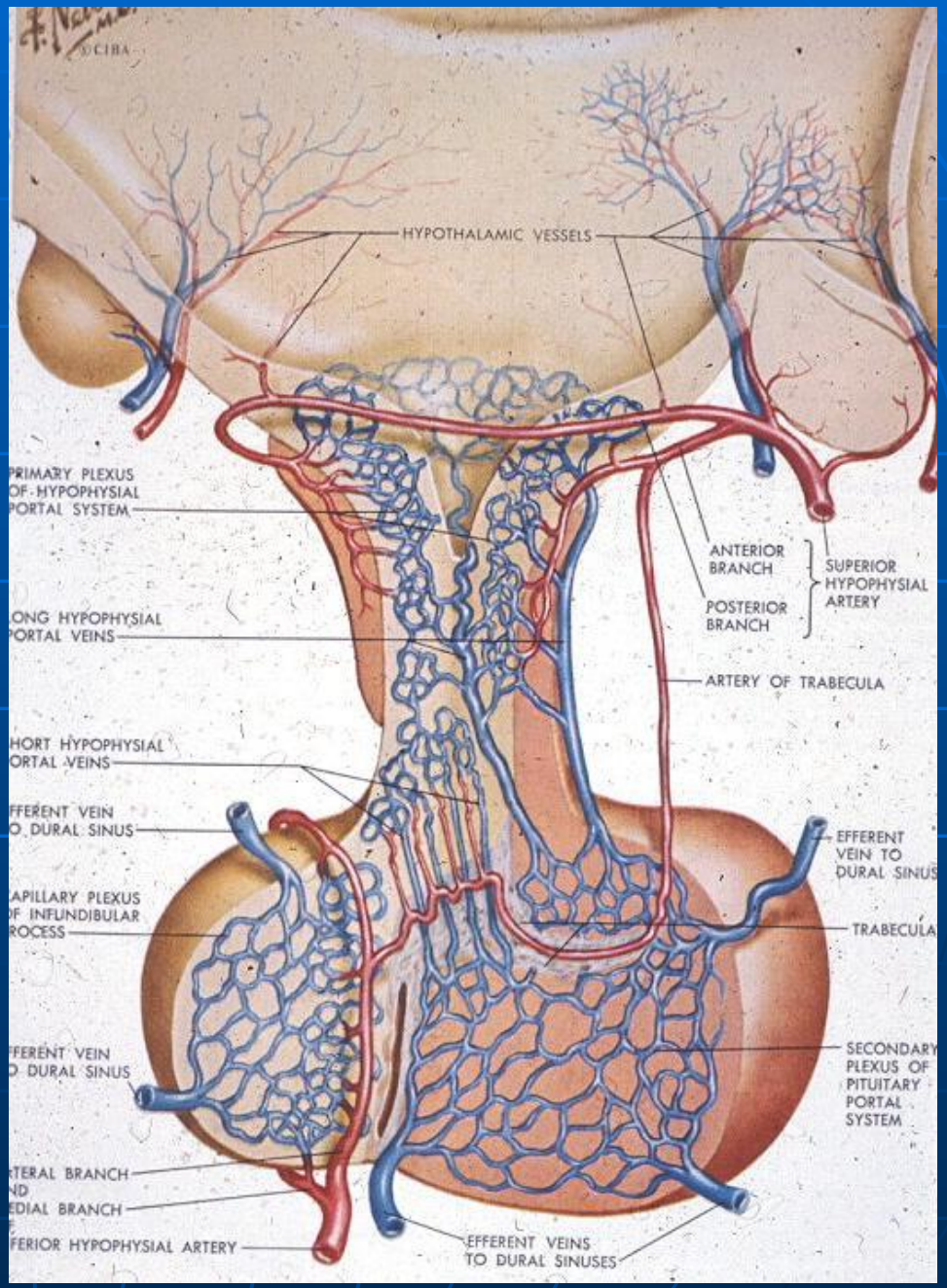
The Basics

- Anterior
  - Comes from GI
  - Controlled by hypothalmus
- Posterior
  - Hormones orginate further up.

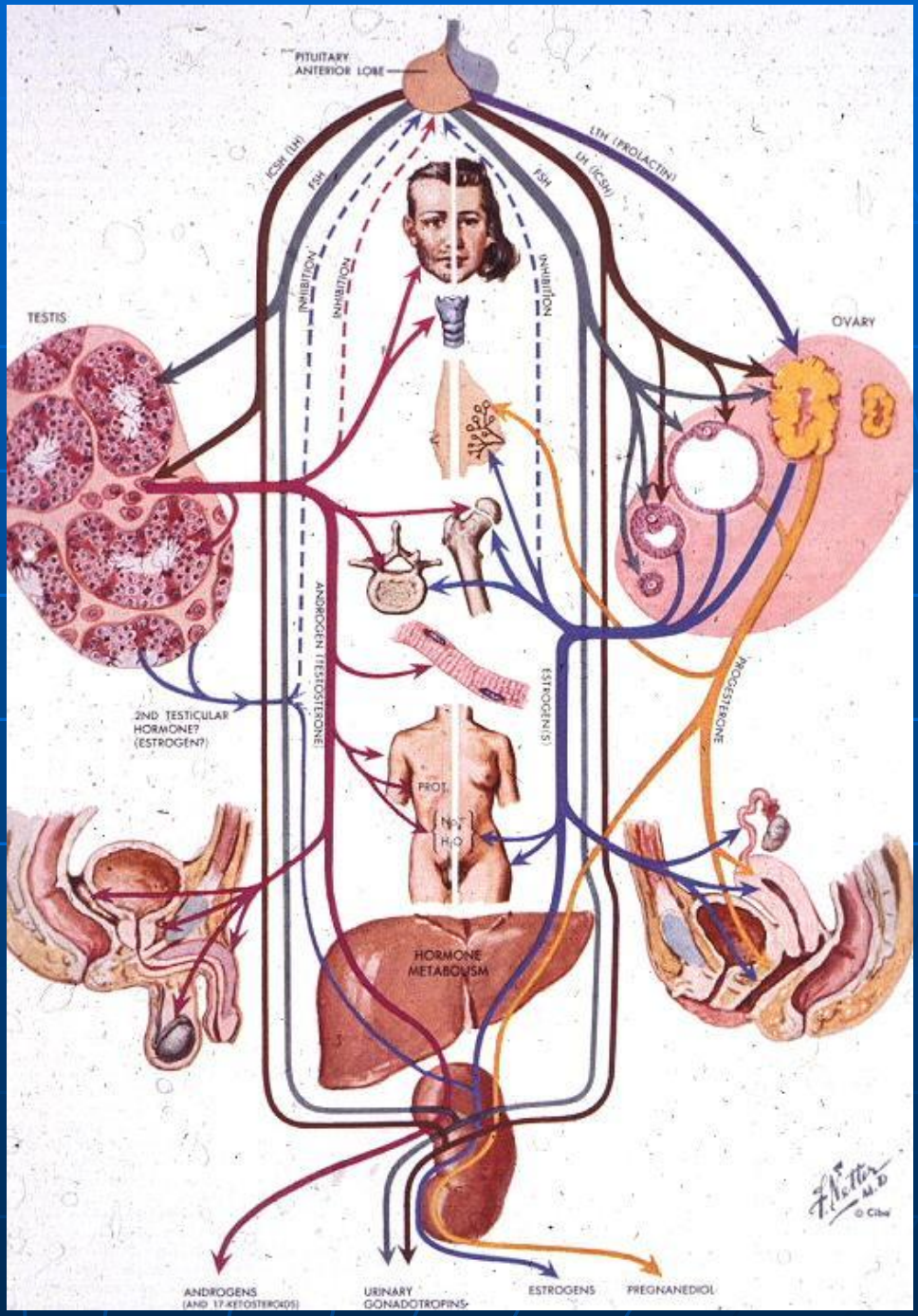


Pituitary Vascular

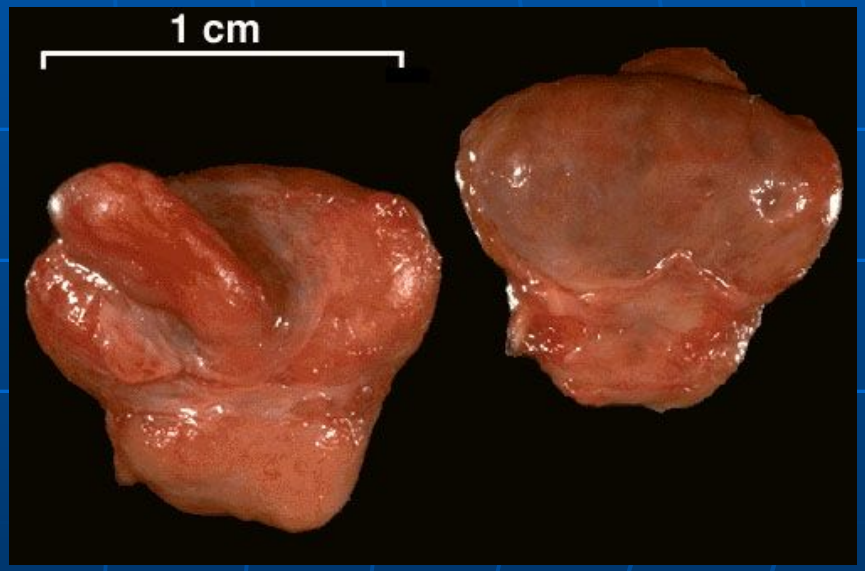
- Signaling proteins are release in hypothalmus.
- Travel by blood to anterior pituitary
- Cause release of many activating hormones
- System of amplification

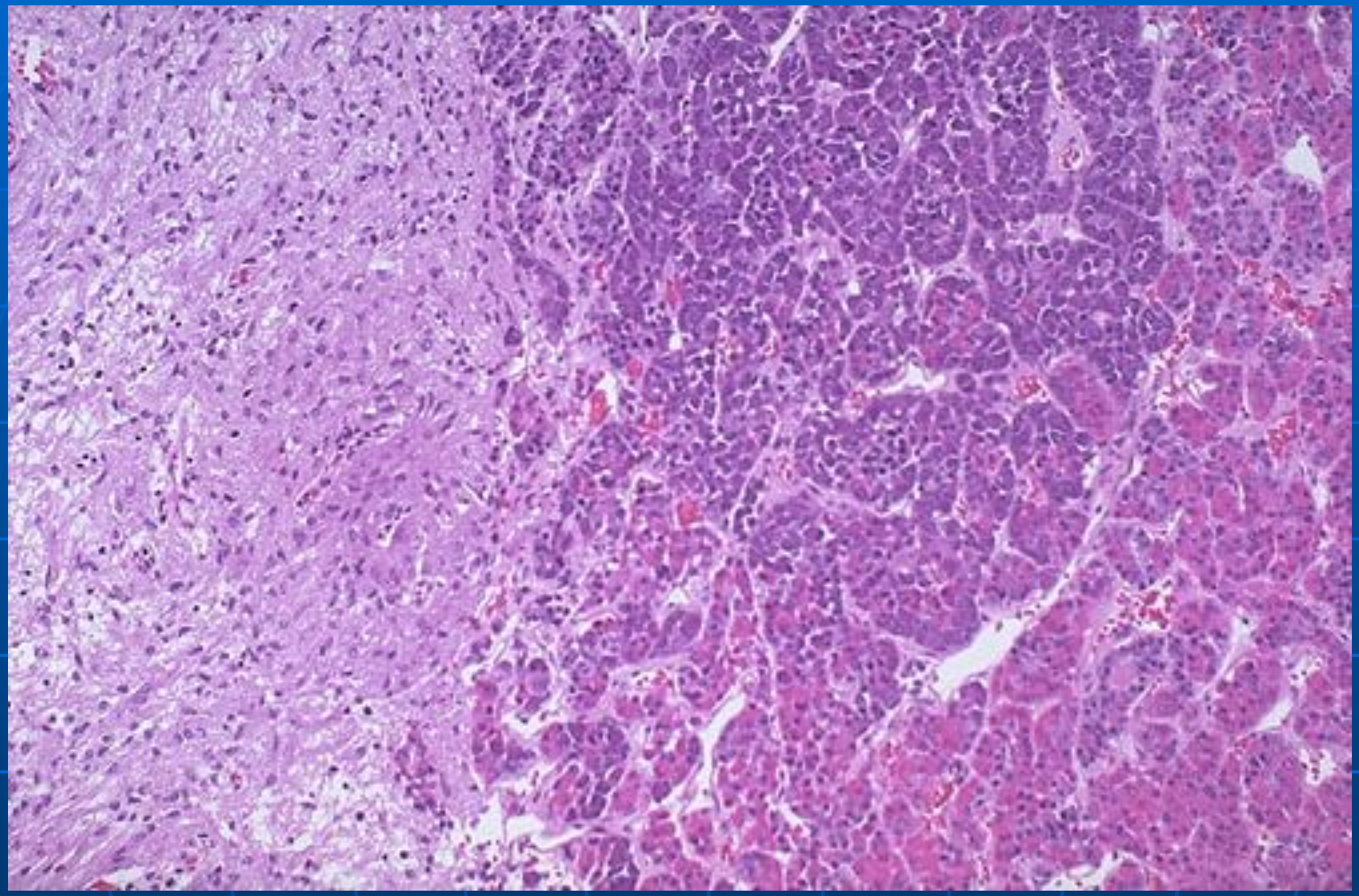


Pituitary Control

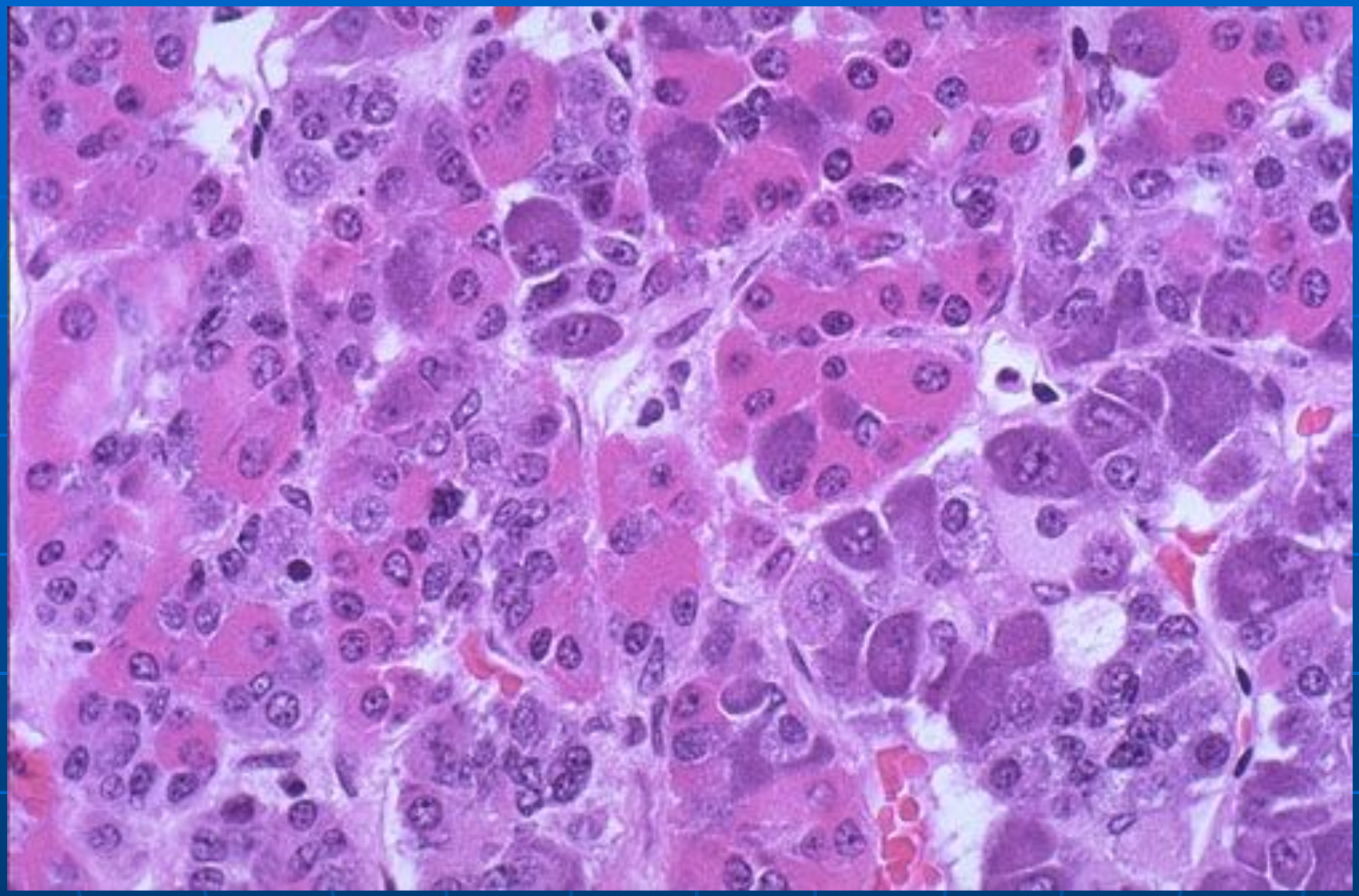


- The normal gross appearance of the pituitary gland removed from the sella turcica is shown here. The larger portion, the anterior pituitary (adenohypophysis), is toward the top. The image at the left shows the superior aspect of the pituitary with the stalk coming from the hypothalamus entering it. The inferior aspect of the pituitary is shown at the right. The posterior pituitary (neurohypophysis) is the smaller portion at the bottom.

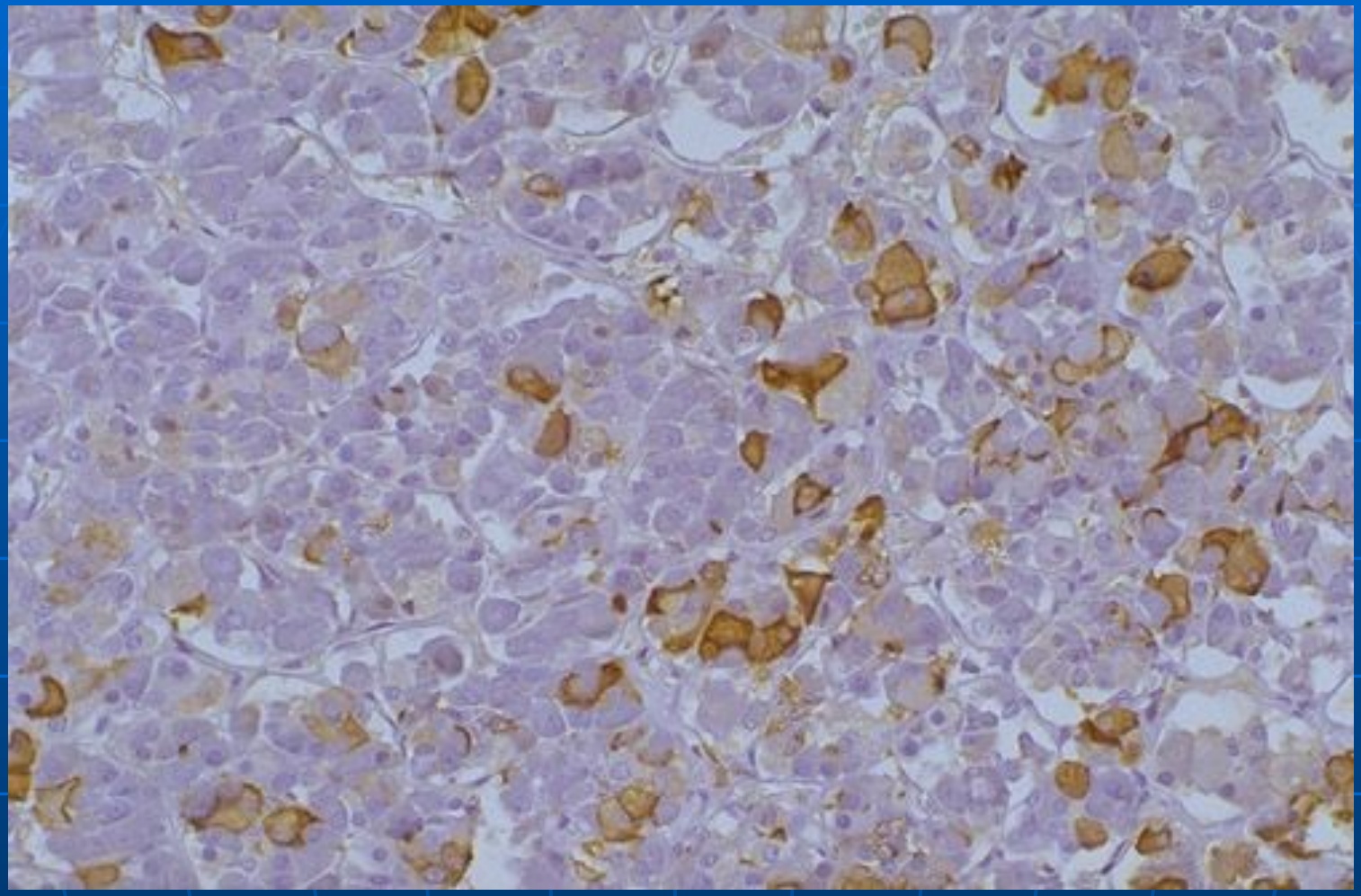




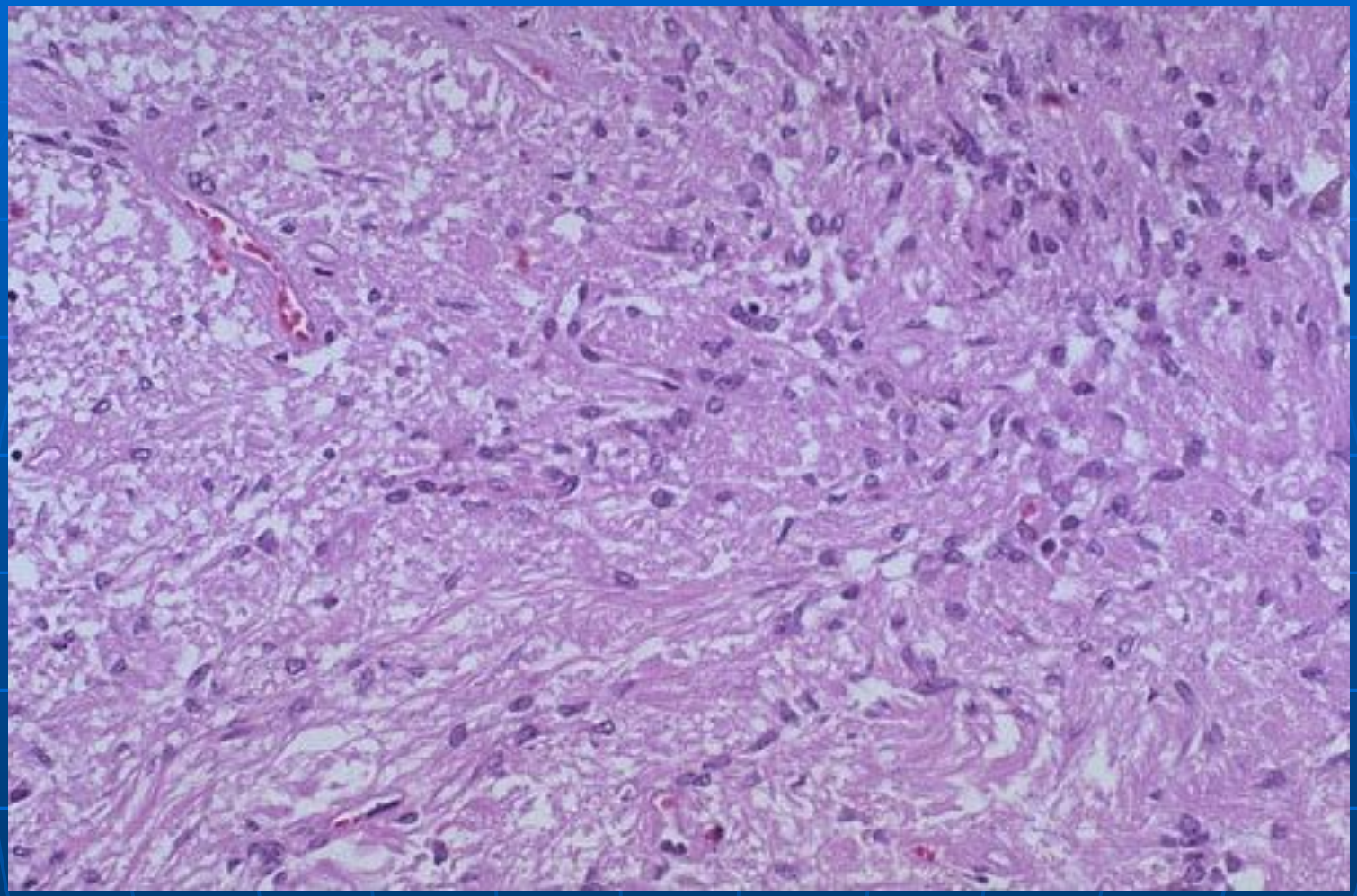
- The normal microscopic appearance of the pituitary gland is shown here. The adenohypophysis is at the right and the neurohypophysis is at the left.



- The normal microscopic appearance of the adenohypophysis is shown here. The adenohypophysis contains three major cell types: acidophils, basophils, and chromophobes. The staining is variable, and to properly identify specific hormone secretion, immunohistochemical staining is necessary. A simplistic classification is as follows:
  - The pink acidophils secrete growth hormone (GH) and prolactin (PRL)
  - The dark purple basophils secrete corticotrophin (ACTH), thyroid stimulating hormone (TSH), and gonadotrophins follicle stimulating hormone-luteinizing hormone (FSH and LH)
  - The pale staining chromophobes have few cytoplasmic granules, but may have secretory activity.



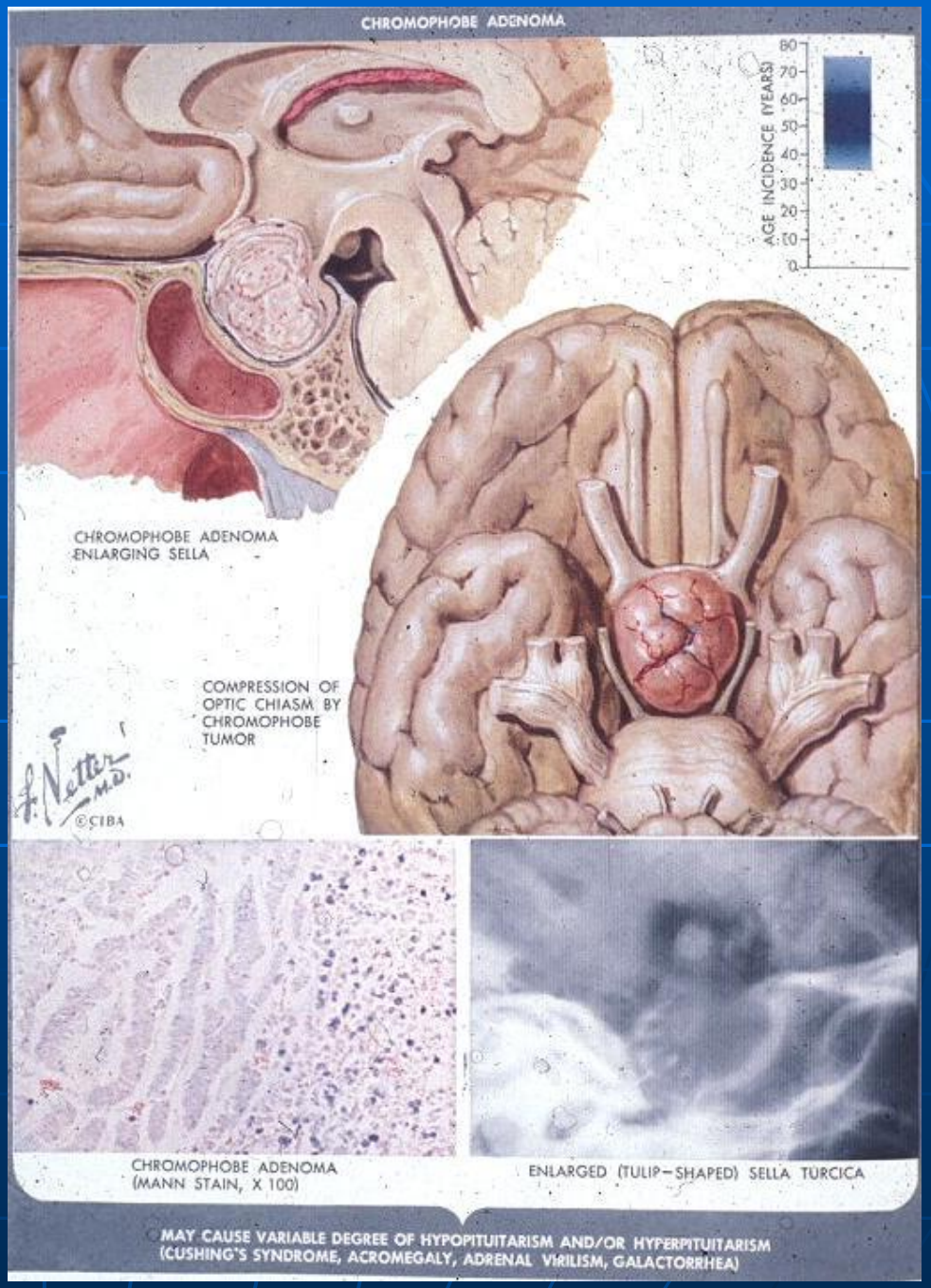
- This immunoperoxidase stain with antibody to prolactin identifies the specific acidophils in the anterior pituitary that secrete prolactin. Note that they are scattered about.



- The neurohypophysis shown here resembles neural tissue, with glial cells, nerve fibers, nerve endings, and intra-axonal neurosecretory granules. The hormones vasopressin (antidiuretic hormone, or ADH) and oxytocin made in the hypothalamus (supraoptic and paraventricular nuclei) are transported into the intra-axonal neurosecretory granules where they are released.

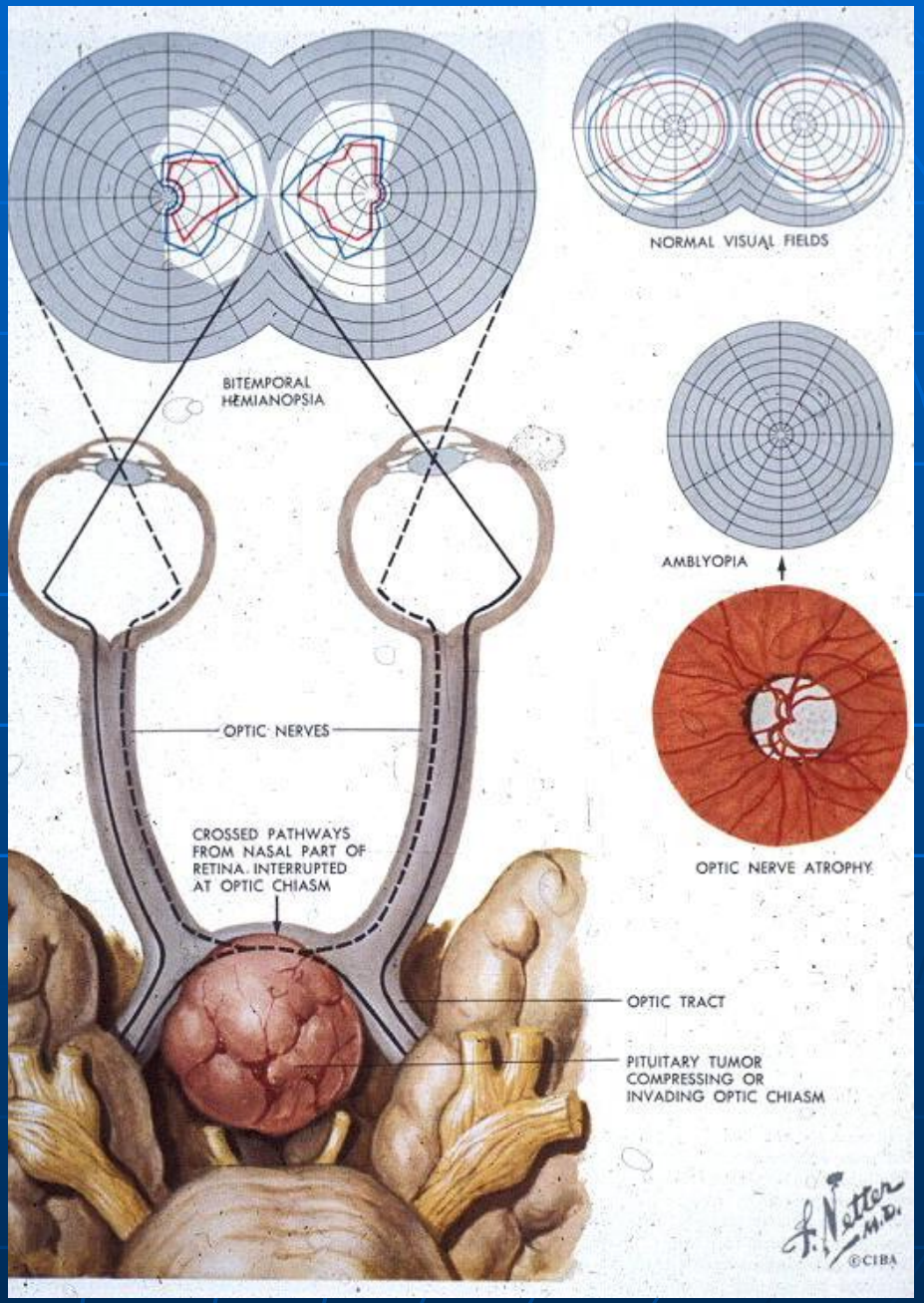
Space Occupying Lesions

- Tumors
- Embryonic rests
- Squeeze gland out of existence.
  - Generalized failure
- Visual field changes



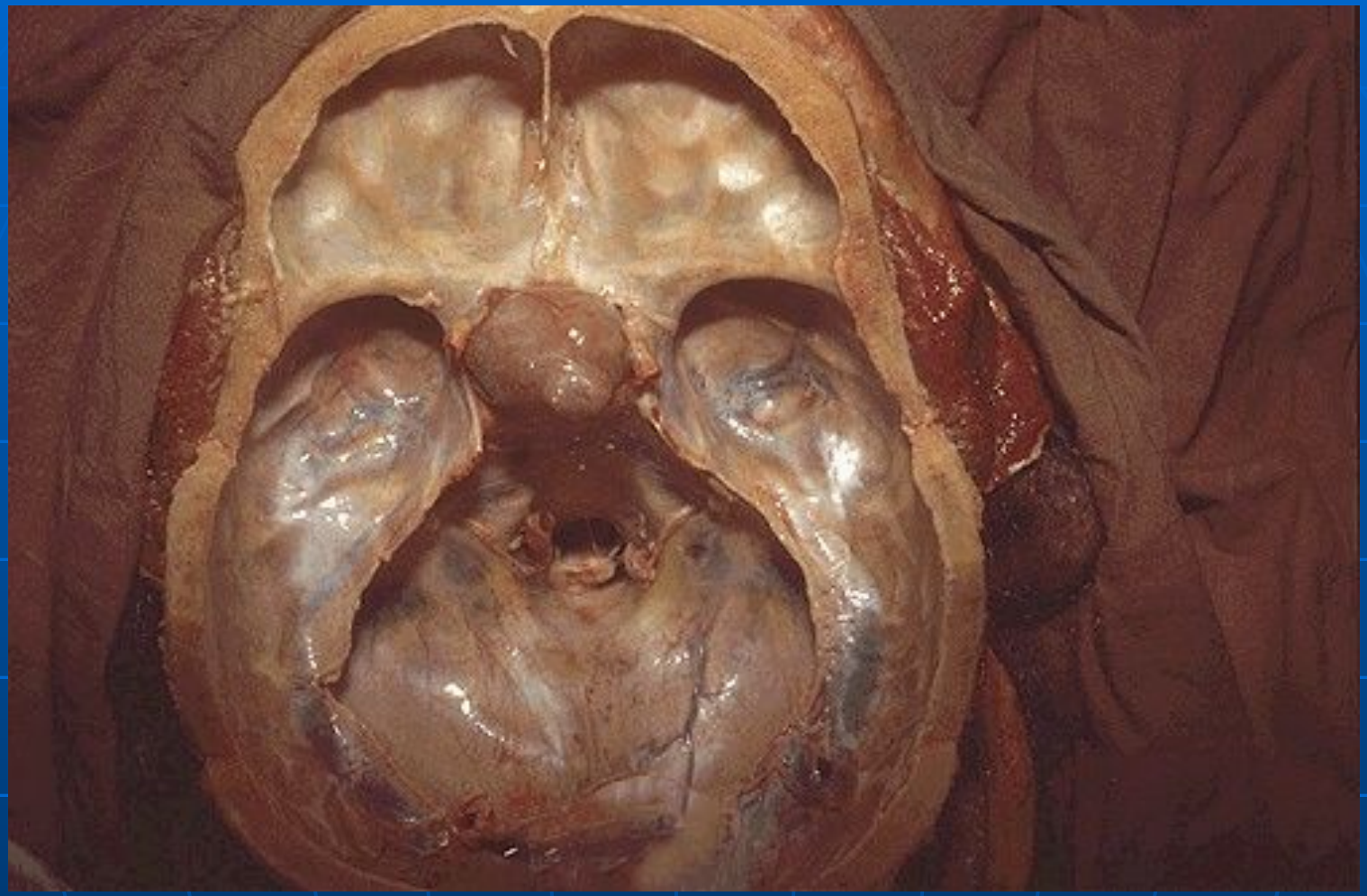
Visual Fields

- Loss of temporal fields.
  - Nasal retina
- Damage to decusating optic nerve fibers

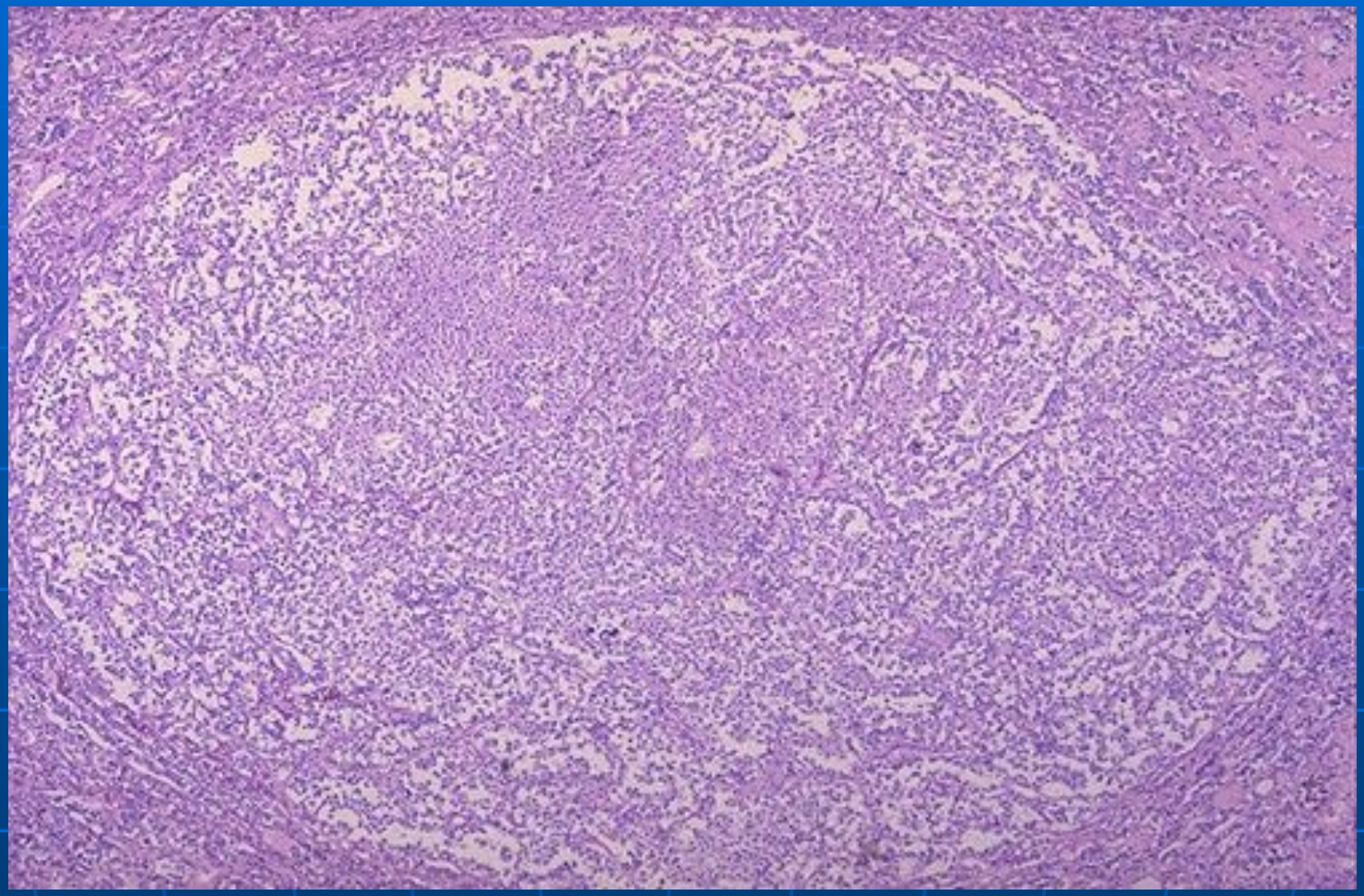


Pituitary Adenomas

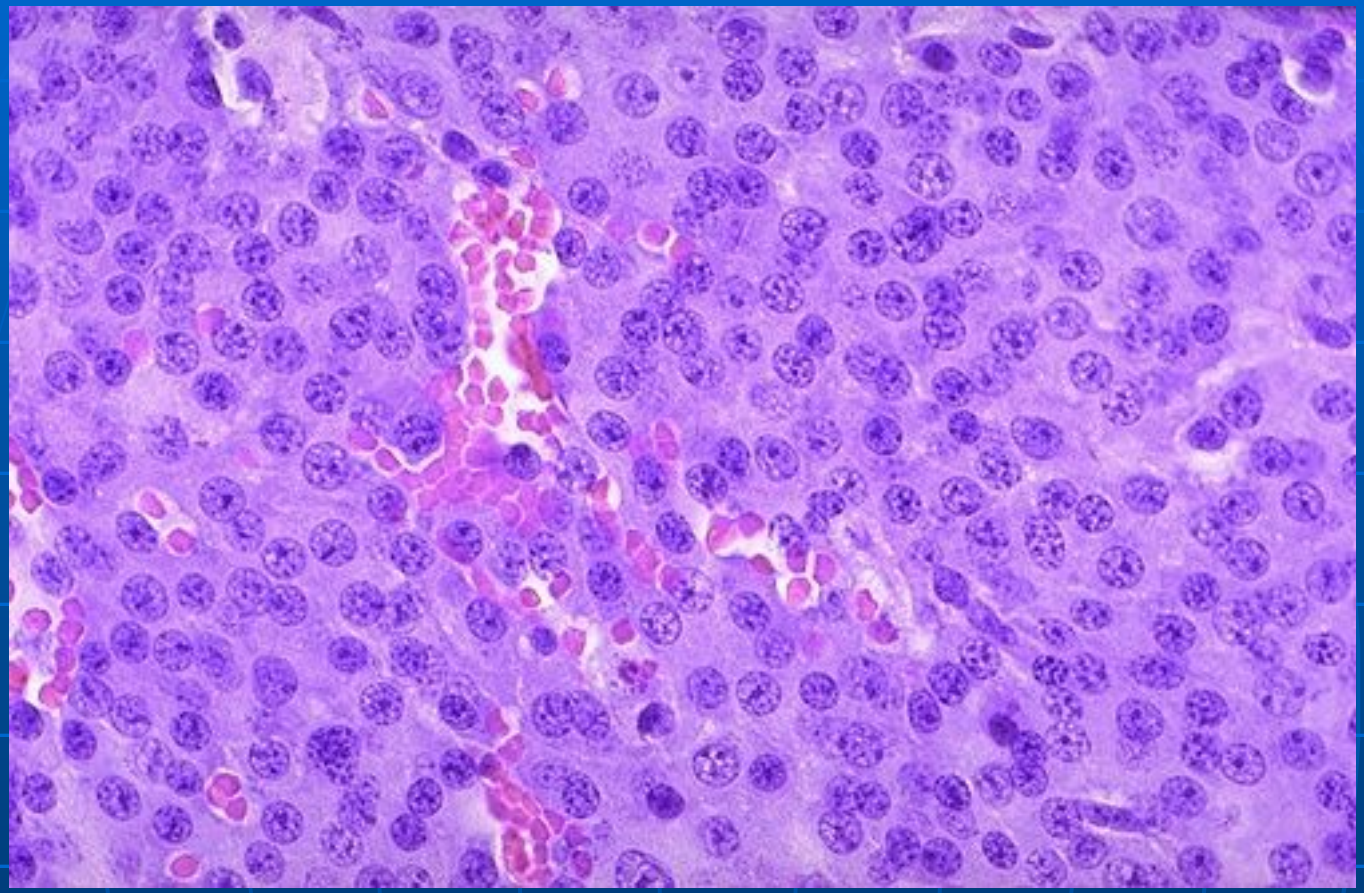
- Rare
- Make nothing or
- Prolactin
- ACTH, GH,TSH are very rare
- More often end up with pituitary failure.
  - Squeeze the daylights out of the gland.



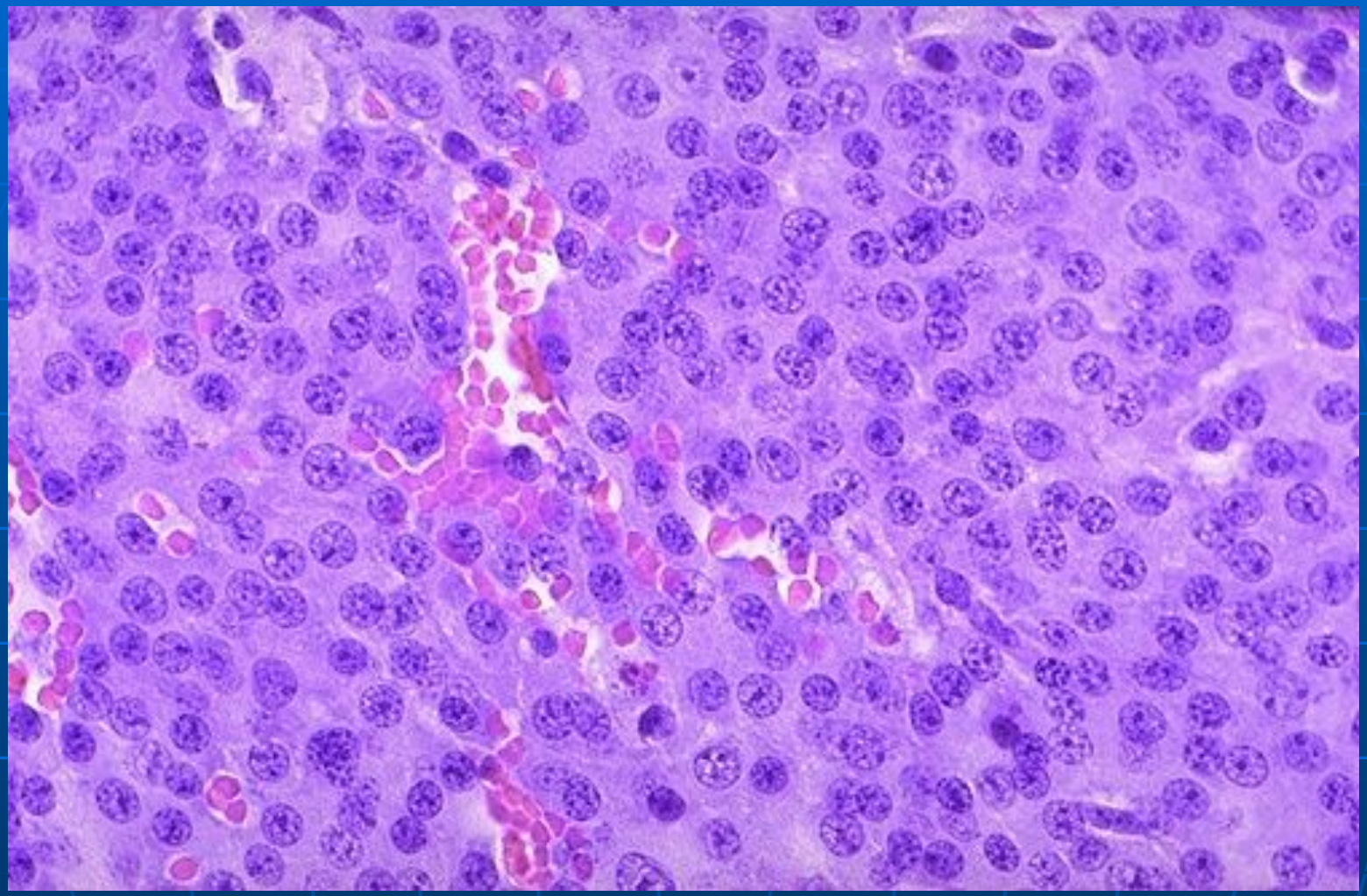
- The circumscribed mass lesion present here in the sella turcica is a pituitary adenoma. Though pituitary adenomas are benign, they can produce problems either from a mass effect (usually visual problems from pressing on the optic chiasm and/or headaches) or from production of hormones such as prolactin or ACTH.



- This is a microadenoma of the anterior pituitary. Such microadenomas may appear in 1 to 5% of adults. These microadenomas rarely have a significant hormonal output that leads to clinical disease.



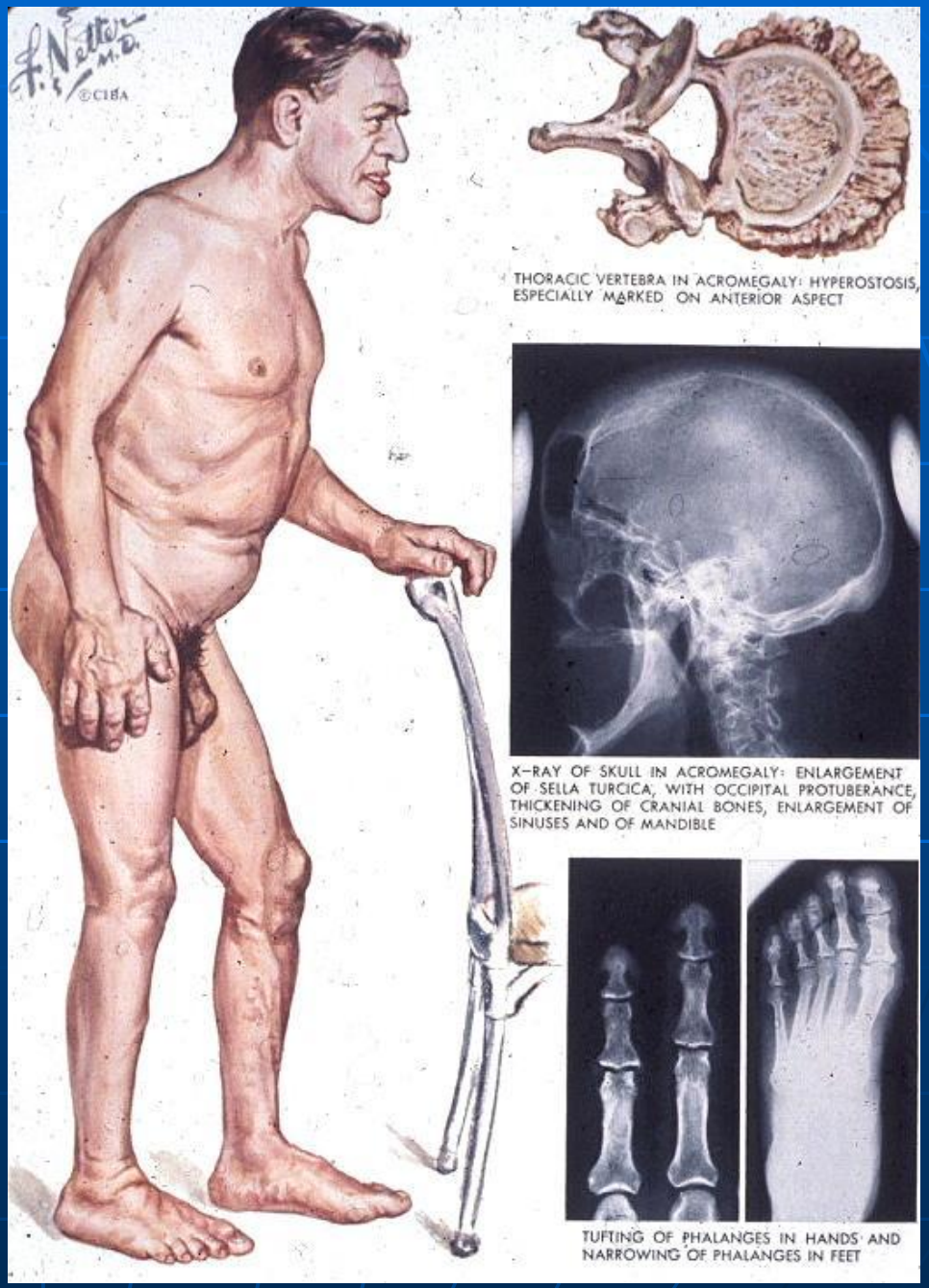
- Here is a high power microscopic view of an adenohypophyseal adenoma. Endocrine neoplasms are composed of small round cells with small round nuclei and pink to blue cytoplasm. The cells may be arranged in nests or cords and endocrine tumors also have prominent vascularity.



- The microscopic appearance of the pituitary adenoma is shown here. Note the monotonous appearance of these small round cells.

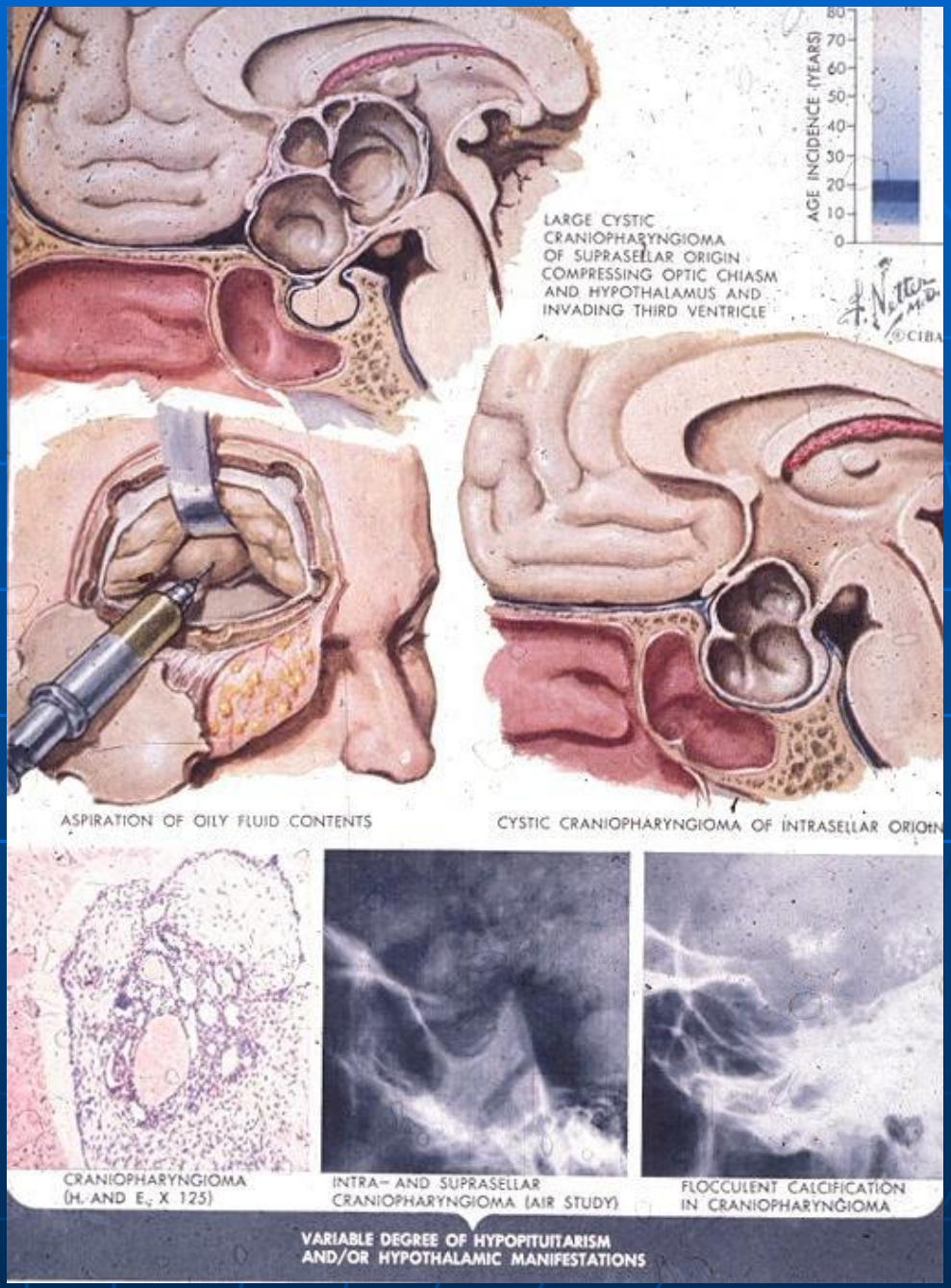
Acromegaly

- Growth hormone excess after closing of epiphyses.
- Periosteal bone growth.
- Diabetes
- Prognathism



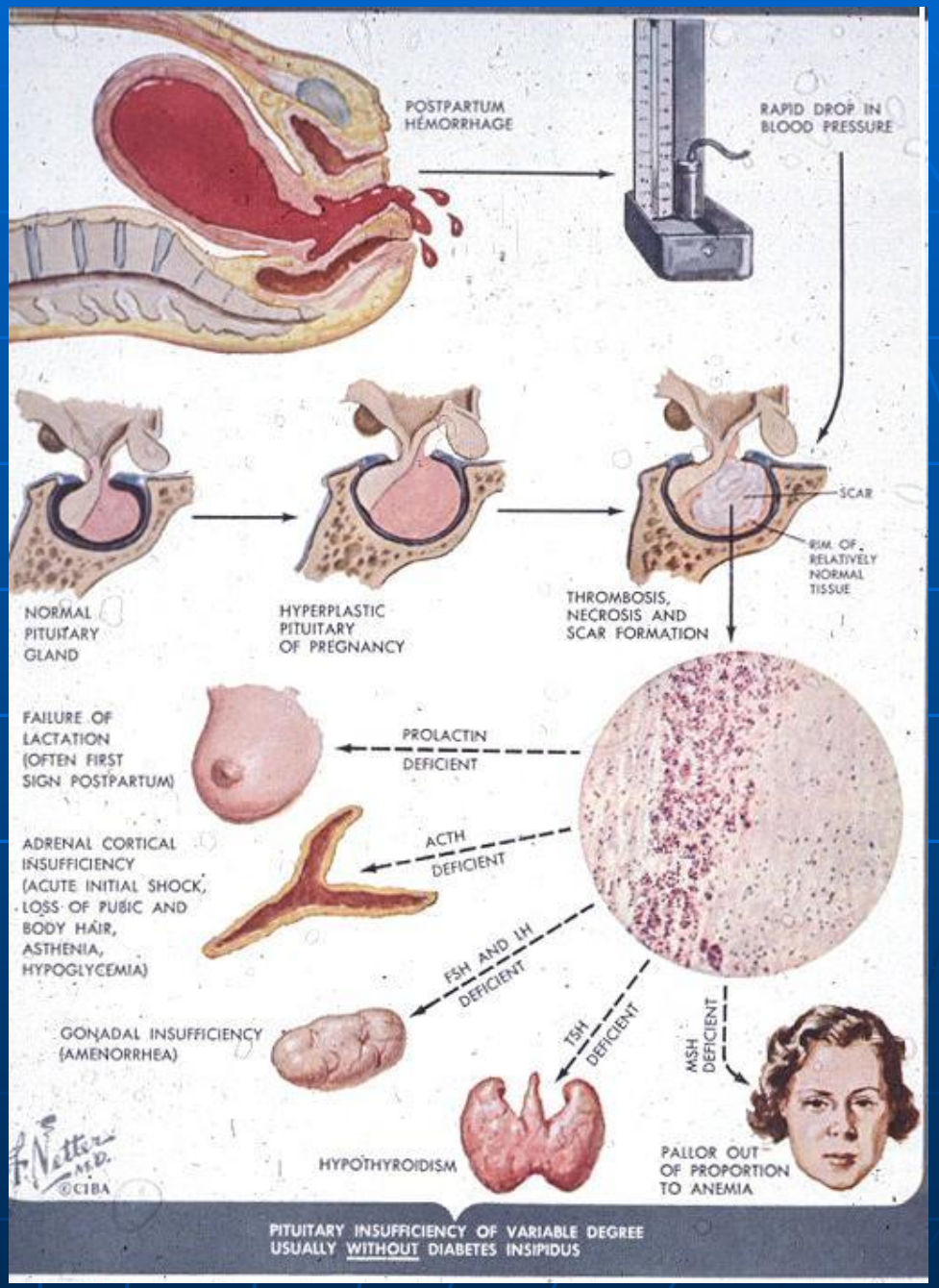
Hypopituitarism

- Destruction of gland.
- Ischemia
- ‘Benign’ adenoma destroying gland
- Craniopharyngioma
  - Rathke’s pouch remenant
  - Benign cyst, but really in the wrong place.

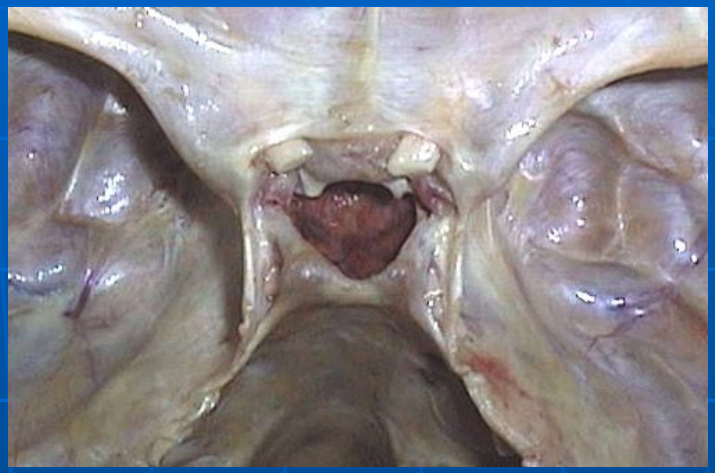


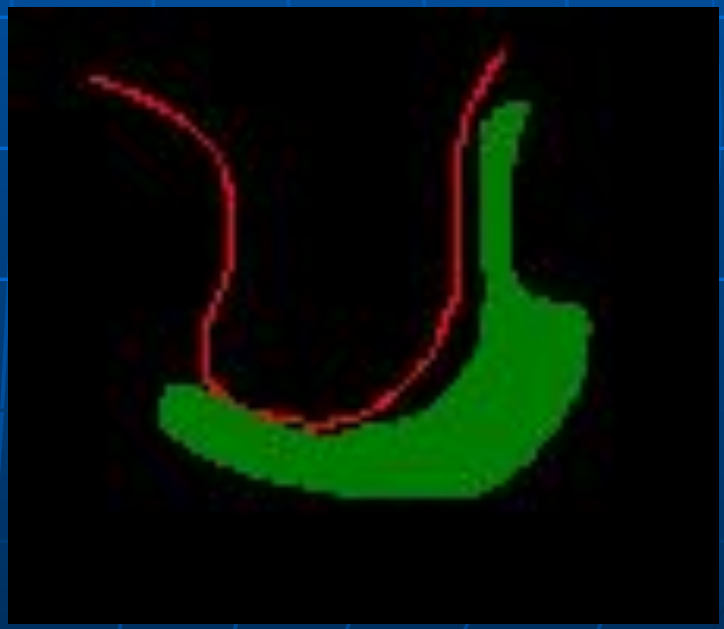
Ischemic Destruction

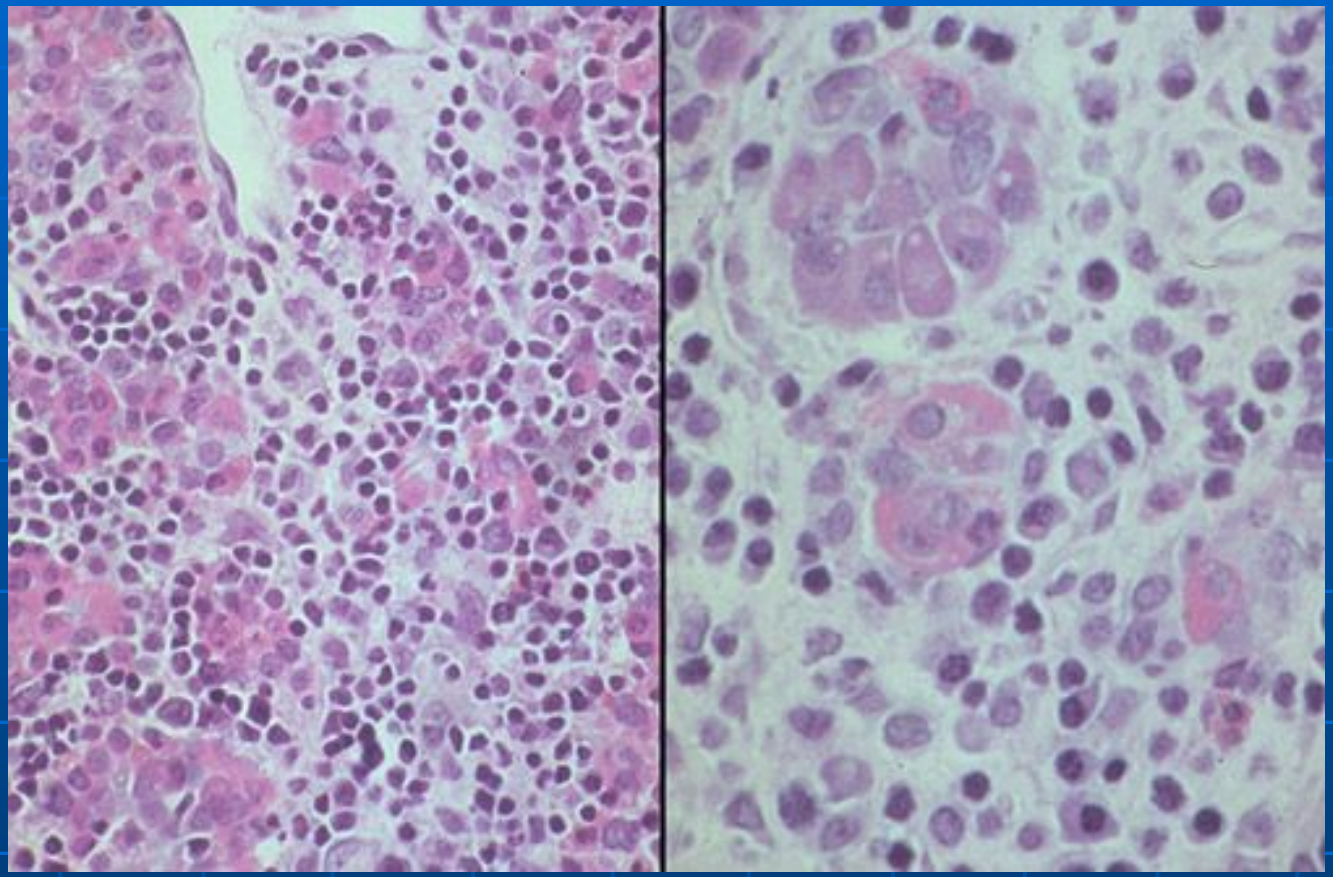
- Shehan's syndrome
- Post delivery problem
- No lactation
- In time general failure of 'downstream' systems
  - Thyroid
  - Adrenal cortex
  - Ovulation



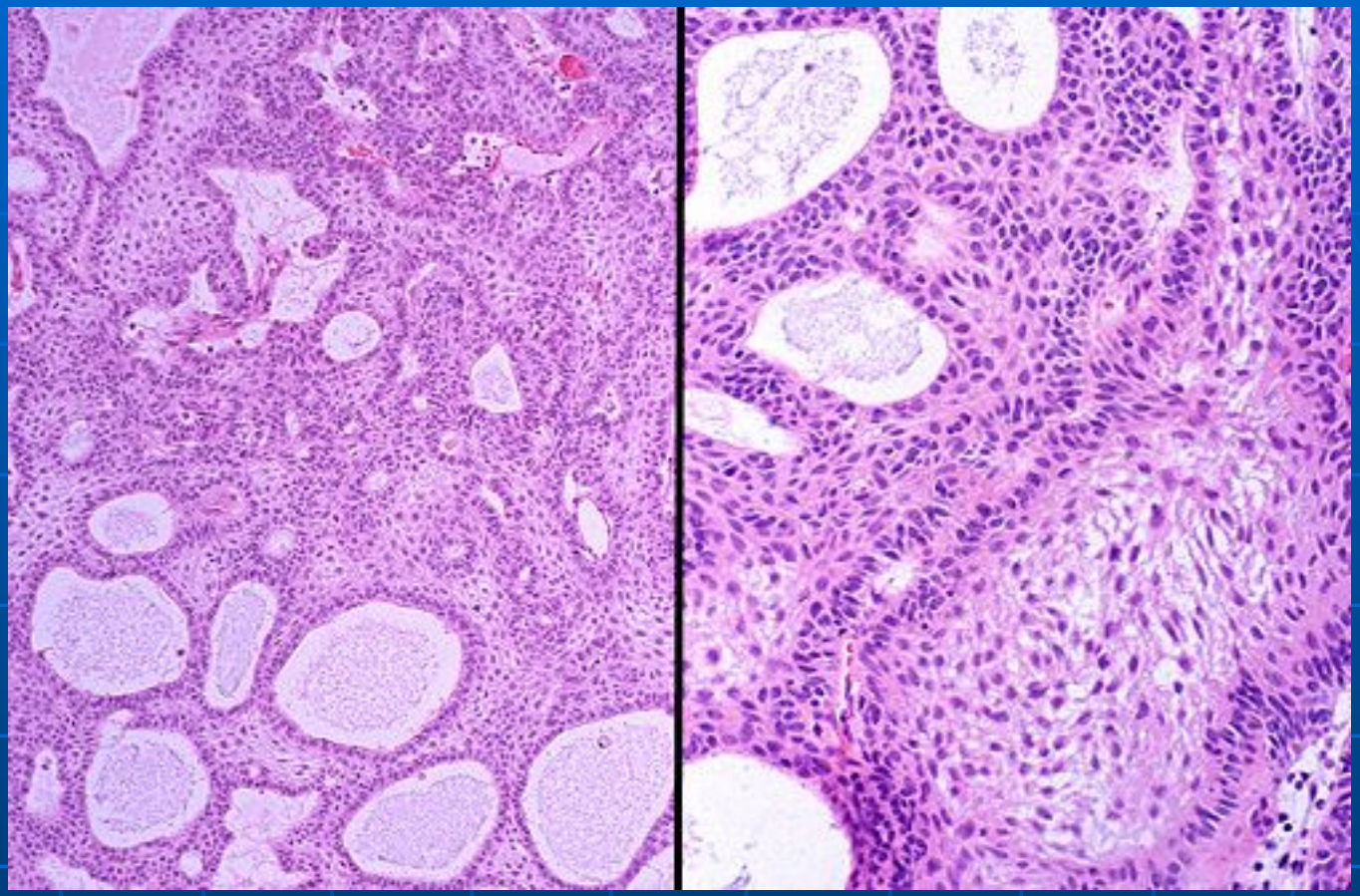
- The sella turcica at the base of the skull shown here contains a flattened pituitary at the base, giving the impression of an "empty sella". The diagram indicates how this occurs from herniation of arachnoid (from an arachnoid cyst) into the sella, compressing the pituitary. This may lead to hypopituitarism, if more than 80 or 90% of the adenohypophysis is destroyed. Hyperprolactinemia may ensue from a "stalk section" effect. Postpartum pituitary necrosis (Sheehan's syndrome) can appear similarly.







- These medium and high power microscopic views of the anterior pituitary demonstrate mononuclear inflammatory cell infiltrates with loss of acini and interstitial fibrosis. These are features of lymphocytic hypophysitis, a rare autoimmune disorder but a significant cause for hypopituitarism.



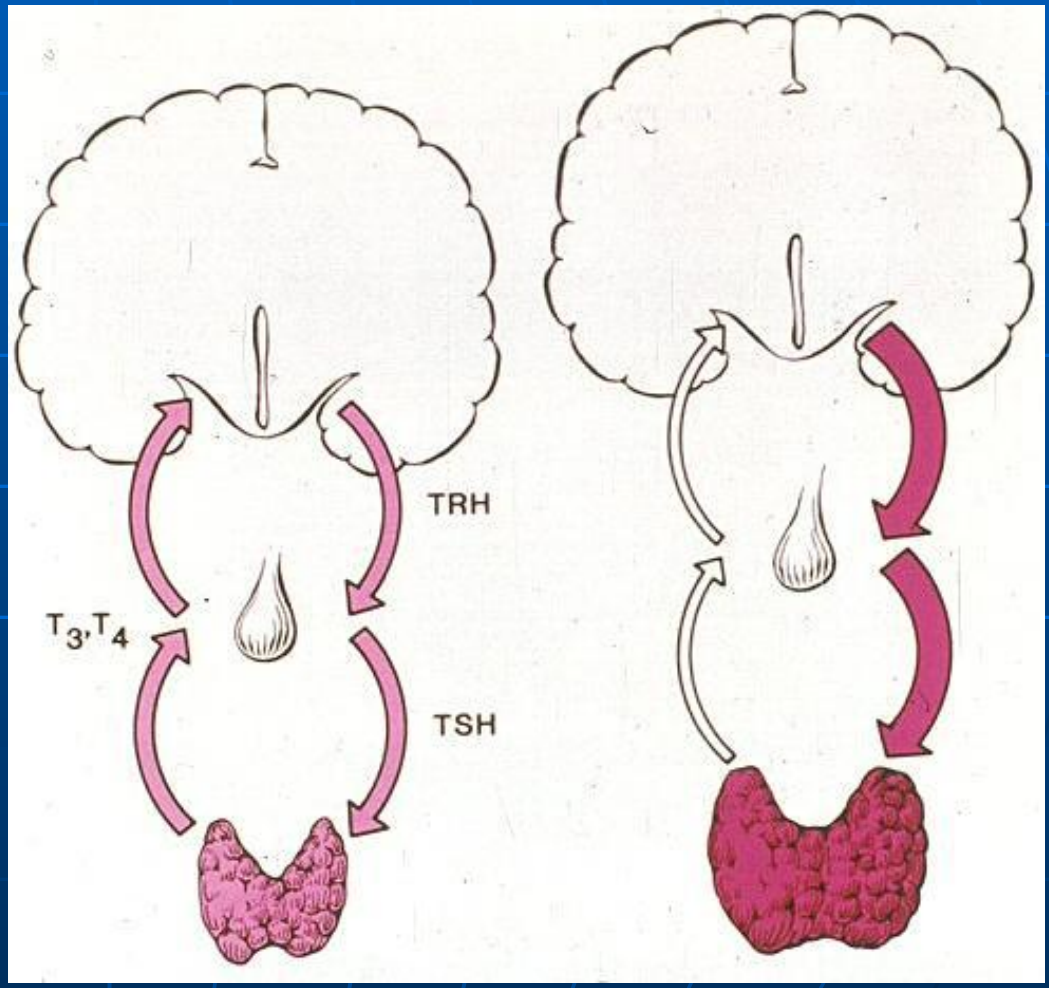
- A craniopharyngioma is seen here at medium and high power. It is derived from remnants of Rathke's pouch and forms an expanding mass arising in the sella turcica that erodes bone and infiltrates into surrounding structures. They are difficult to eradicate, even though they are composed of histologically appearing squamoid and columnar epithelium lining cystic spaces filled with oily fluid.

Posterior Pituitary

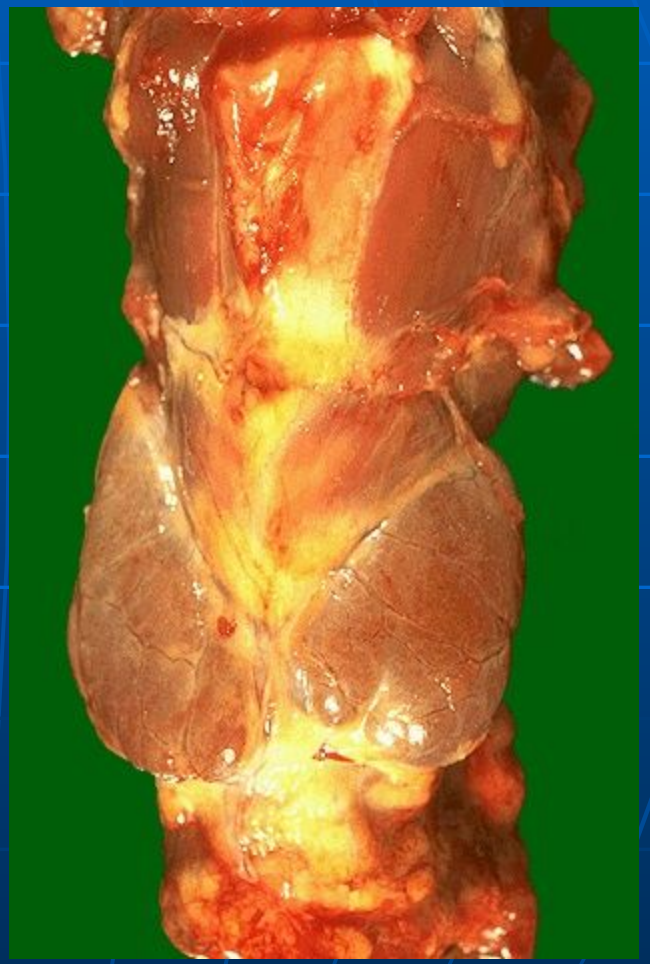
- Loss of ADH
  - Diabetes insipidis
  - Dose not make concentrated urine
  - Large volumes of dilute urine
- Head injuries
- Tumors of periventricular area

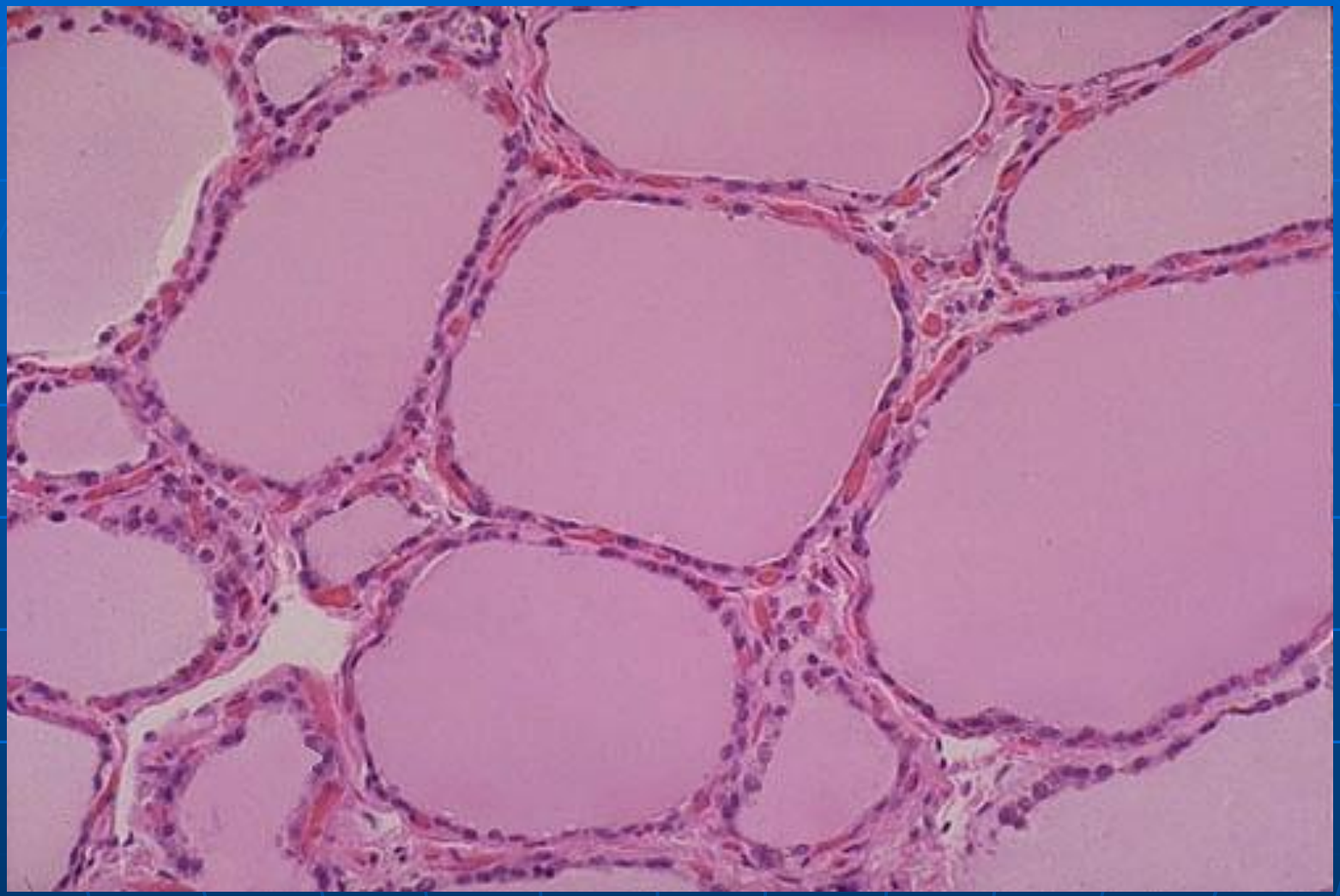
Control of Thyroid Hormone

- Hypothalmus
- Pituitary
- Thyroid
- Tissue level
  - Establishes metabolic rate for the whole organism

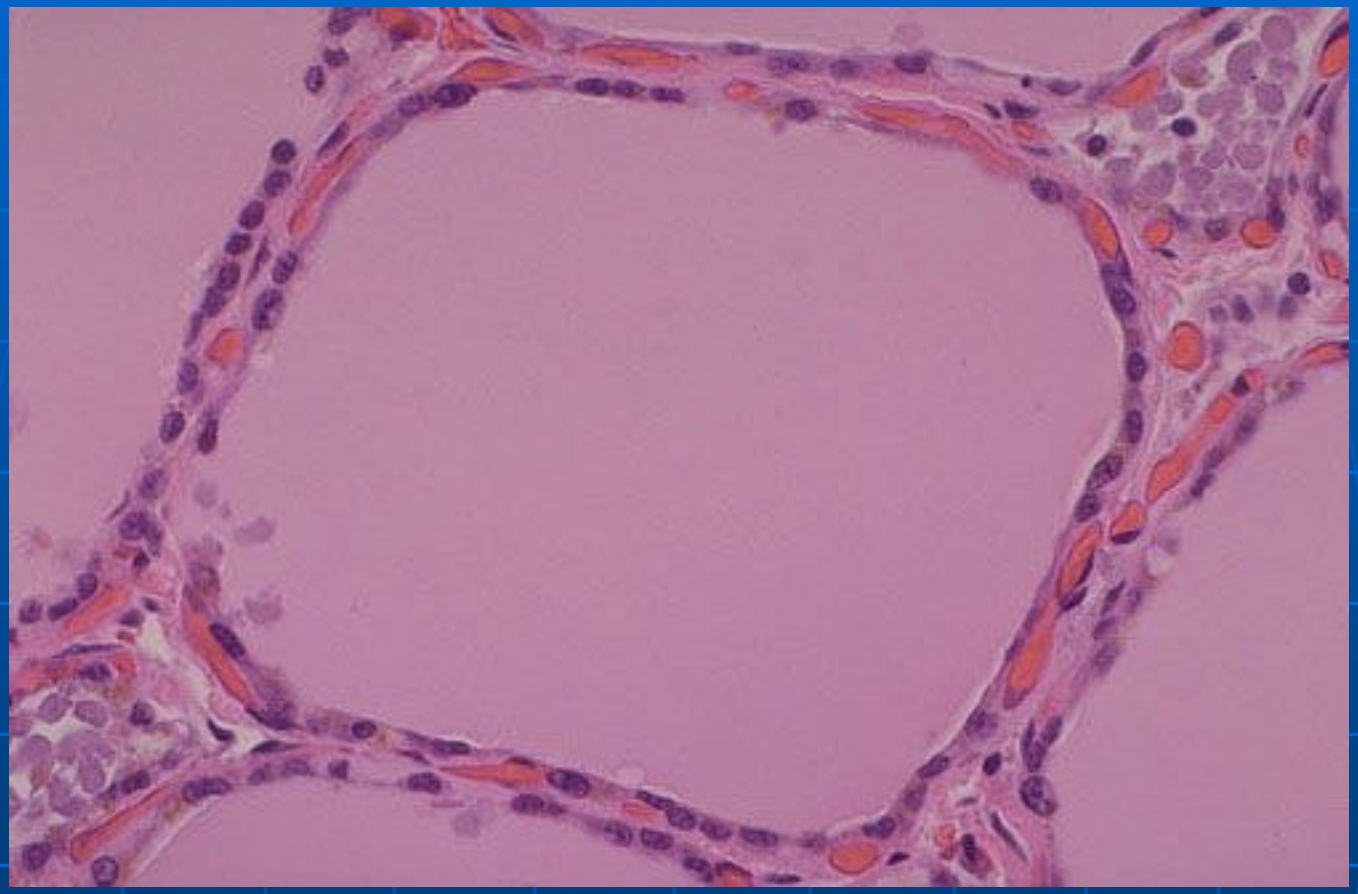


- This is the normal appearance of the thyroid gland on the anterior trachea of the neck. The thyroid gland has a right lobe and a left lobe connected by a narrow isthmus. The normal weight of the thyroid is 10 to 30 grams. It cannot easily be palpated on physical examination.





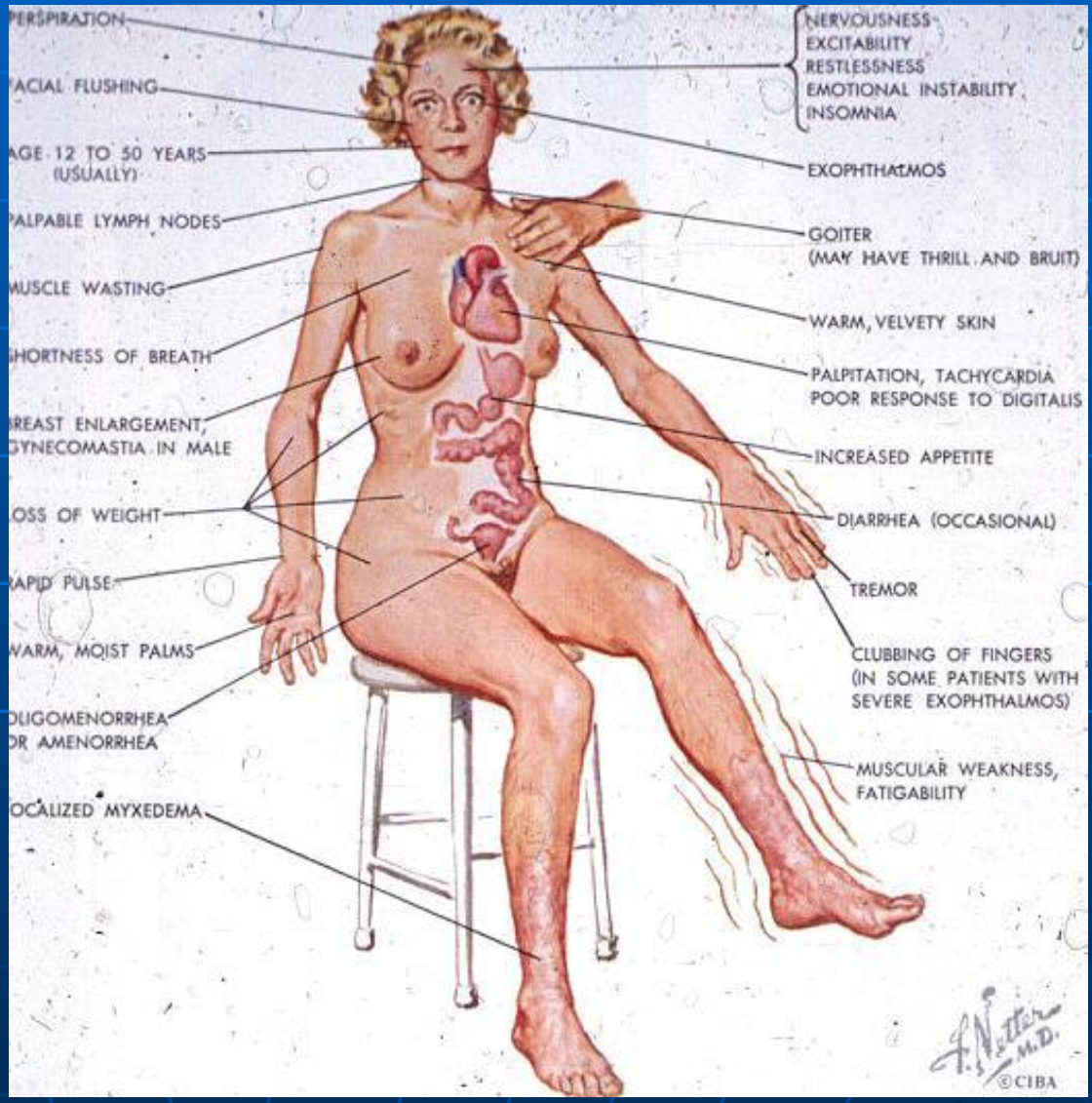
- Normal thyroid seen microscopically consists of follicles lined by a an epithelium and filled with colloid. The follicles vary somewhat in size. The interstitium, which may contain "C" cells, is not prominent.



- This normal thyroid follicle is lined by a cuboidal follicular epithelium with cells that can add or subtract colloid depending upon the degree of stimulation from TSH (thyroid stimulating hormone) released by the pituitary gland. As in all endocrine glands, the interstitium has a rich vascular supply into which hormone is secreted.

Hyperthyroidism

- Clinical findings
  - Heat intolerance
  - Tremor
  - Tachycardia
  - Hyperactive
  - Increased body metabolism and temperature
  - Ocular changes
- Main causes
  - Graves Disease
  - Toxic goiter
  - Toxic adenoma



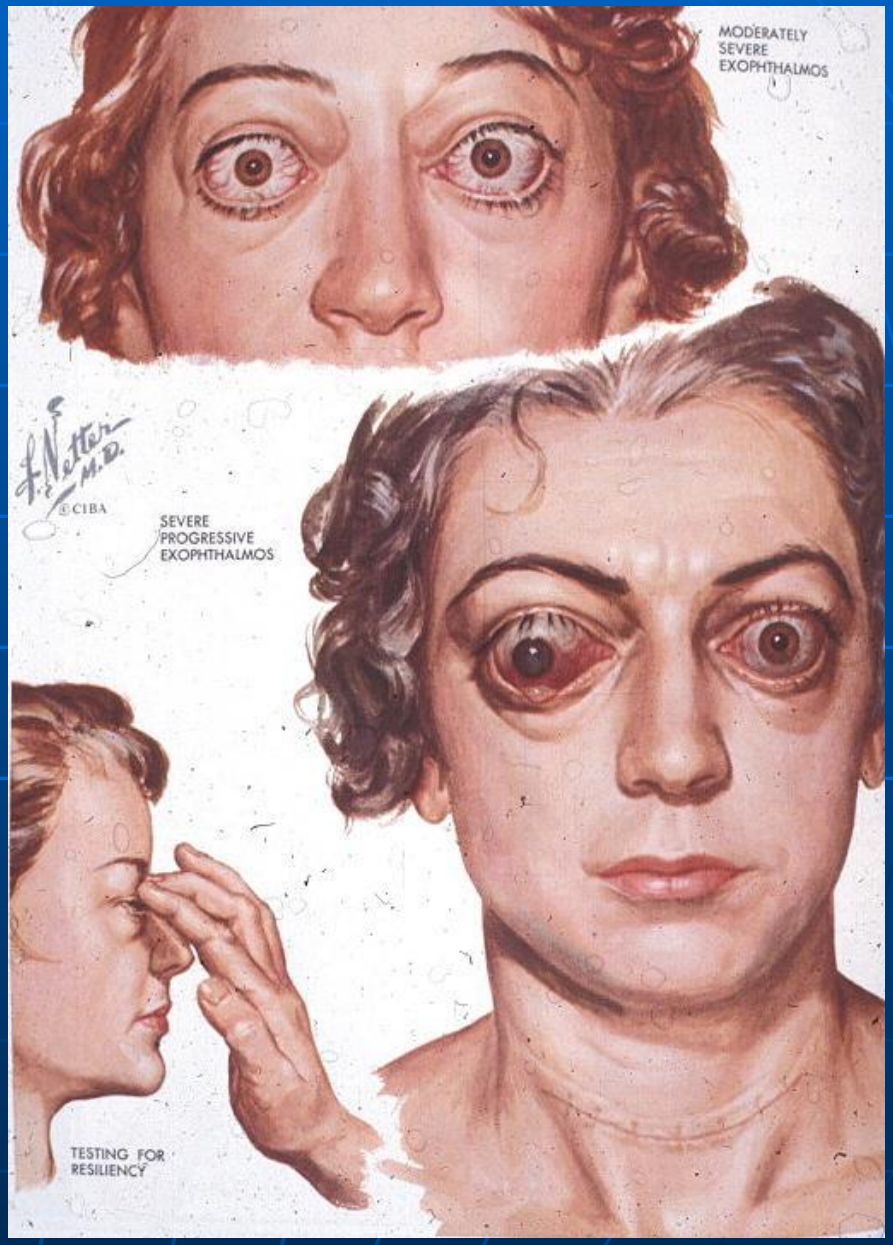
Grave's disease

Grave's disease is multi-organ systemic autoimmune disorder, manifested by the triad of basic features:

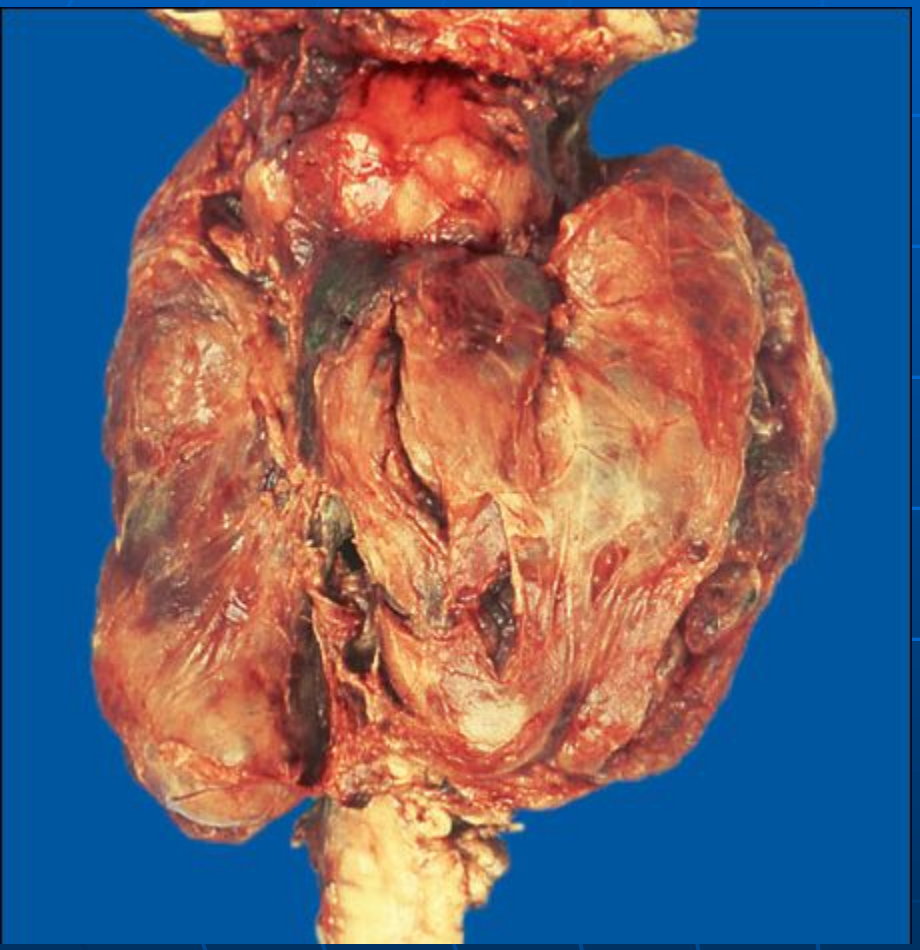
- hyperthyroidism with diffuse goiter
- ophthalmopathy
- dermopathy

Hyperophthalmia

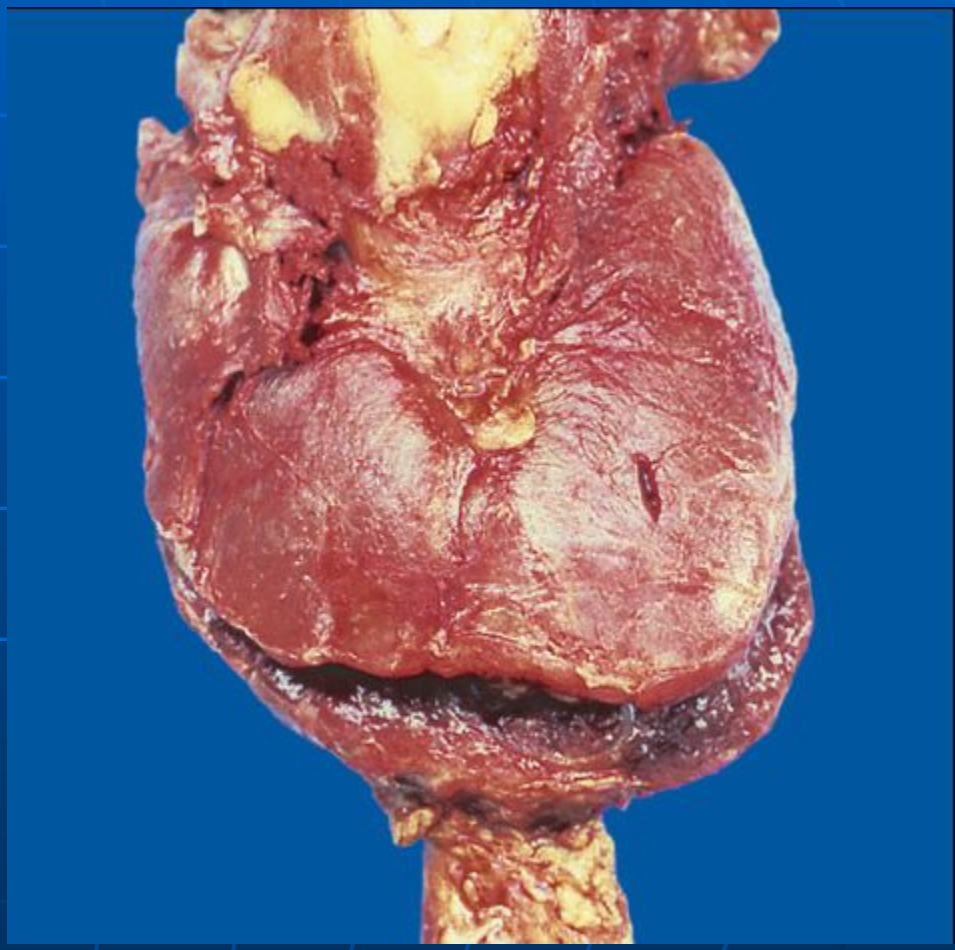
- Grave's disease
  - Antibody stimulates
- TSH receptors in extraocular muscles.
- Increased tissue in orbit causes eye to protrude.
- Won't go down
- Dry conjunctiva and increased risk of eye infections.



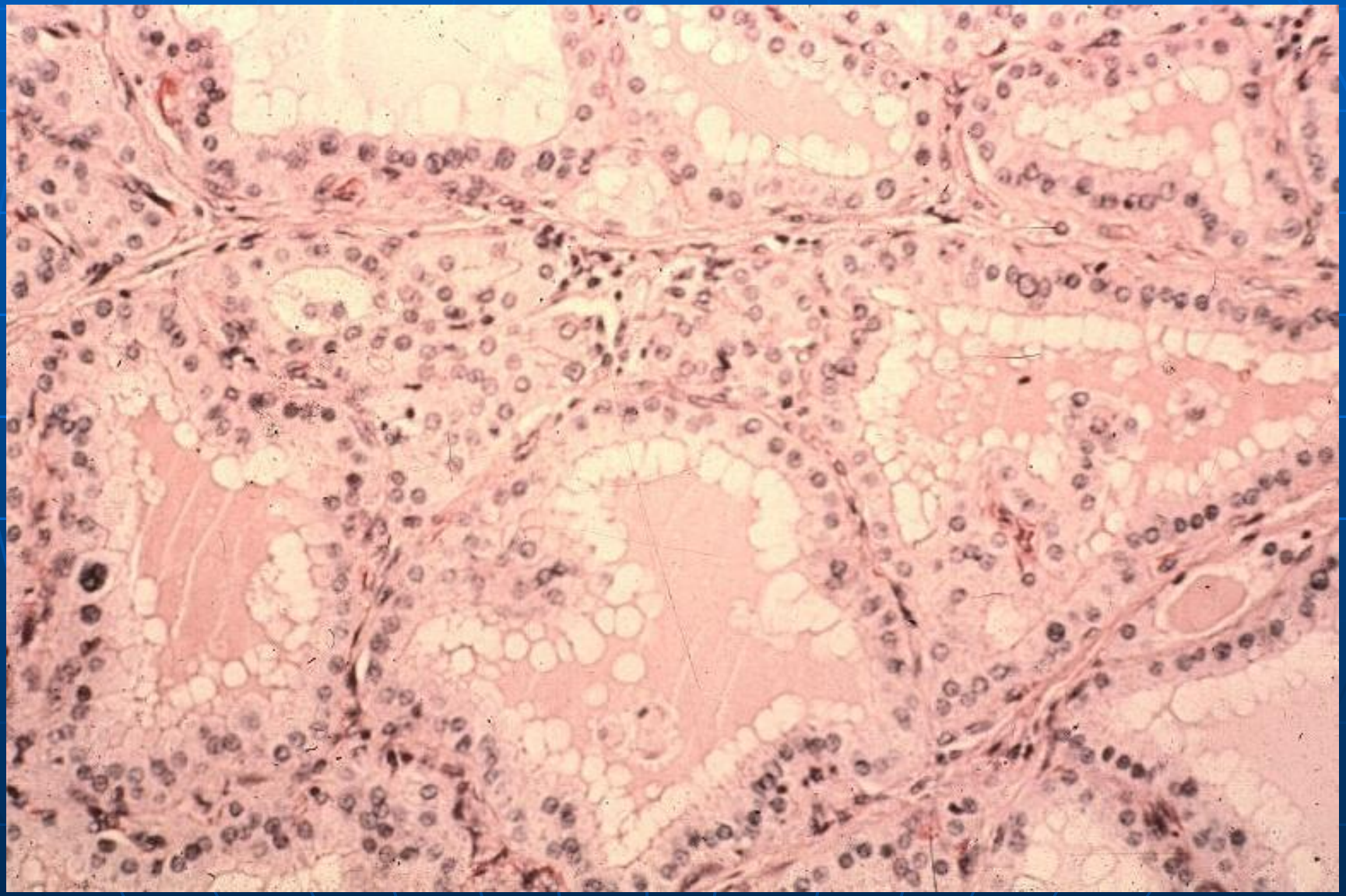
Nodular goiter

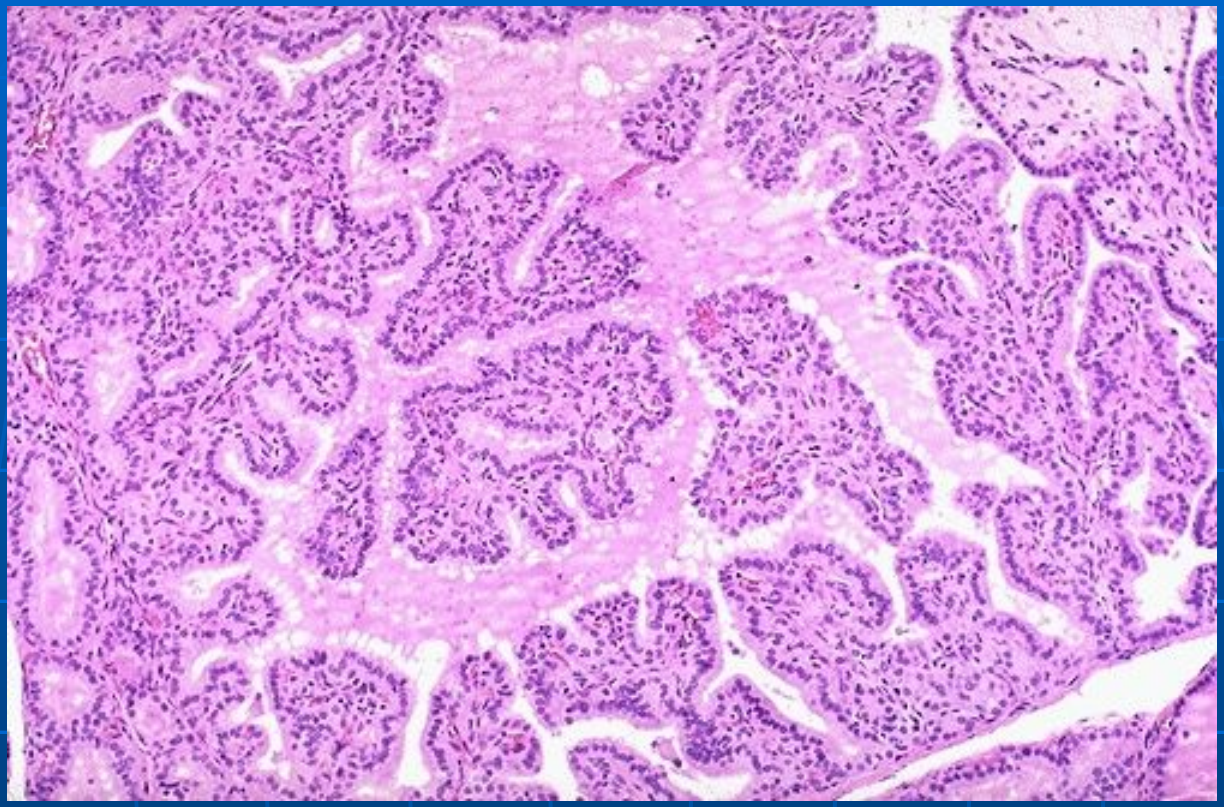


Diffuse goiter

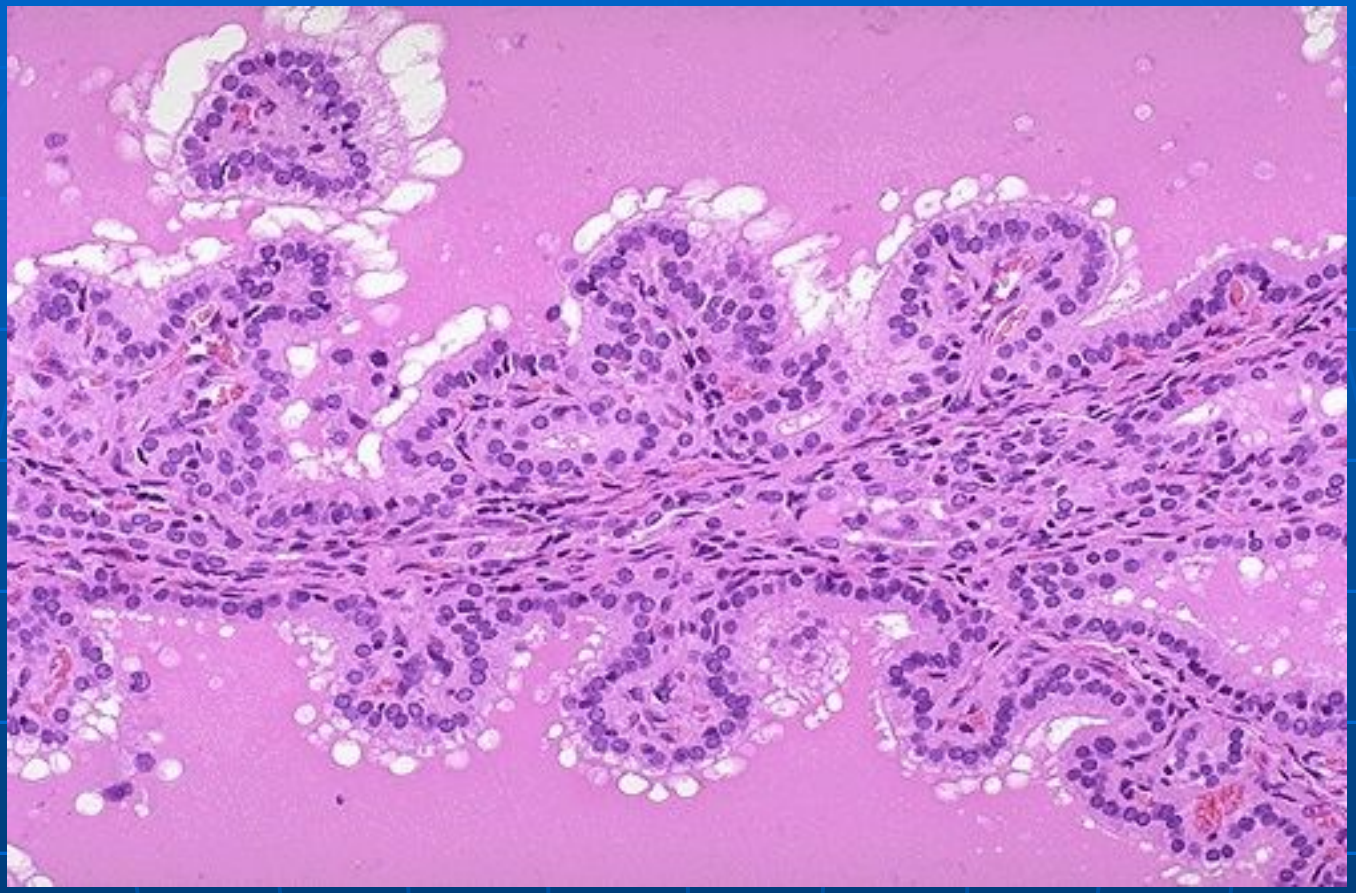


Hyperthyroidism



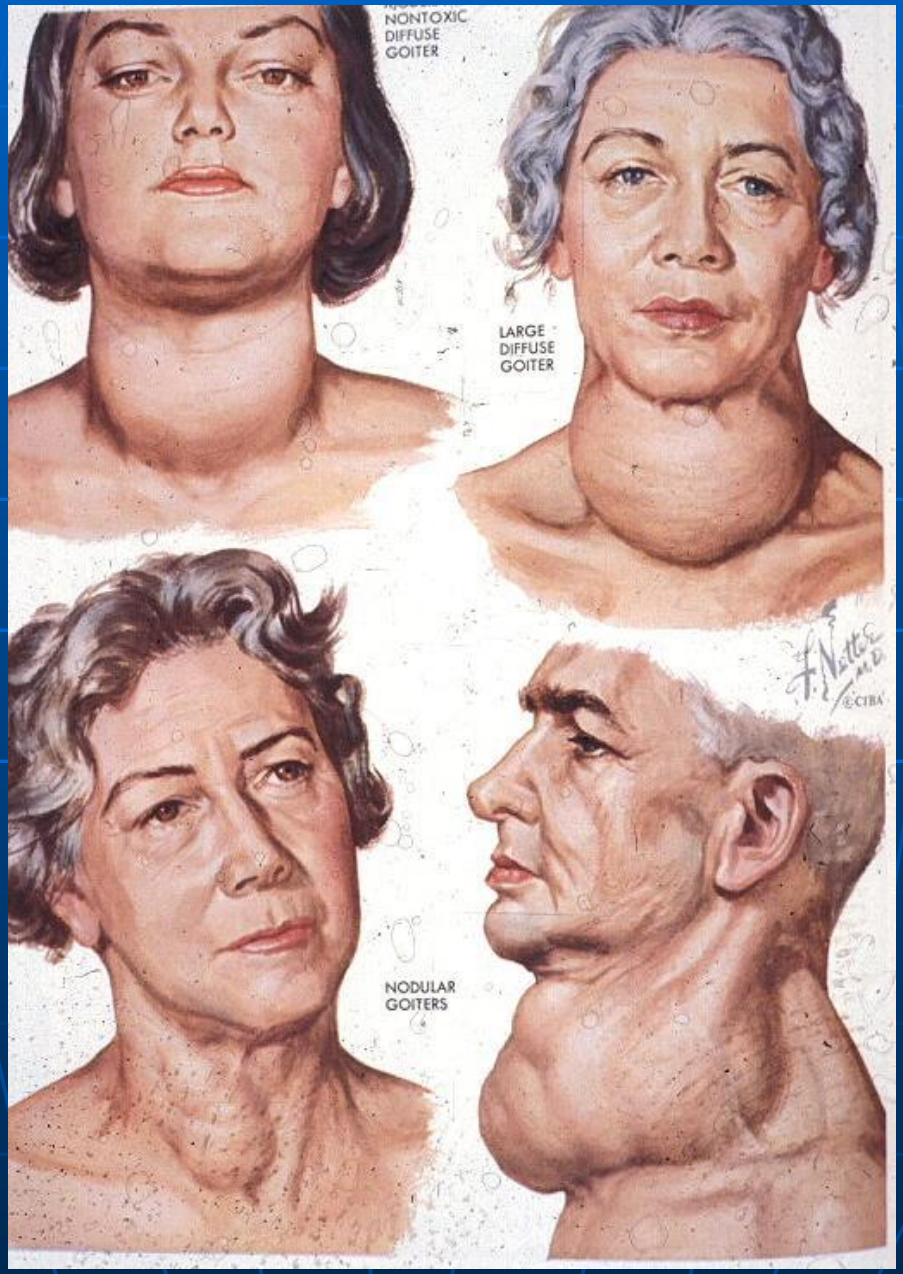


- A diffusely enlarged thyroid gland associated with hyperthyroidism is known as Grave's disease. At low power here, note the prominent infoldings of the hyperplastic epithelium. In this autoimmune disease the action of TSI's predominates over that of TGI's.



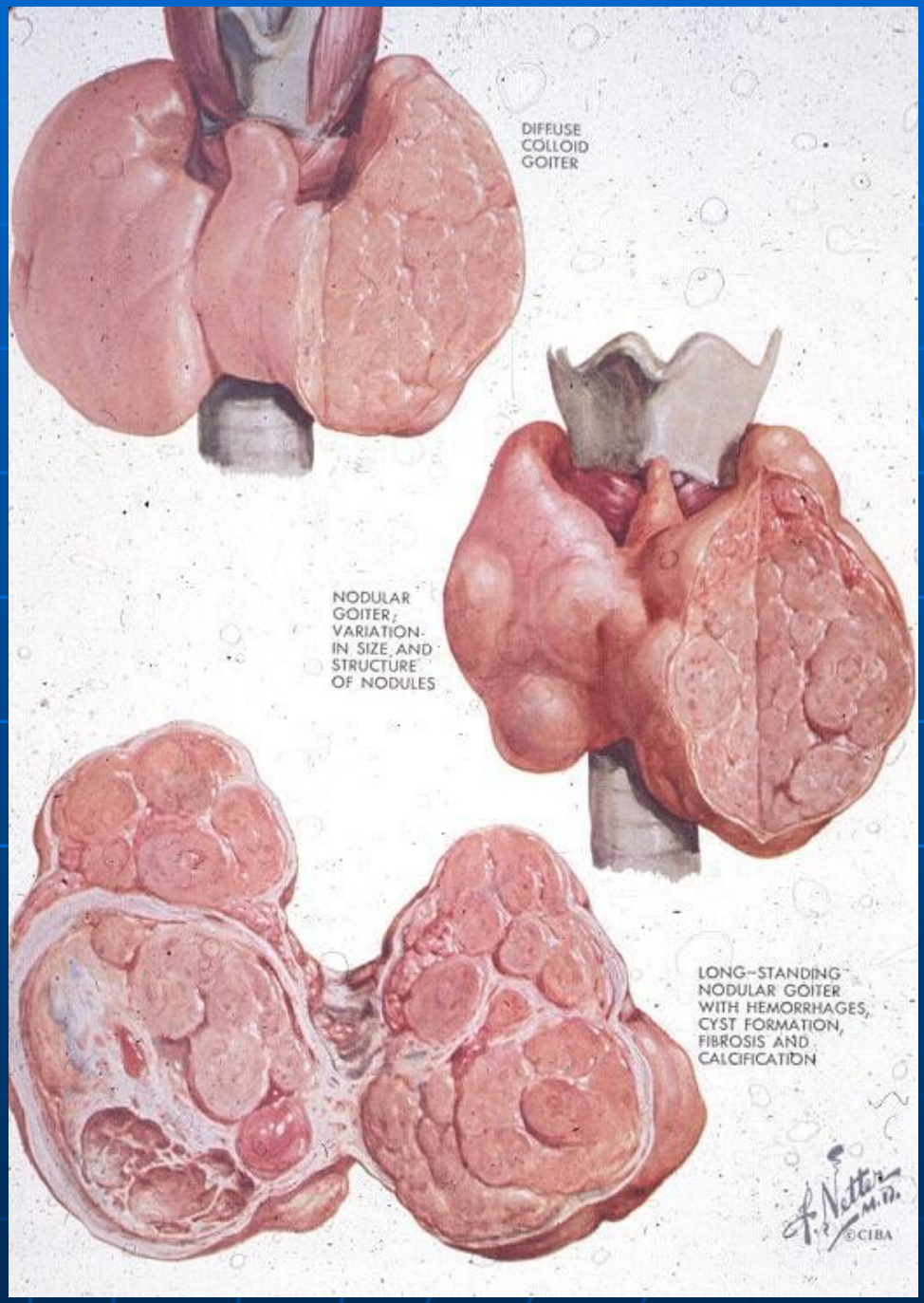
- At high power, the tall columnar thyroid epithelium with Grave's disease lines the hyperplastic infoldings into the colloid. Note the clear vacuoles in the colloid next to the epithelium where the increased activity of the epithelium to produce increased thyroid hormone has led to scalloping out of the colloid.

Tumors and Changes in Size



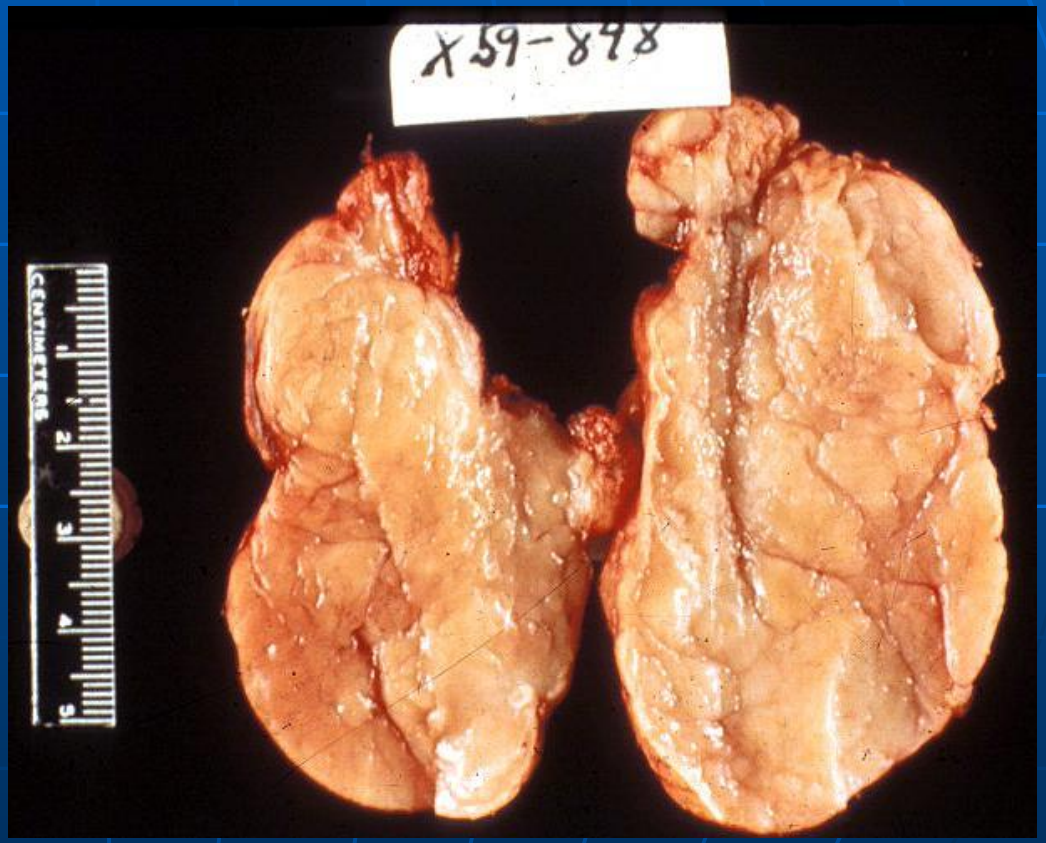
Goiter

- Nodular
- Uniform increase
- Scarring
- Cysts
- Generally euthyroid
- May cause airway compression

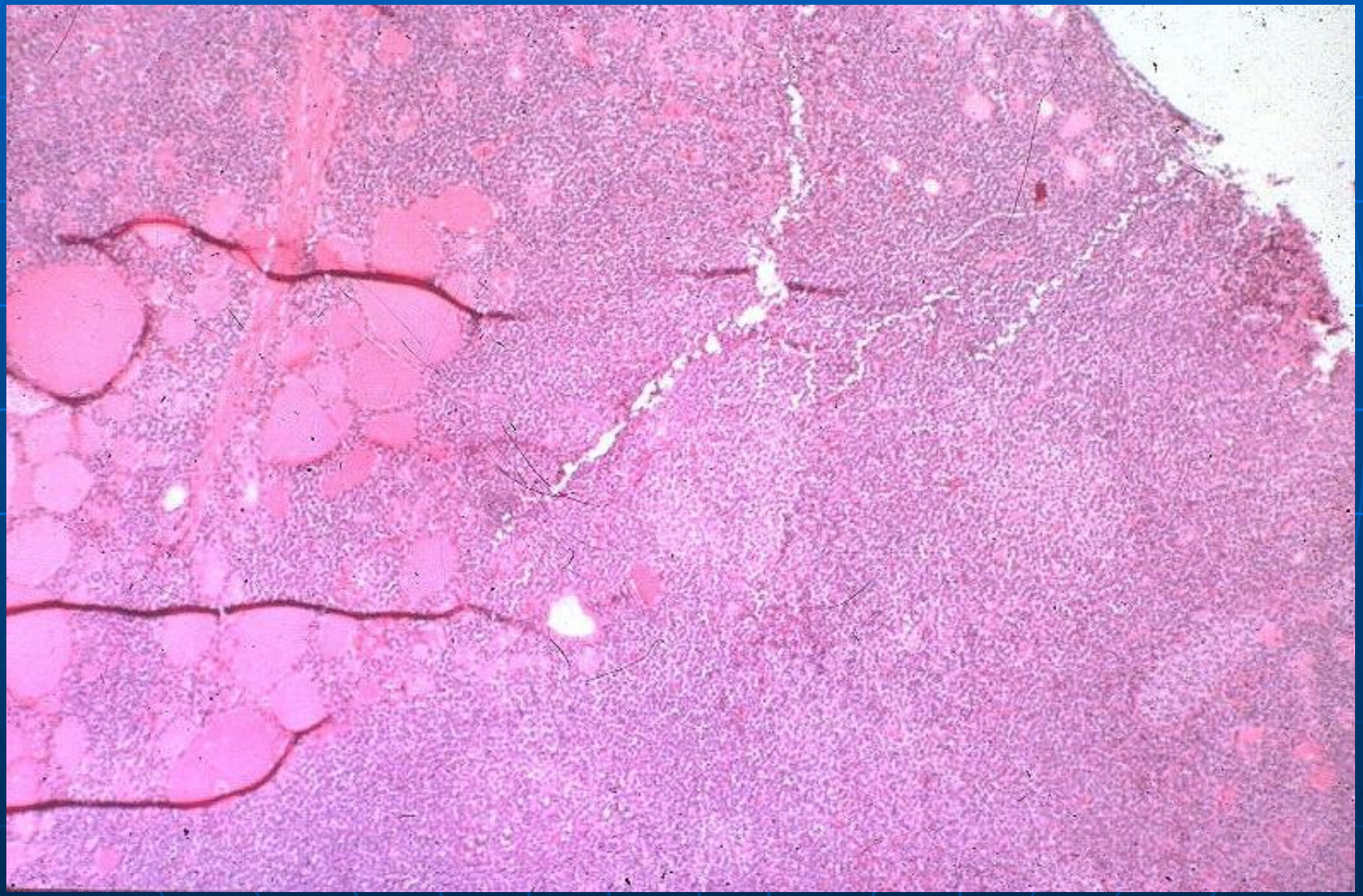


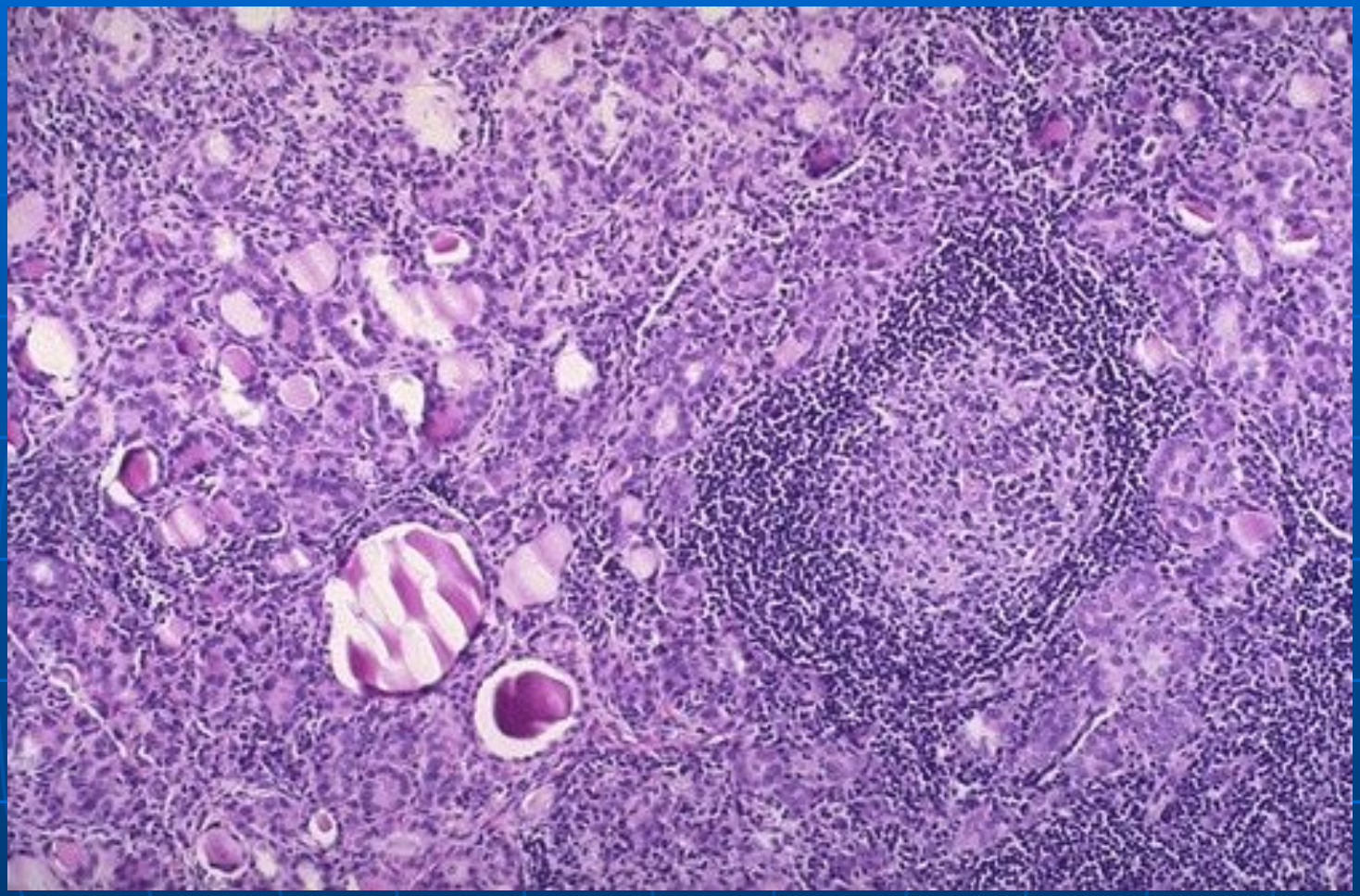
Hashimoto's Thyroiditis

- Many antibodies
- T & B cells
- Active germinal centers
- Women 5:1
- Scarring
- In time hypothyroid
- Other autoimmune
  - Arthritis
  - PA
  - Lupus
  - Addison's

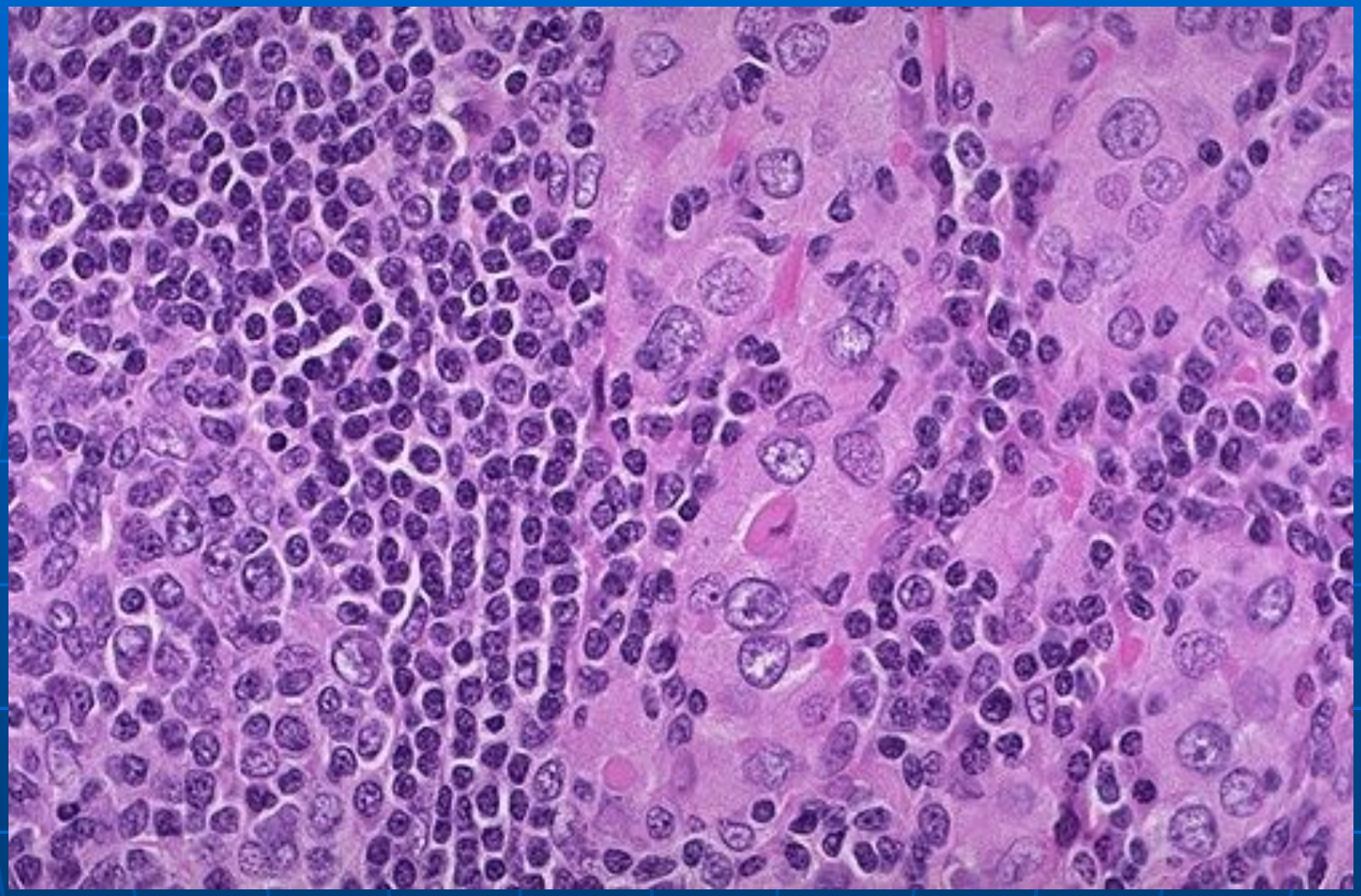


Hashimoto's Thryoiditis

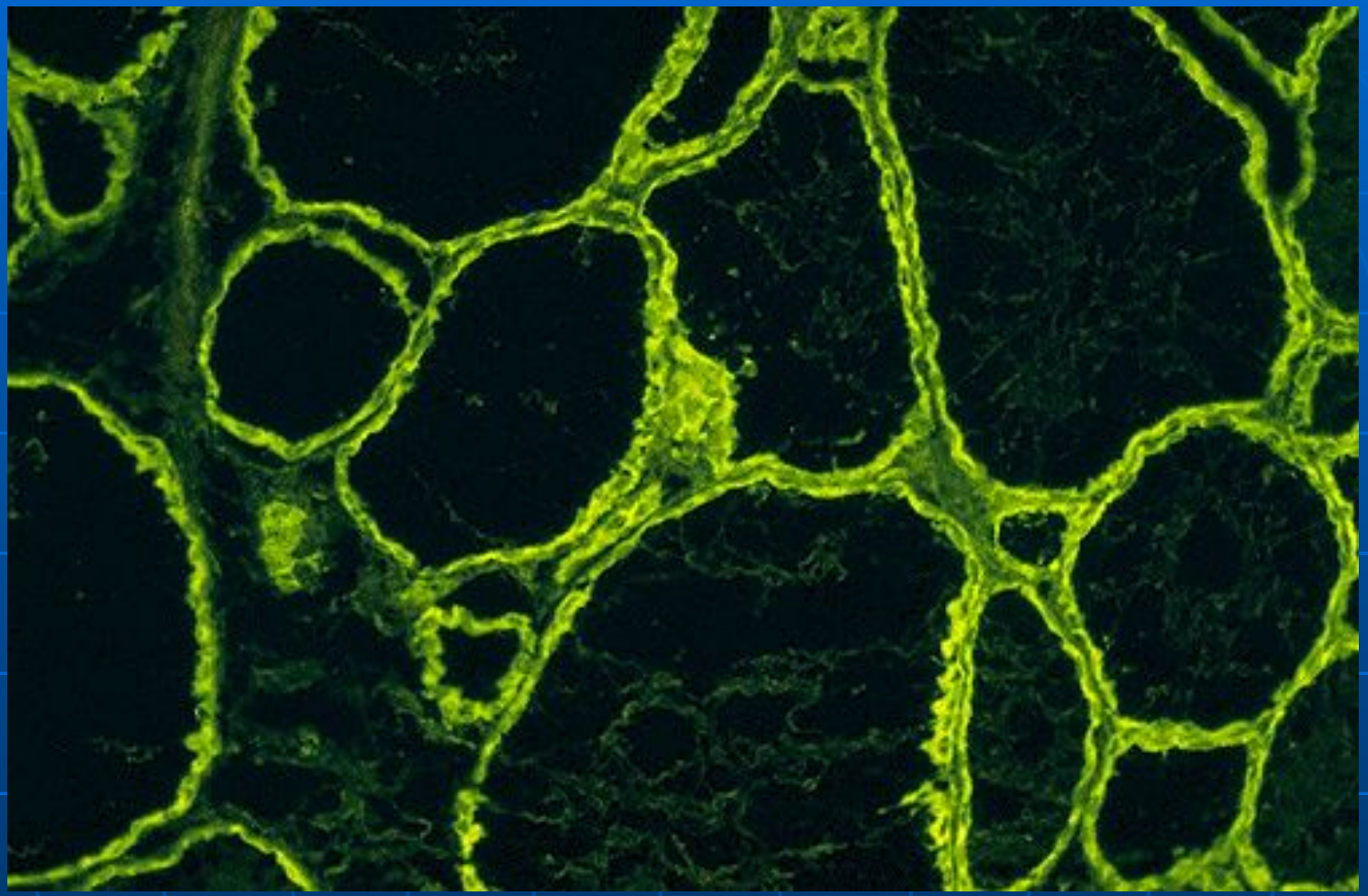




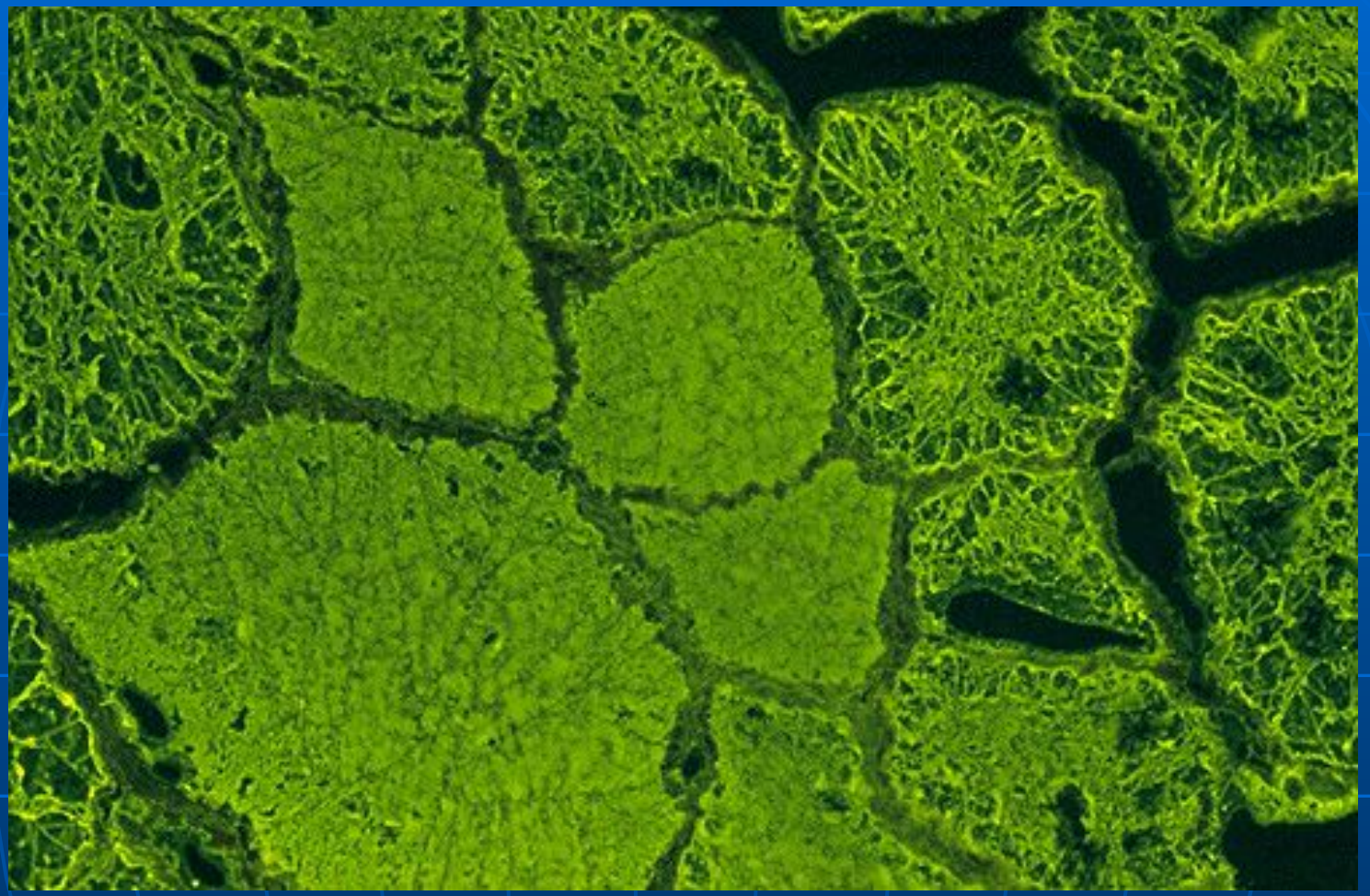
- Here is a low power microscopic view of a thyroid with Hashimoto's thyroiditis. Note the lymphoid follicle at the right center. This is an autoimmune disease and often antithyroglobulin and antimicrosomal antibodies can be detected. Other autoimmune diseases such as Addison's disease or pernicious anemia may also be present. Both thyroid growth immunoglobulins (TGI) and thyroid stimulating immunoglobulins (TSI) are present, though blocking antibodies to TSI mitigate their effect.



- This high power microscopic view of the thyroid with Hashimoto's thyroiditis demonstrates the pink Hurthle cells at the center and right. The lymphoid follicle is at the left. Hashimoto's thyroiditis initially leads to painless enlargement of the thyroid, followed by atrophy years later.



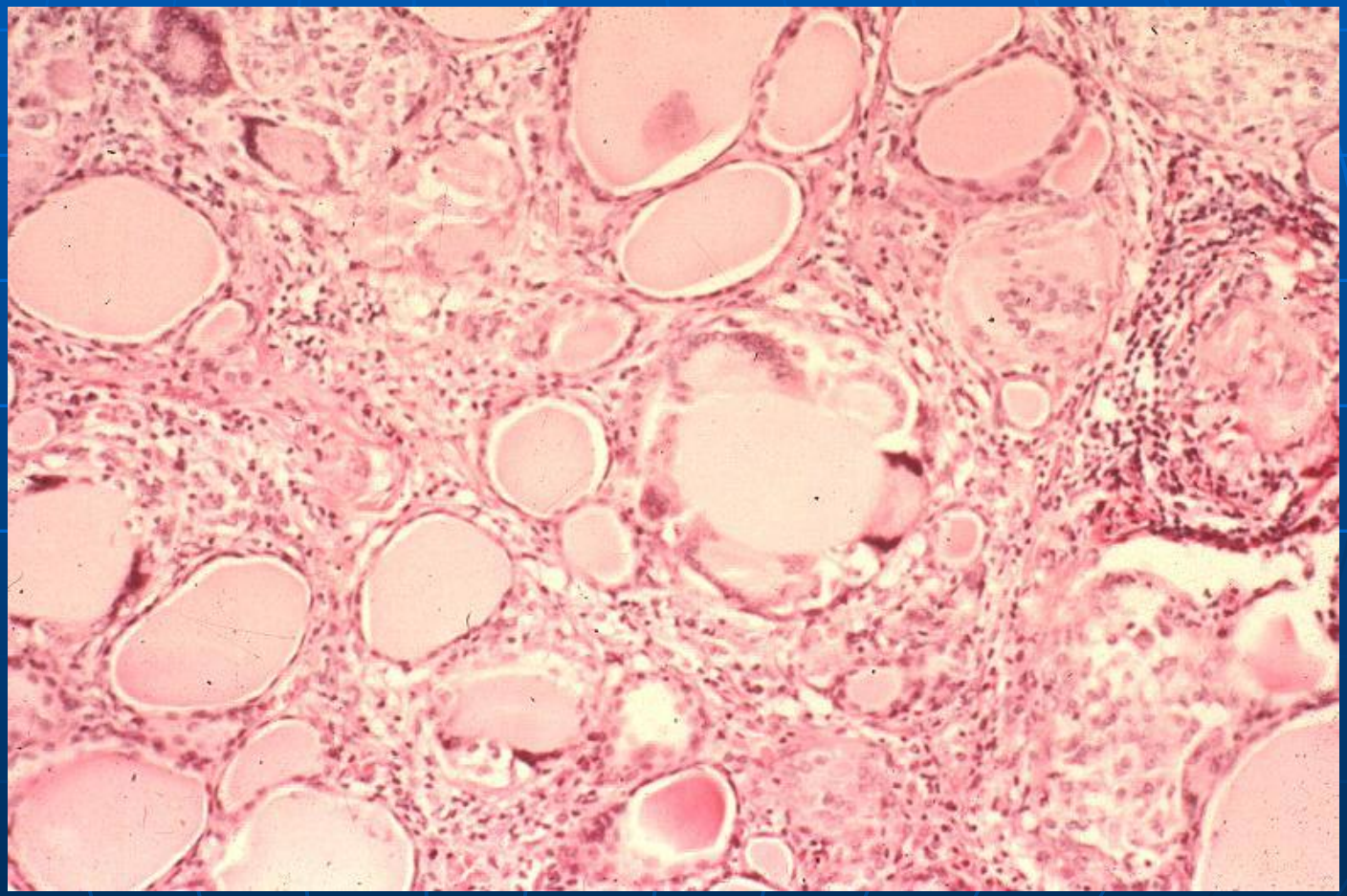
- This is an example of an immunofluorescence test positive for anti-microsomal antibody, one of the autoantibodies that can be seen with autoimmune diseases of the thyroid. Note the bright green fluorescence in the thyroid epithelial cells, whereas the colloid in the center of the follicles is dark.

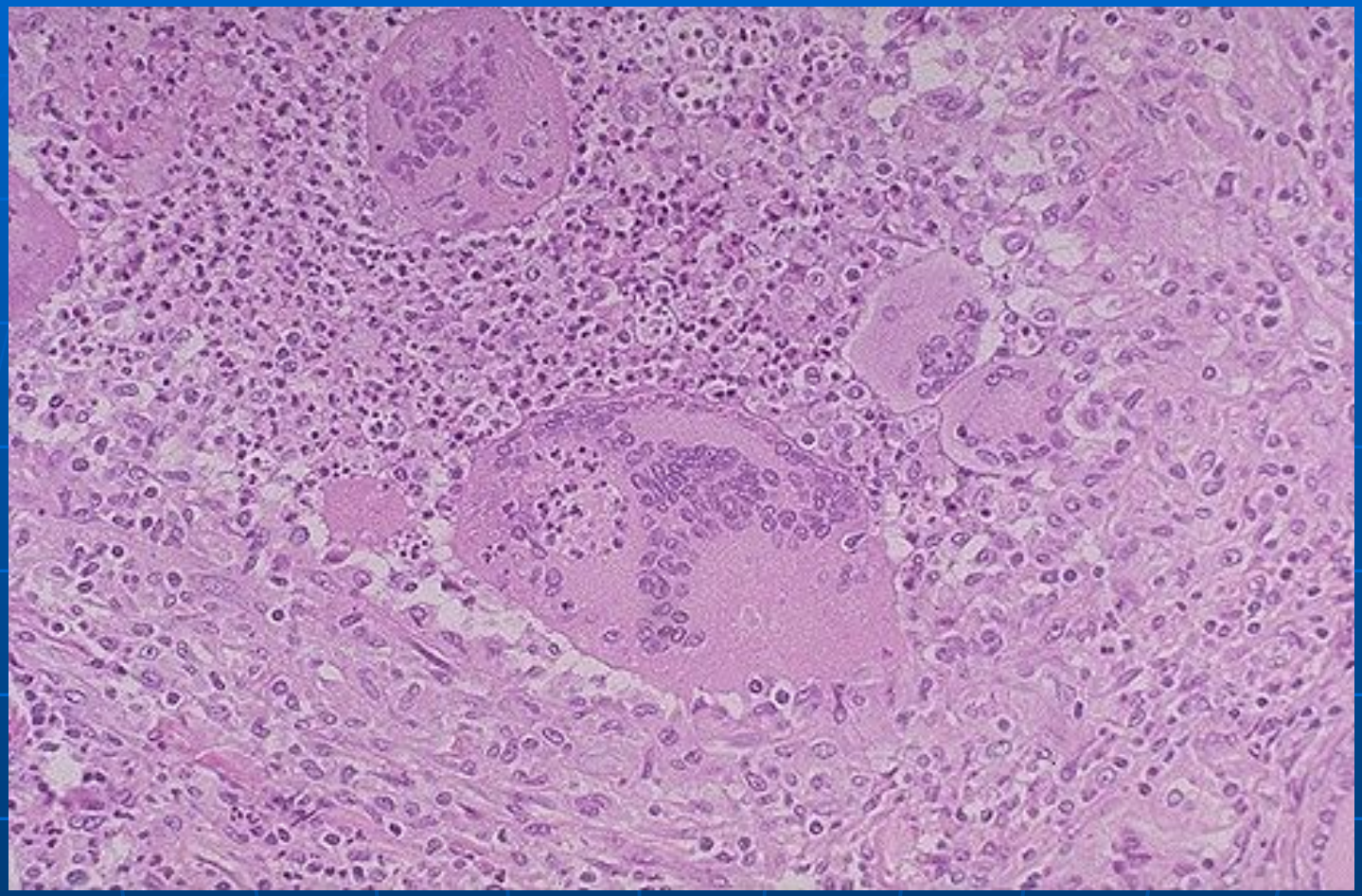


- Here is an example of immunofluorescence positivity for anti-thyroglobulin antibody. Patients with Hashimoto's thyroiditis may also have other autoimmune conditions including Grave's disease, SLE, rheumatoid arthritis, pernicious anemia, and Sjogren's syndrome.

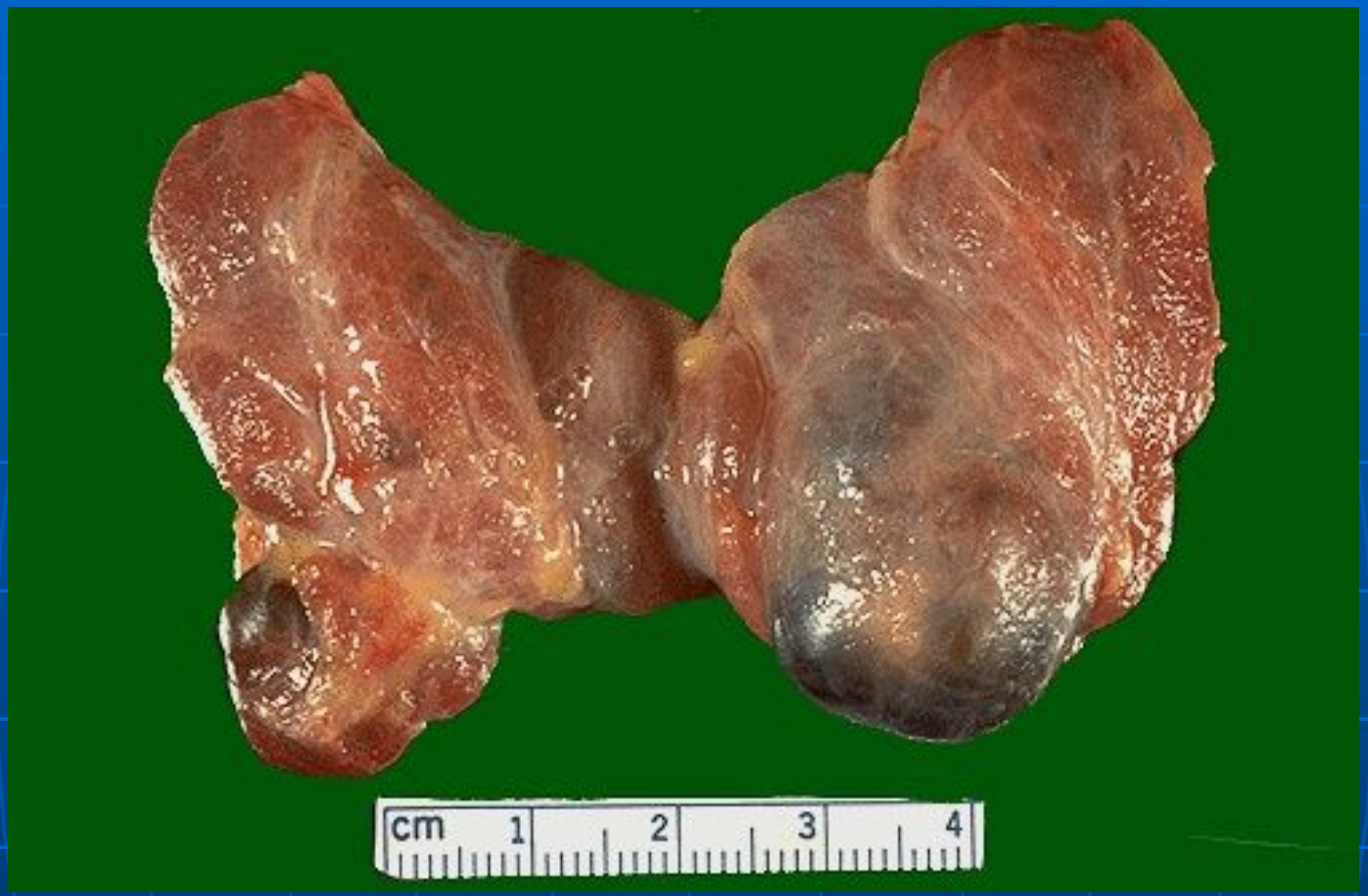
De Quervain's Thyroiditis

- Subacute
- Giant cells
- Granulomas
- Viral?
- Painful neck

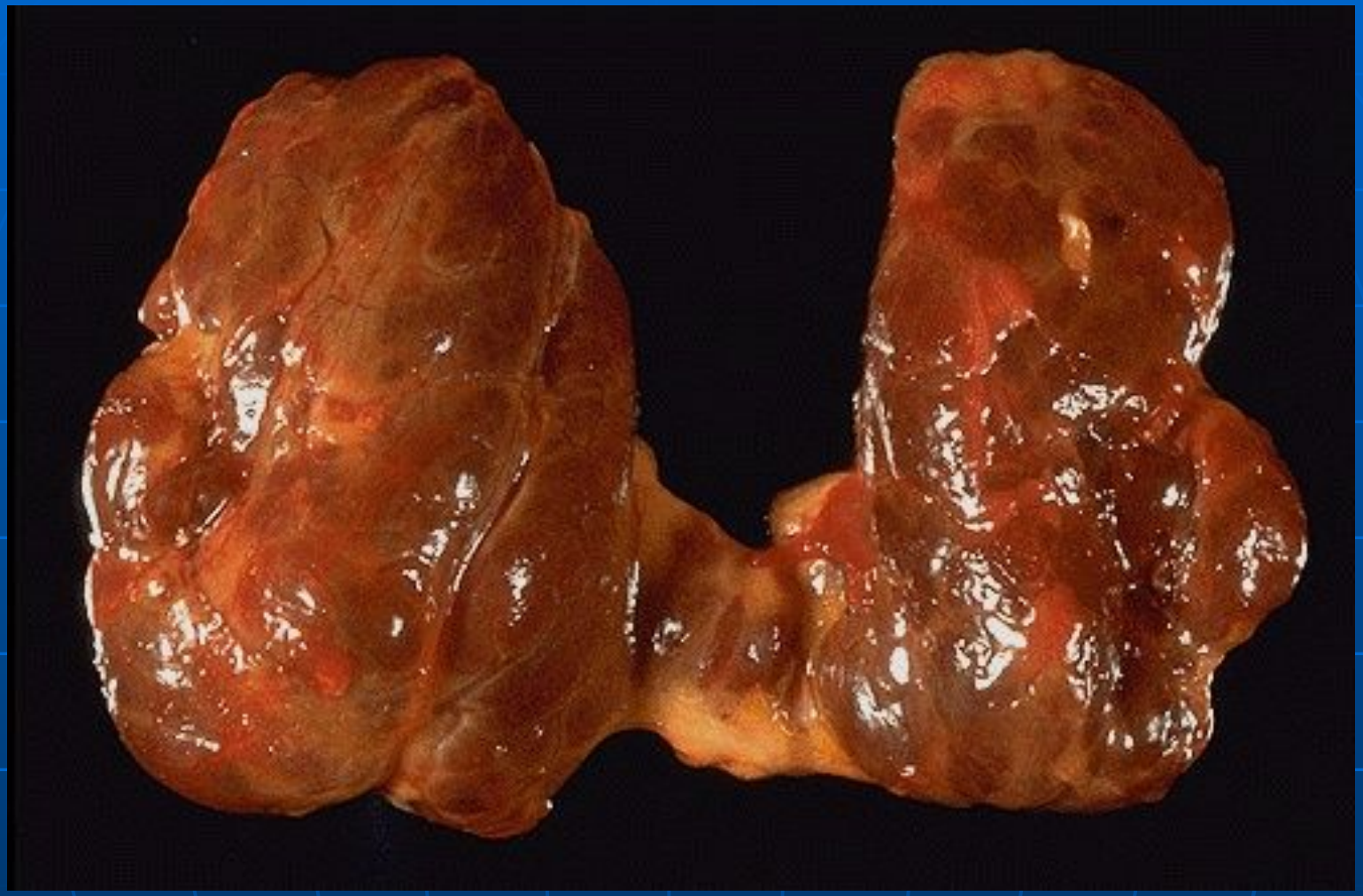




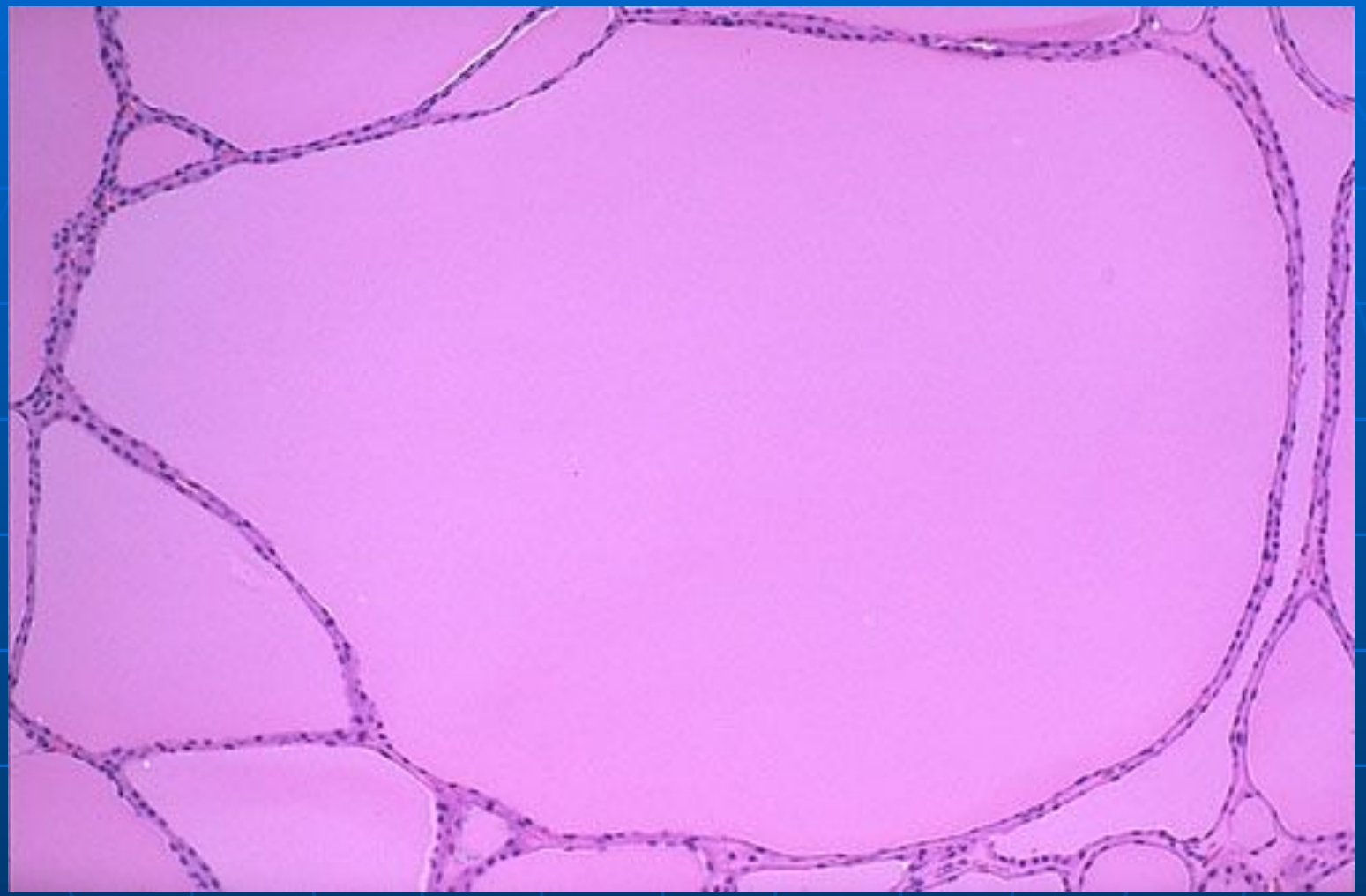
- This is subacute granulomatous thyroiditis (DeQuervain's disease), which probably follows a viral infection and leads to a painful enlarged thyroid. This disease is usually self-limited over weeks to months and the patients return to a euthyroid state. Note the foreign body giant cells with destruction of thyroid follicles.



- This thyroid gland is about normal in size, but there is a larger colloid cyst at the left lower pole and a smaller colloid cyst at the right lower pole. Such cysts could appear as "cold" nodules on a thyroid scan. They are incidental benign lesions but can appear as a mass to be distinguished from possible carcinoma.



- This diffusely enlarged thyroid gland is somewhat nodular. This patient was euthyroid. This represents the most common cause for an enlarged thyroid gland and the most common disease of the thyroid – a nodular goiter.



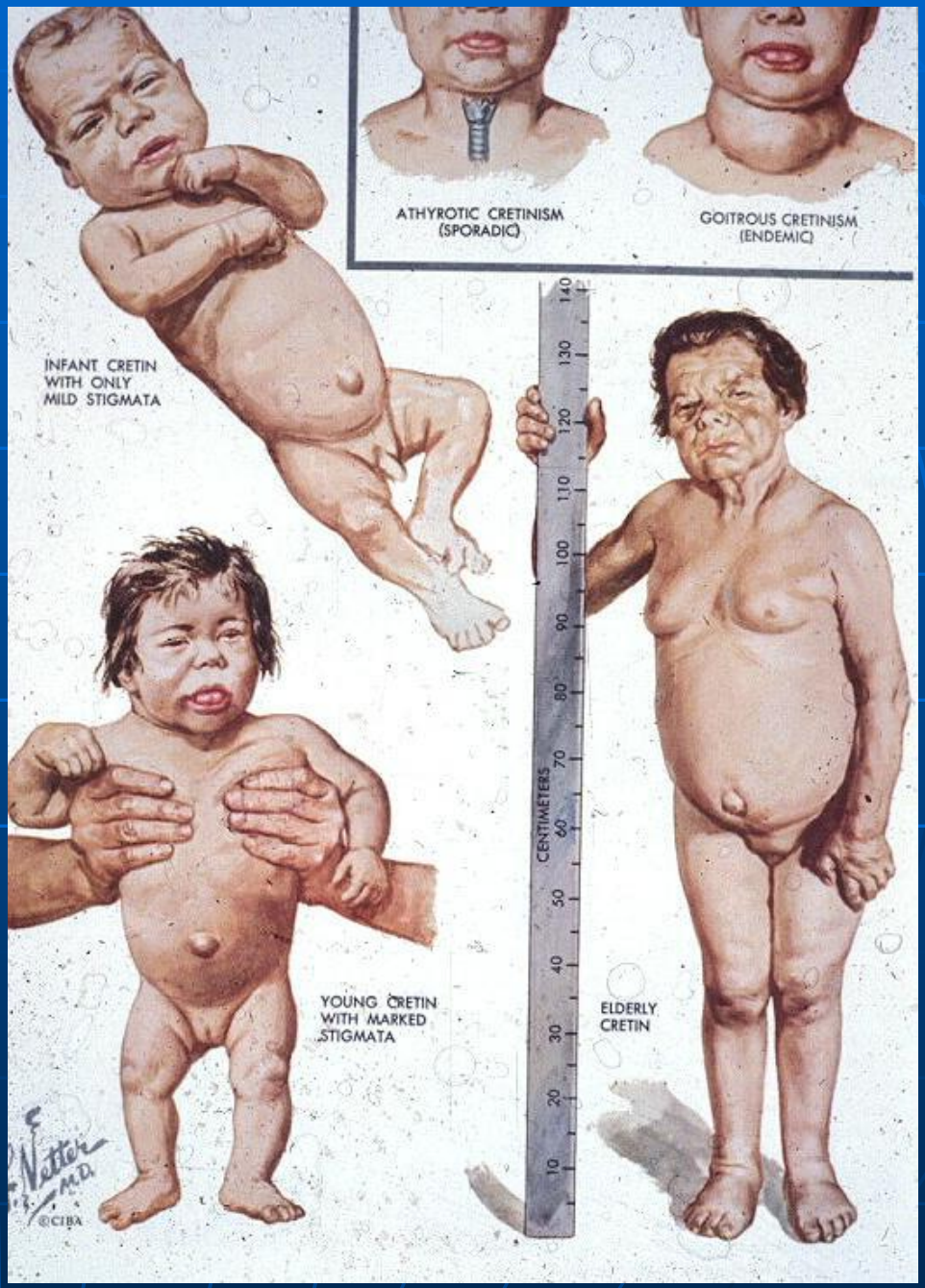
- The follicles are irregularly enlarged, with flattened epithelium, consistent with inactivity, in this microscopic appearance at low power of a multinodular goiter. The earlier phase of a diffuse (non-toxic) goiter leading up to this point may have resulted from either "endemic" goiter (seen in parts of the world where dietary deficiency of iodine may occur) or the uncommon "nonendemic" or sporadic goiter (young adult women are most often affected). Inborn errors of thyroid hormone biosynthesis leading to goiter are extremely uncommon.

Hypothyroidism

- Genetics
- Gland destruction
  - Inflammatory
  - Surgical removal
  - Radiation treatment for hyperthyroidism
- Iodine deficiency
  - Can’t make T4
- Hypothalmic and/or pituitary failure

Hypothyroidism

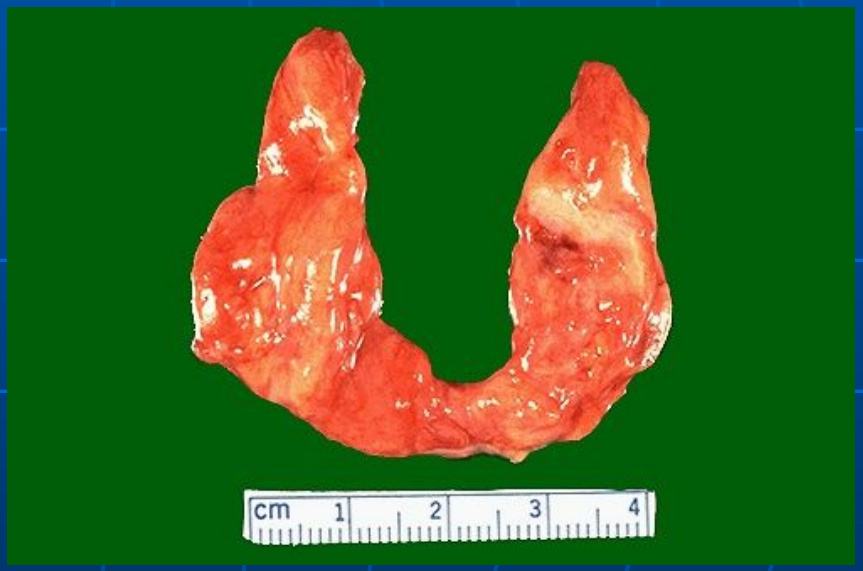
- Genetics: Cretinism
- Cannot make T4
- Growth retarded
- Severe mental retardation
- Must recognize early



Hypothyroidism

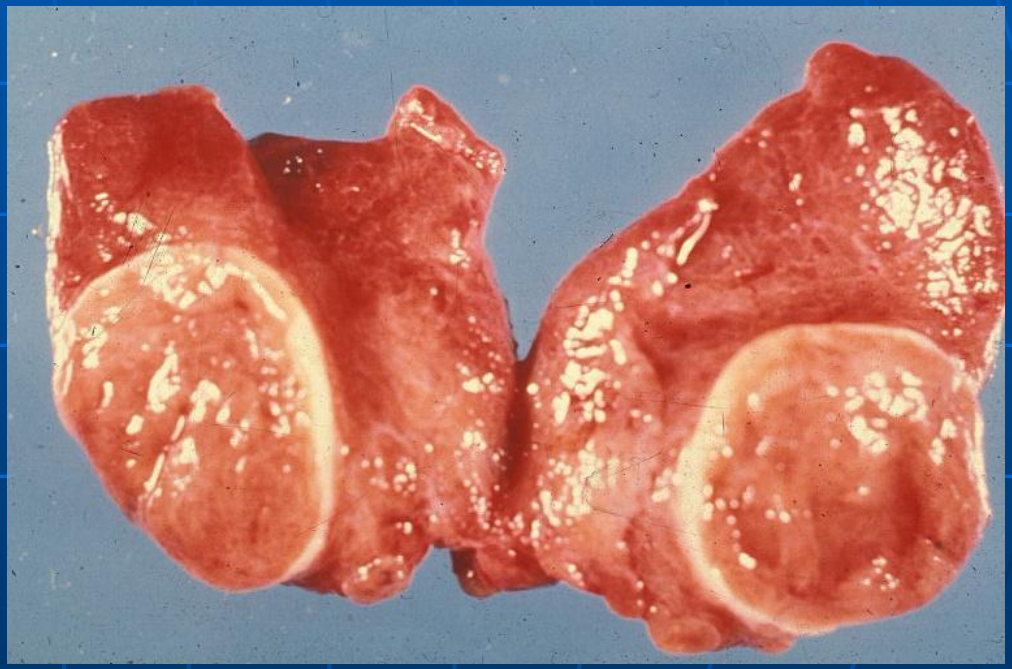
- Clinical
  - Cold intolerance
  - Bradycardia
  - Heart failure
  - High lipids
  - Lethargic
  - Photophobia
  - Myxedema
  - Skin and hair changes

- This symmetrically small thyroid gland demonstrates atrophy. This patient was hypothyroid. This is the end result of Hashimoto's thyroiditis. Initially, the thyroid is enlarged and there may be transient hyperthyroidism, followed by a euthyroid state and then hypothyroidism with eventual atrophy years later.

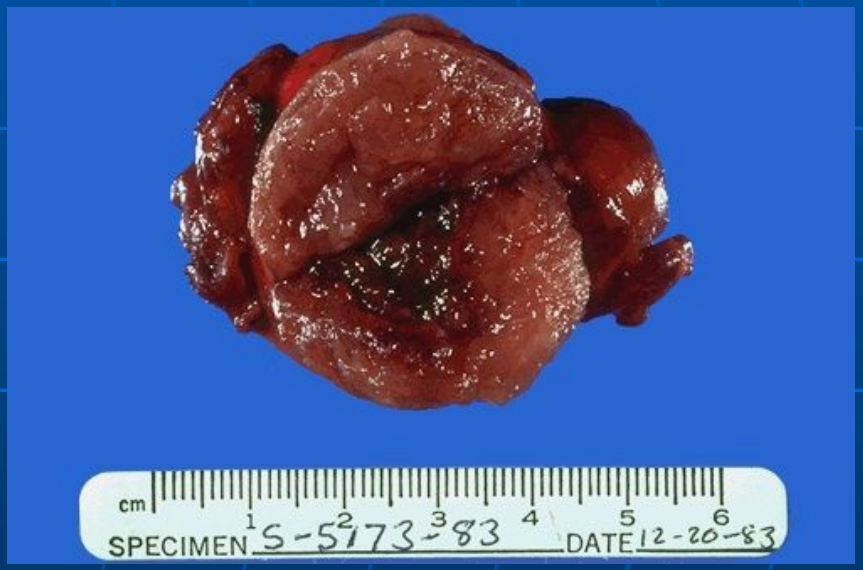


Thyroid Adenomas

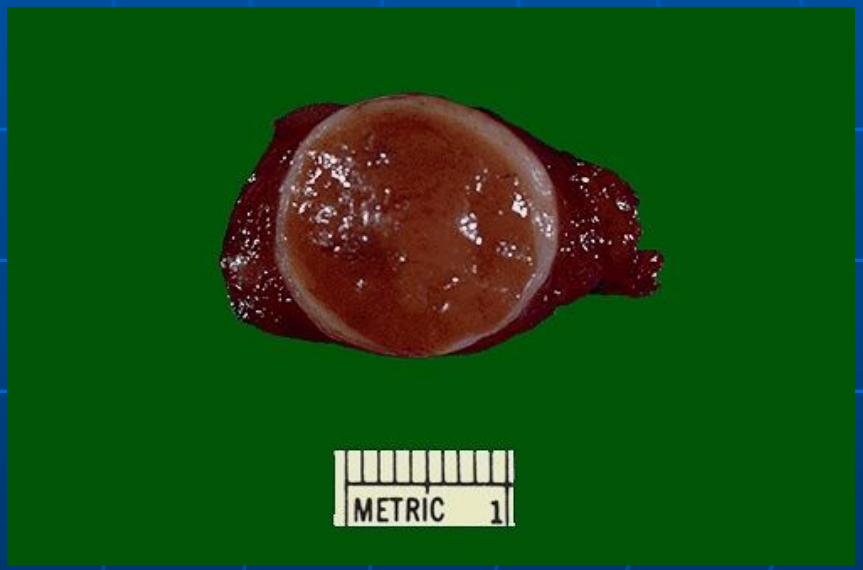
- Benign
- Solitary
- Common
- Encapsulated
- Generally not hyperactive

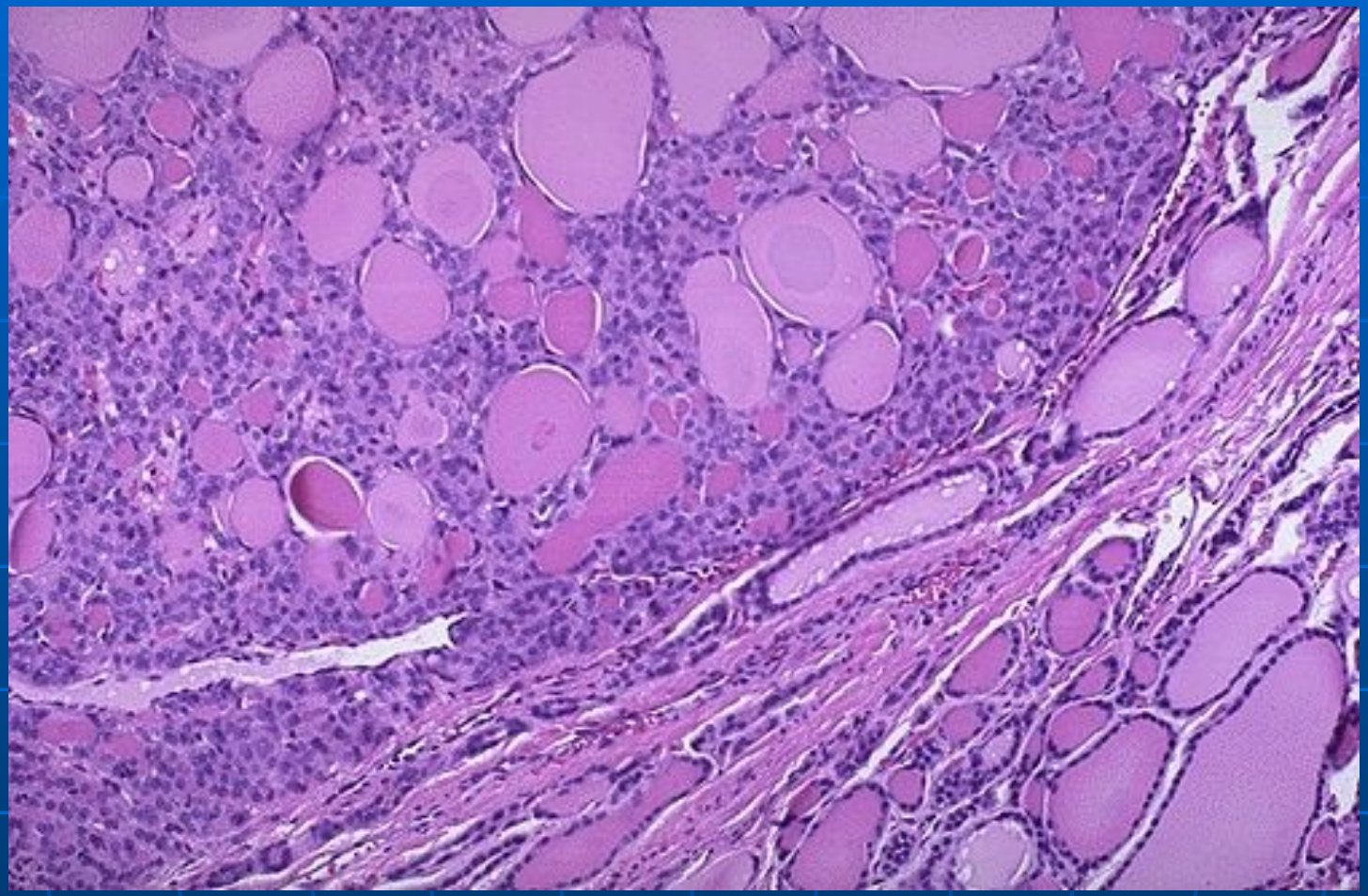


- Here is a surgical excision of a small mass from the thyroid gland that has been cut in half. A rim of slightly darker thyroid parenchyma is seen at the left. The mass is well-circumscribed. Grossly it felt firm. By scintigraphic scan it was "cold." This is a follicular adenoma.



- Here is another follicular neoplasm (a follicular adenoma histologically) that is surrounded by a thin white capsule. It is sometimes difficult to tell a well-differentiated follicular carcinoma from a follicular adenoma. Thus, patients with follicular neoplasms are treated with subtotal thyroidectomy just to be on the safe side.





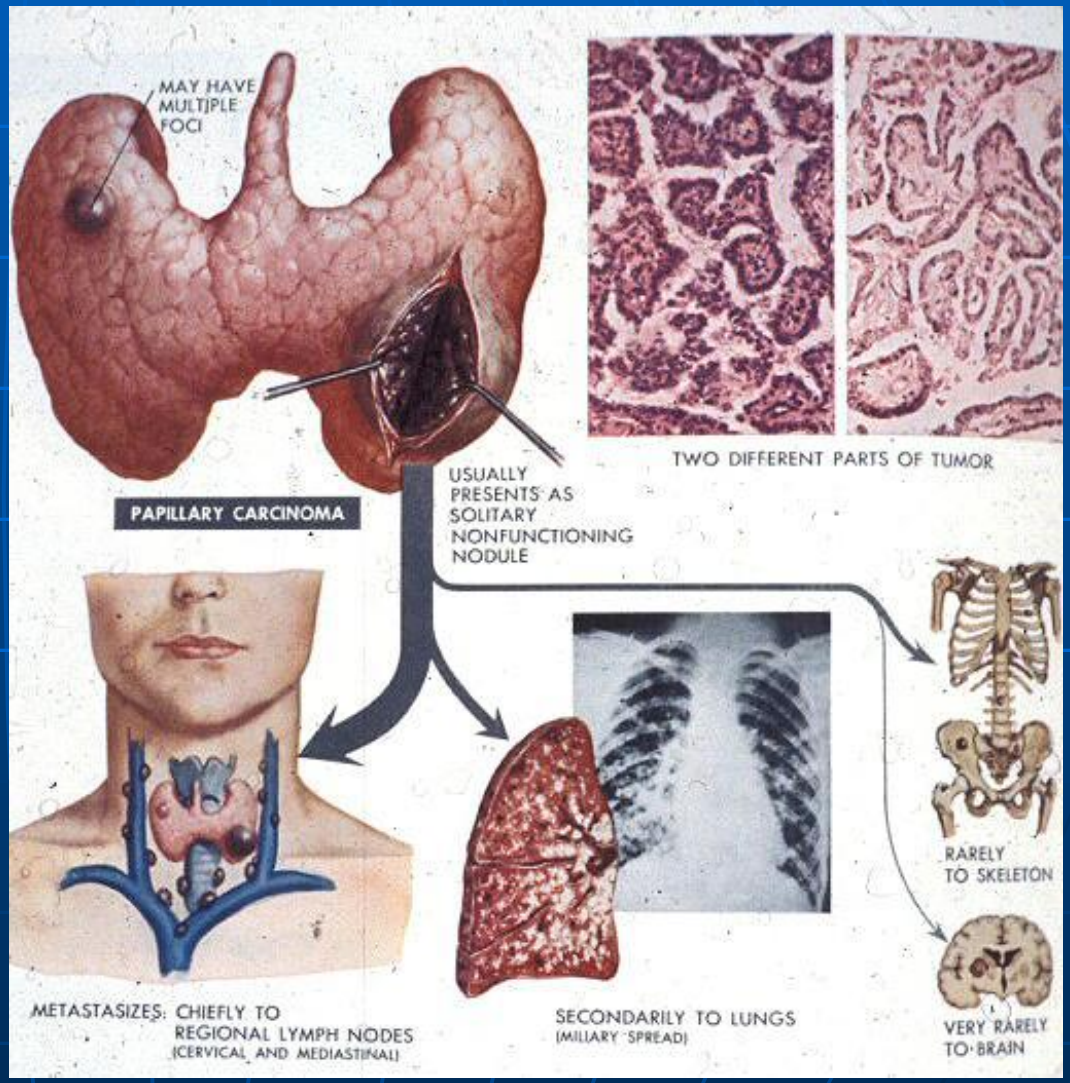
- Normal thyroid follicles appear at the lower right. The follicular adenoma is at the center to upper left. This adenoma is a well- differentiated neoplasm because it closely resemble normal tissue. The follicles of the adenoma contain colloid, but there is greater variability in size than normal.

Malignancies of Thyroid Origin

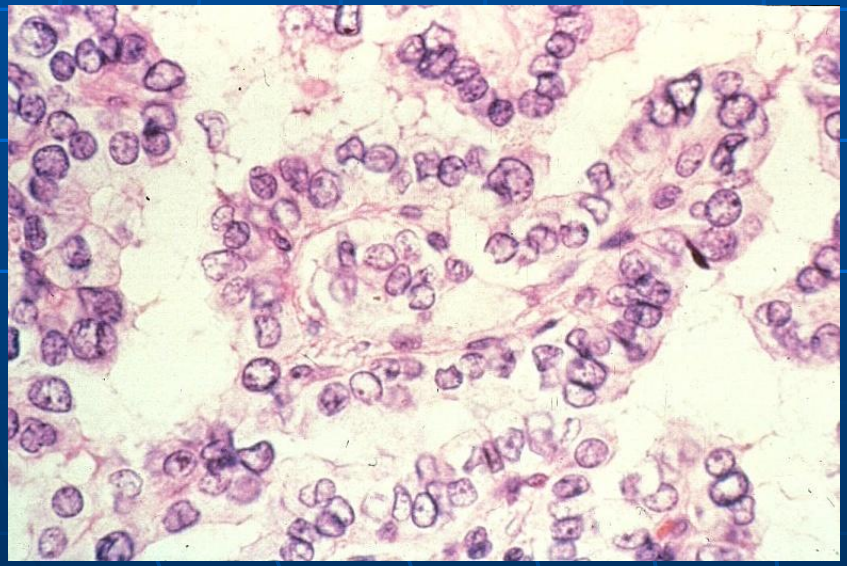
- Arising from follicular cells
  - Papillary Carcinoma
  - Follicular Carcinoma
  - Mixed pattern
- Interstitial cells (Calcitonin producing cells)
- Anaplastic, who knows
  - Very aggressive tumor

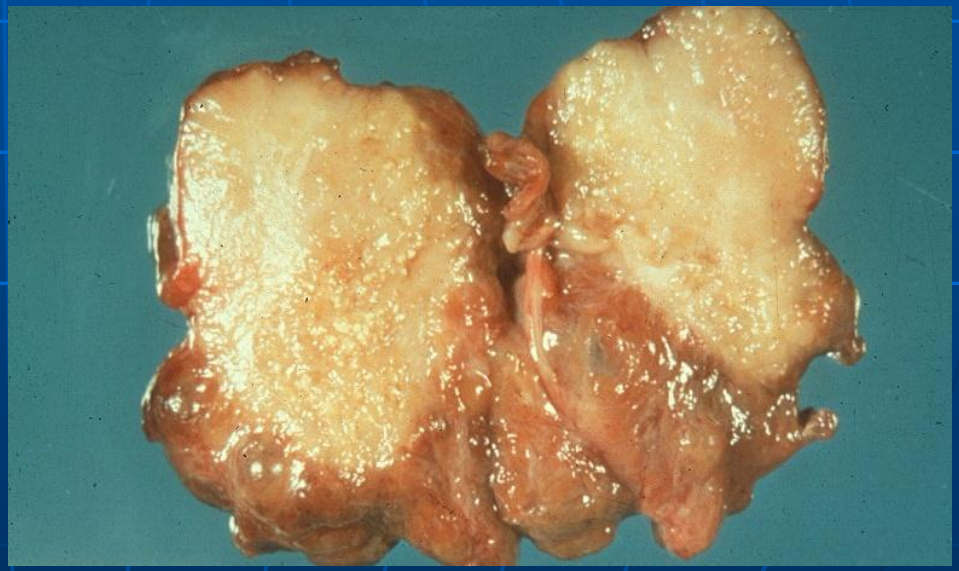
Papillary Carcinoma

- Papillary groups
- May have multiple sites
- Not actively producing T4
- Readily treated
- Spread
  - Nodes
  - Lung
  - Bone
  - Brain

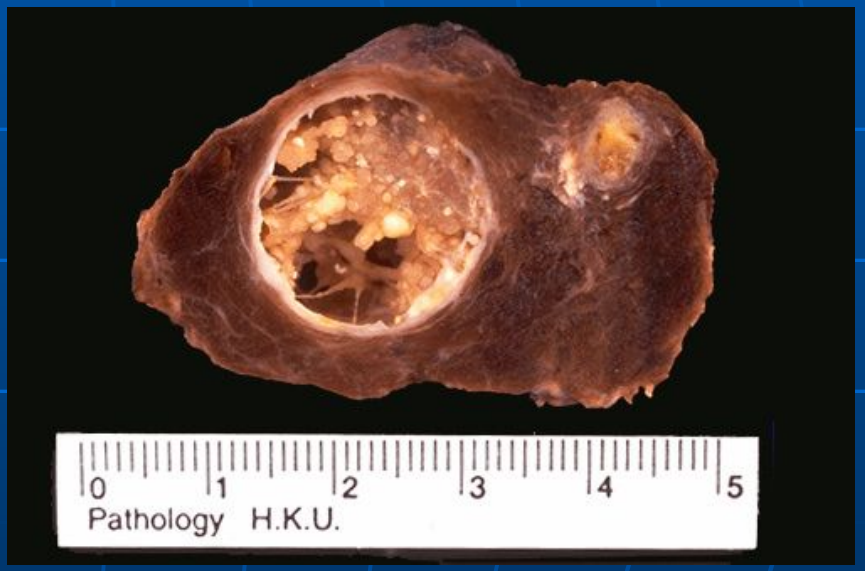


Papillary Carcinoma



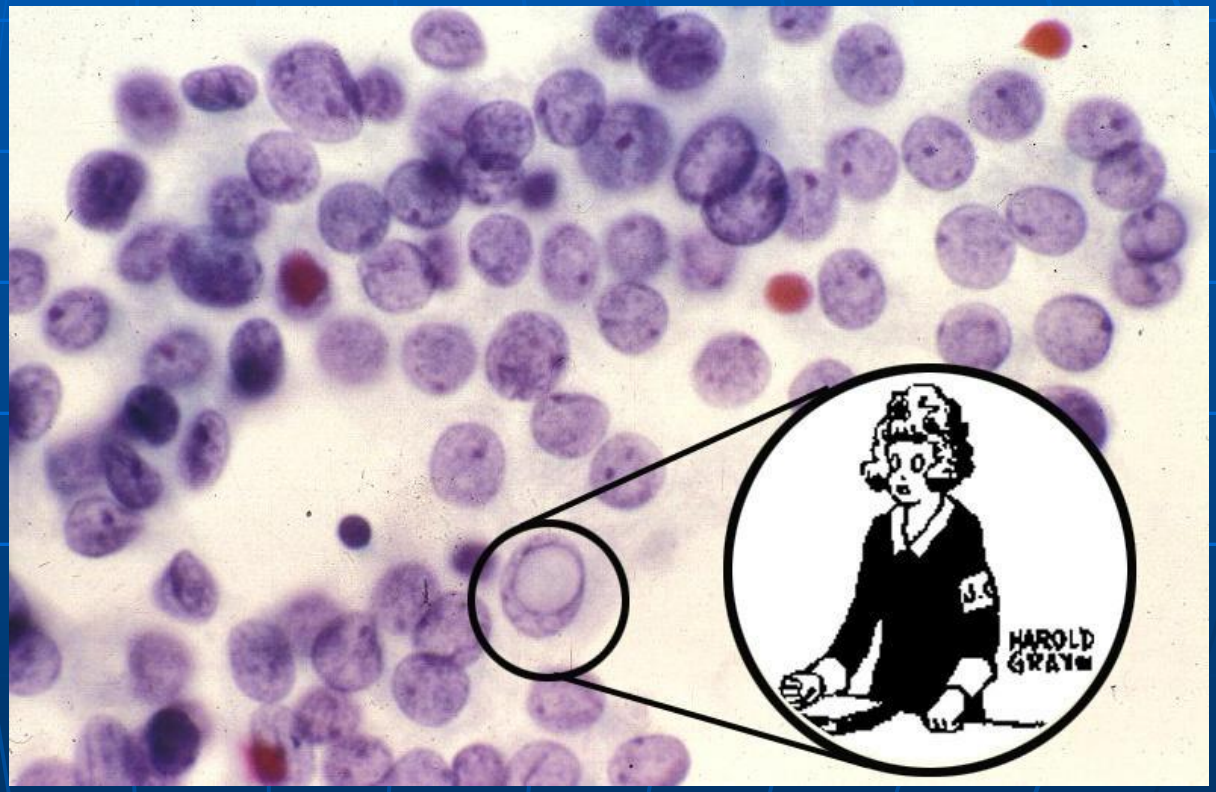


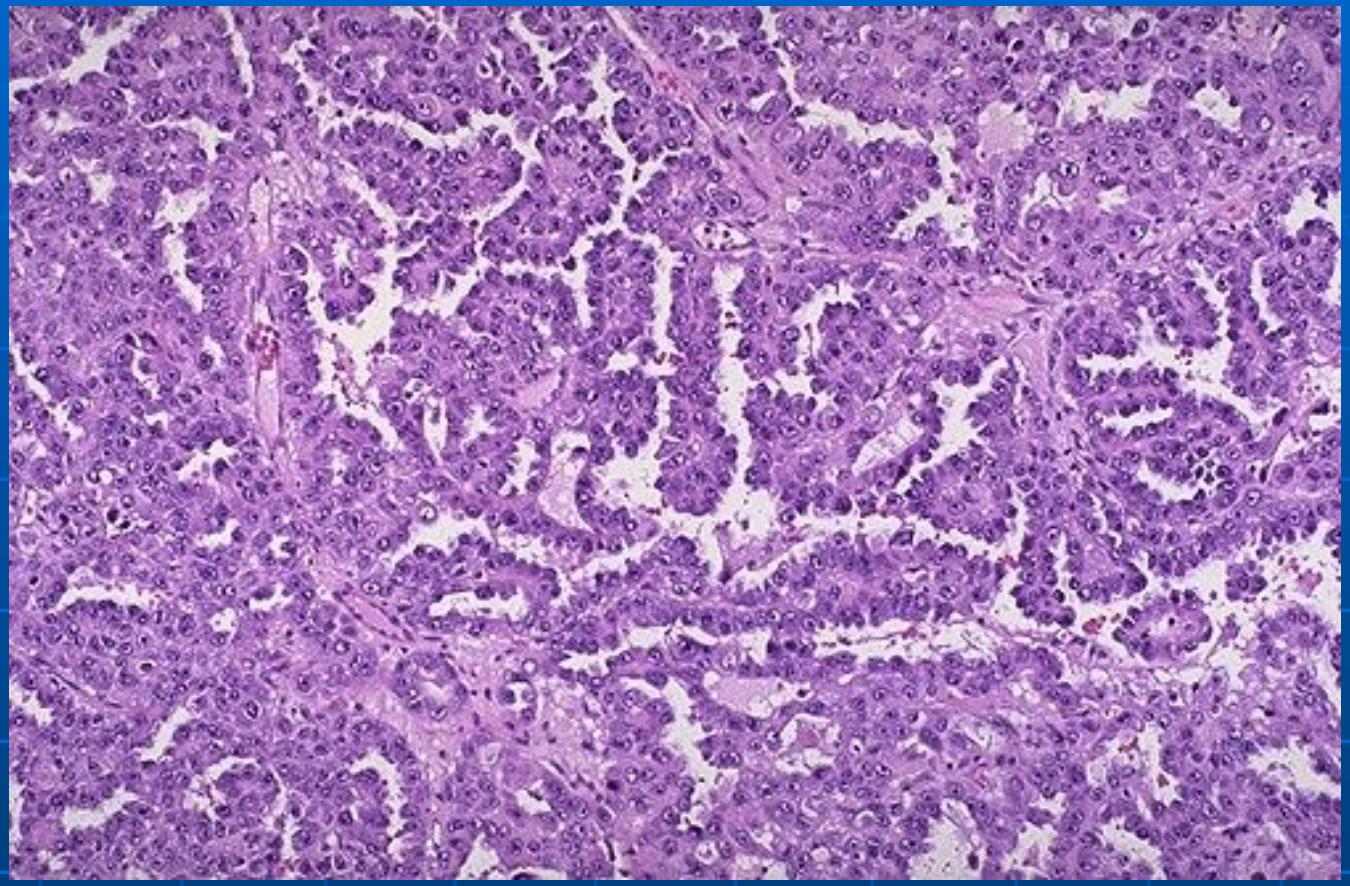
- Sectioning through a lobe of excised thyroid gland reveals papillary carcinoma. This neoplasm can be multifocal, as seen here, because of the propensity to invade lymphatics within thyroid, and lymph node metastases are common. The larger mass is cystic and contains papillary excresences. These tumors most often arise in middle-aged females.



Orphan Annie Nuclei

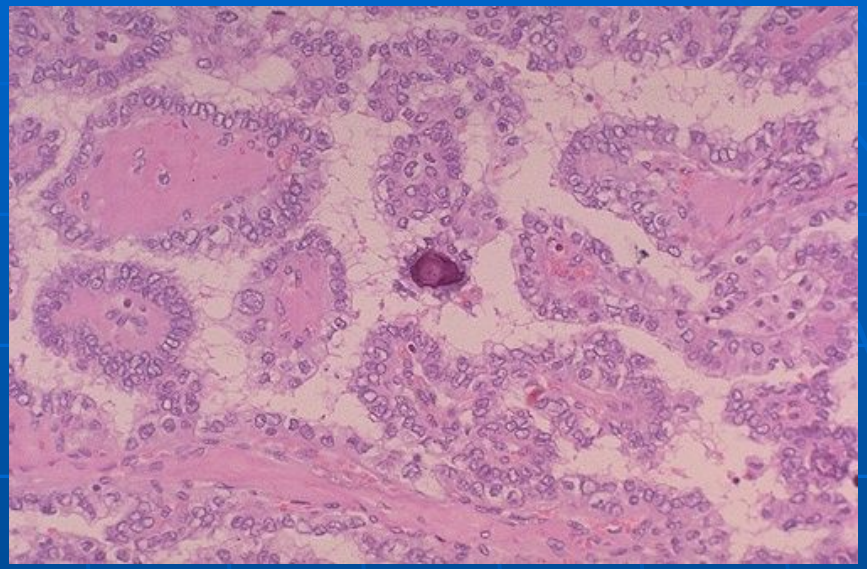
- Needle aspirates
- Open eyed nuclei
- indicative of papillary ca

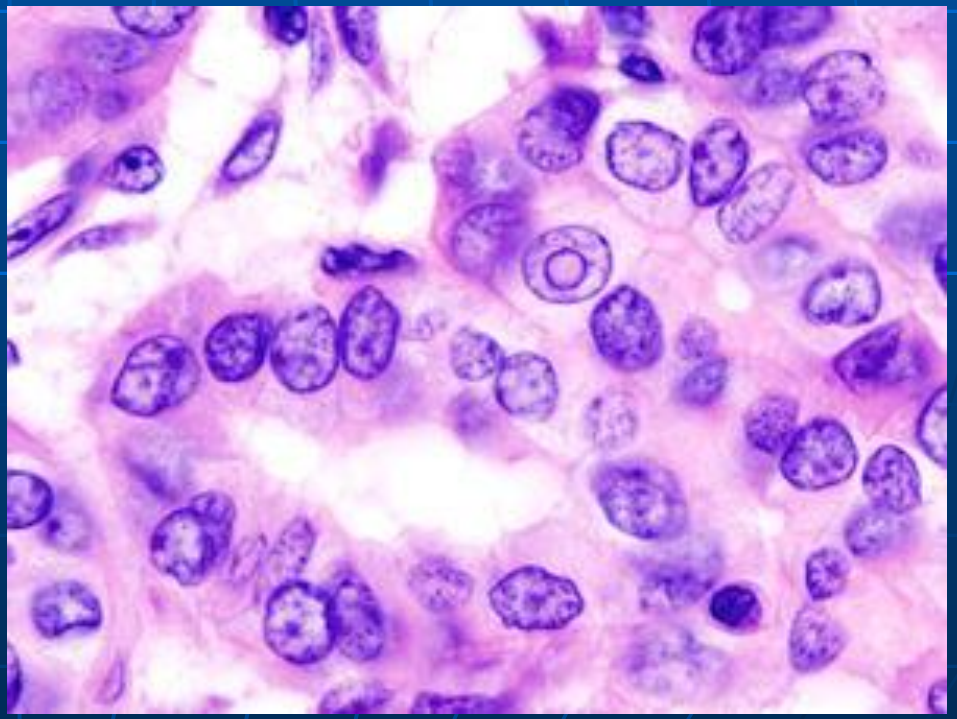




- This is the microscopic appearance of a papillary carcinoma of the thyroid. The fronds of tissue have thin fibrovascular cores. The fronds have a papillary pattern. There is no such thing as a papillary adenoma, and all papillary neoplasms of the thyroid should be considered malignant.

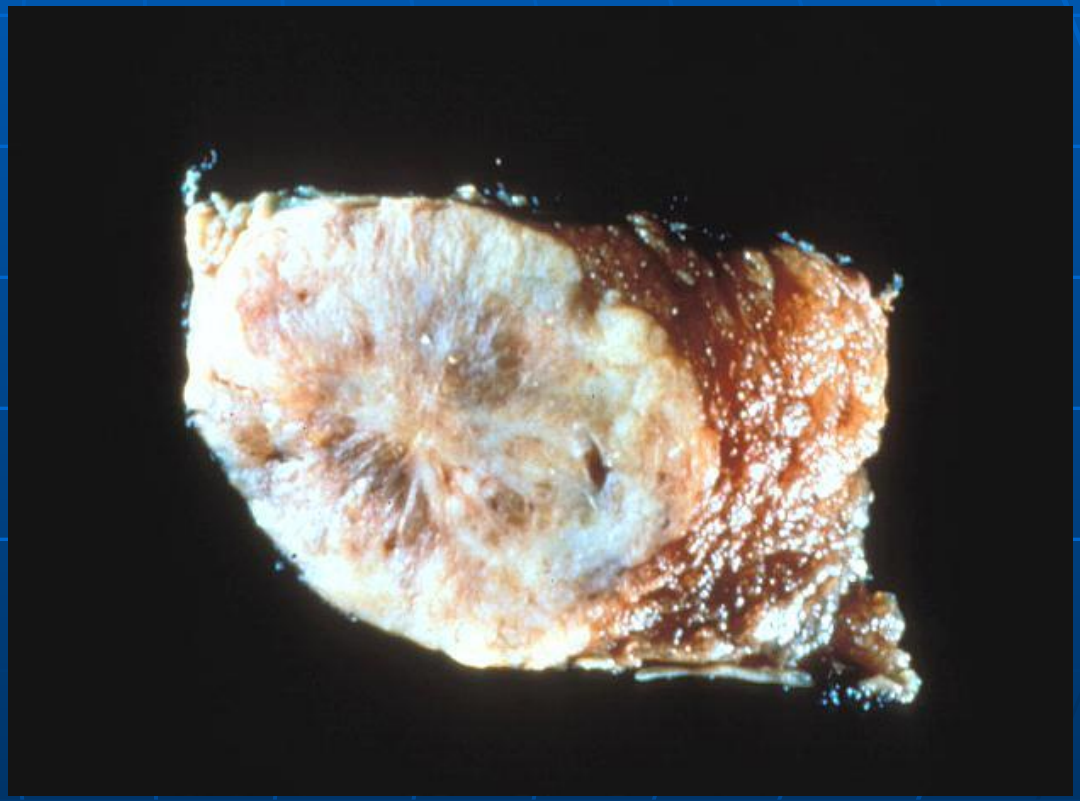
- This is another papillary carcinoma of thyroid. Note the small psammoma body in the center. The cells of the neoplasm have clear nuclei. Papillary carcinomas are indolent tumors that have a long survival, even with metastases. The most favorite site of metastasis is to local lymph nodes in the neck. In fact, some papillary carcinomas may first present as nodal metastases.



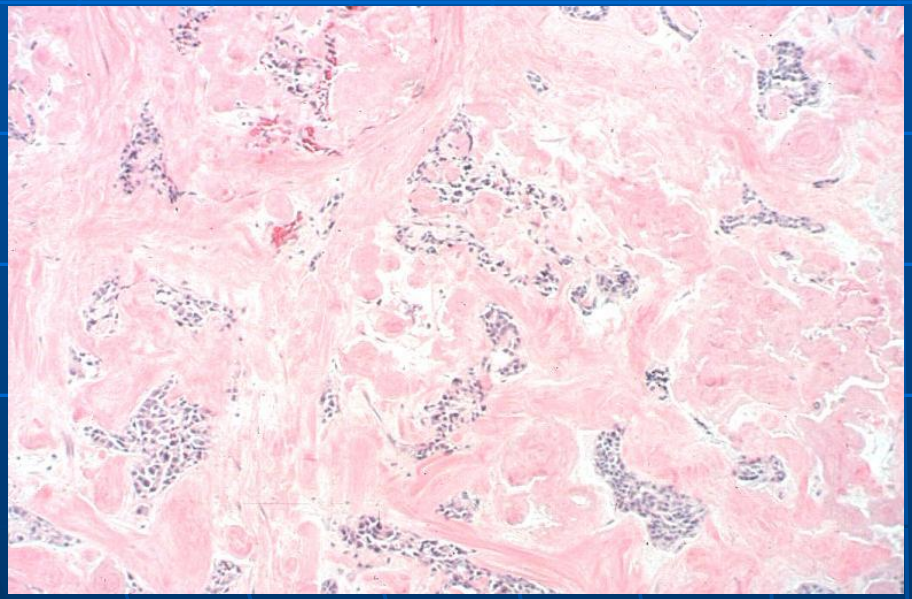


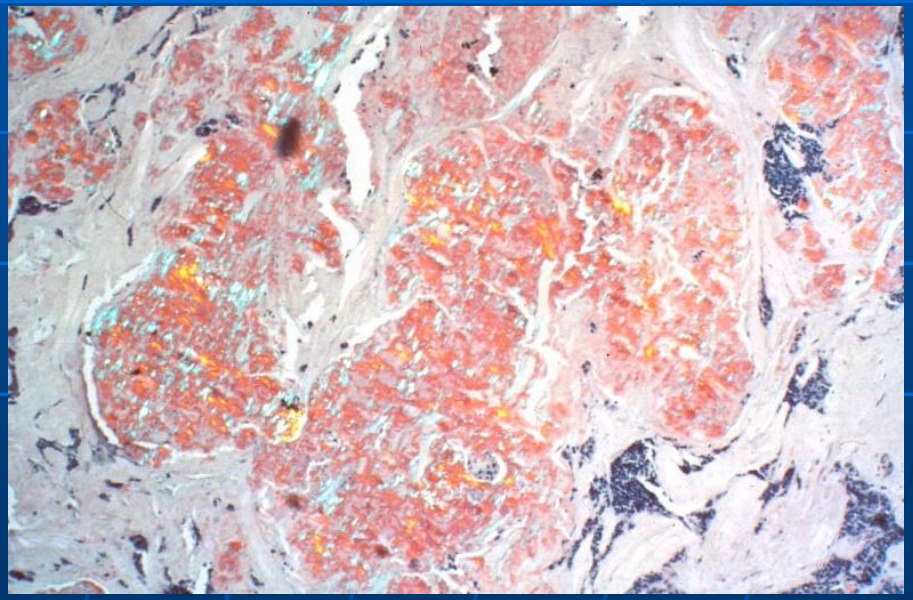
C Cell Carcinoma

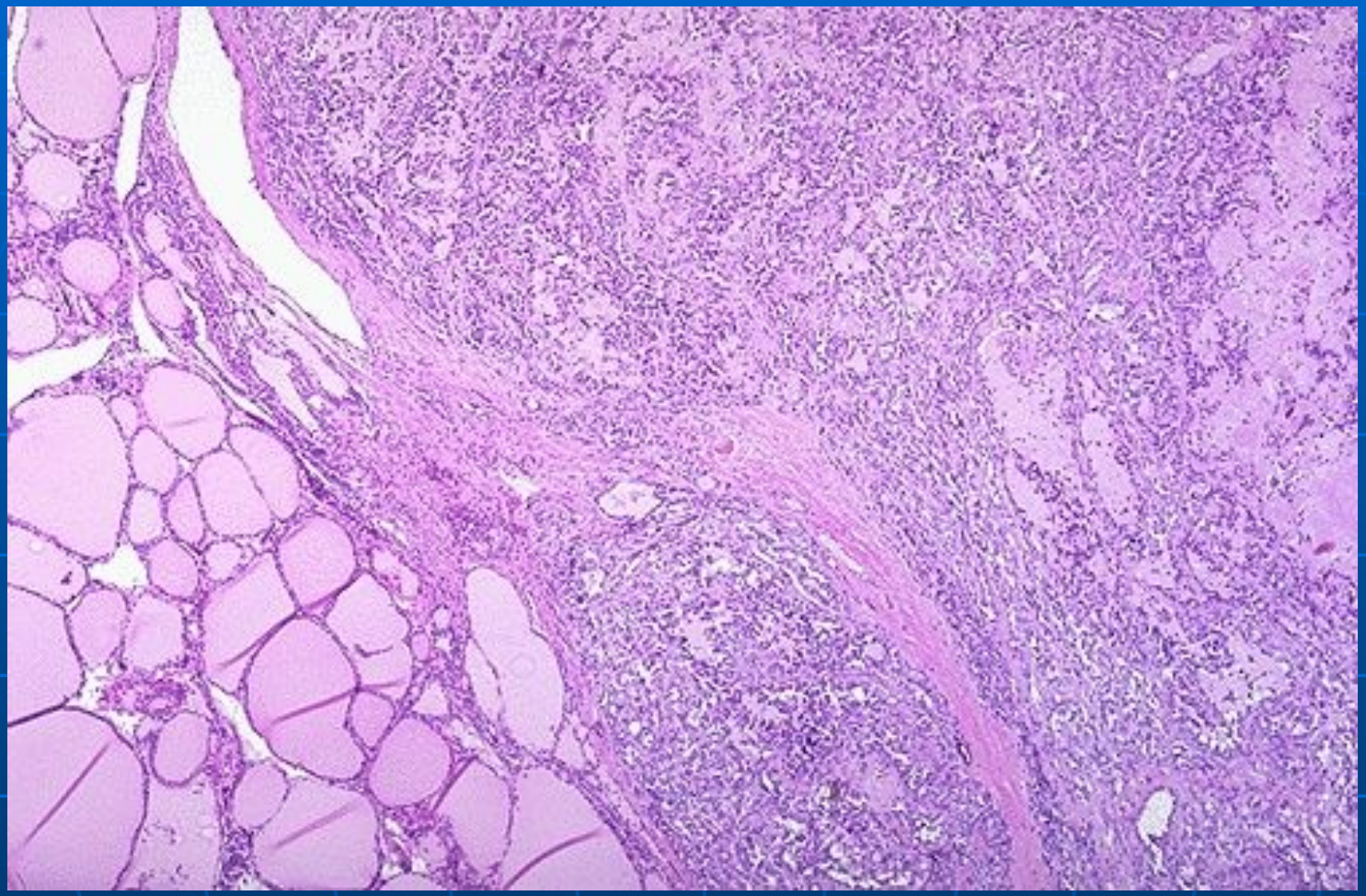
- Interstitial cells
- Makes calcitonin
- Makes amyloid
  - Beta pleated sheet protein
- Often part of a multiple endocrine neoplasia syndrome



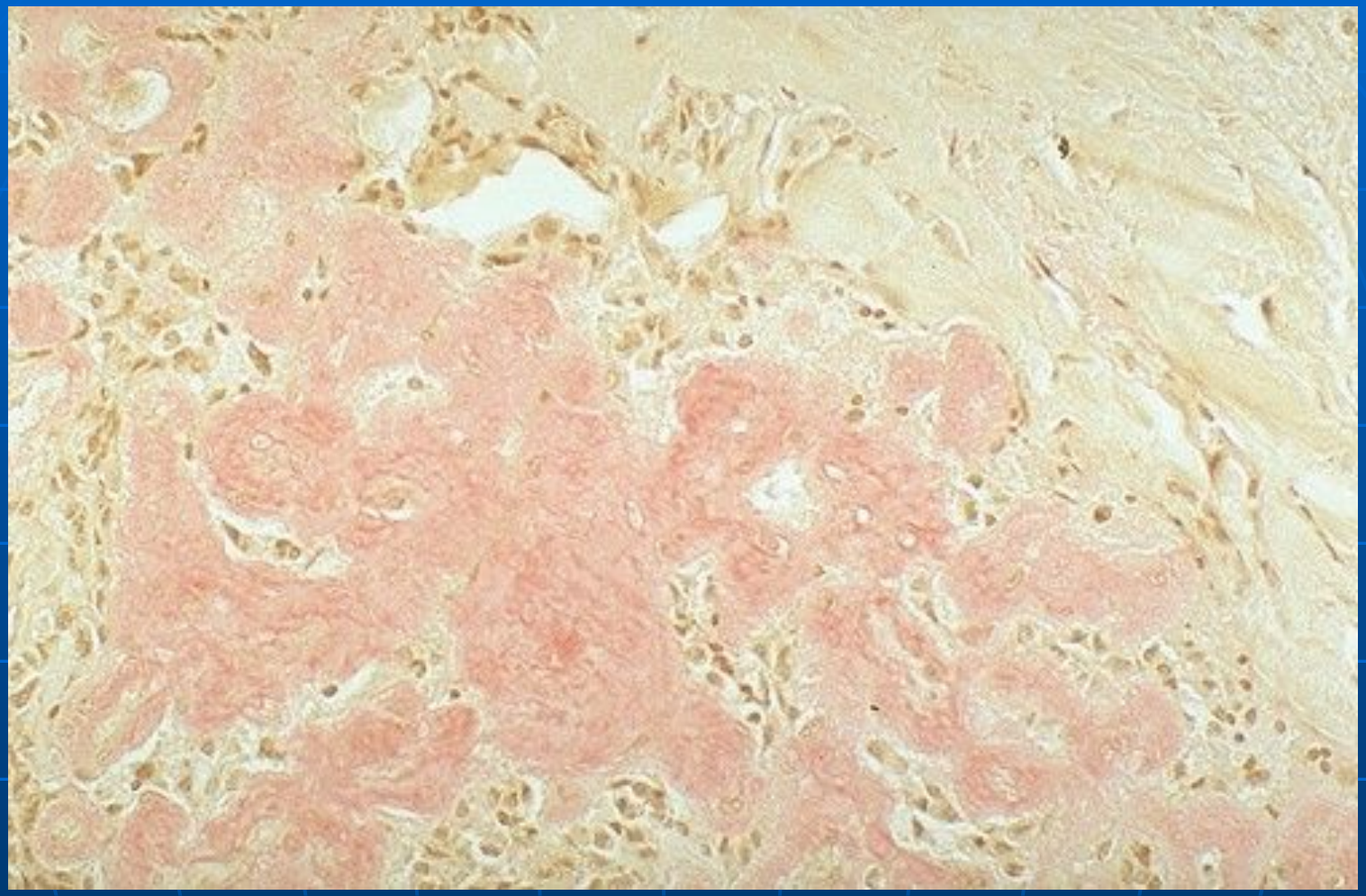
C Cell Carcinoma



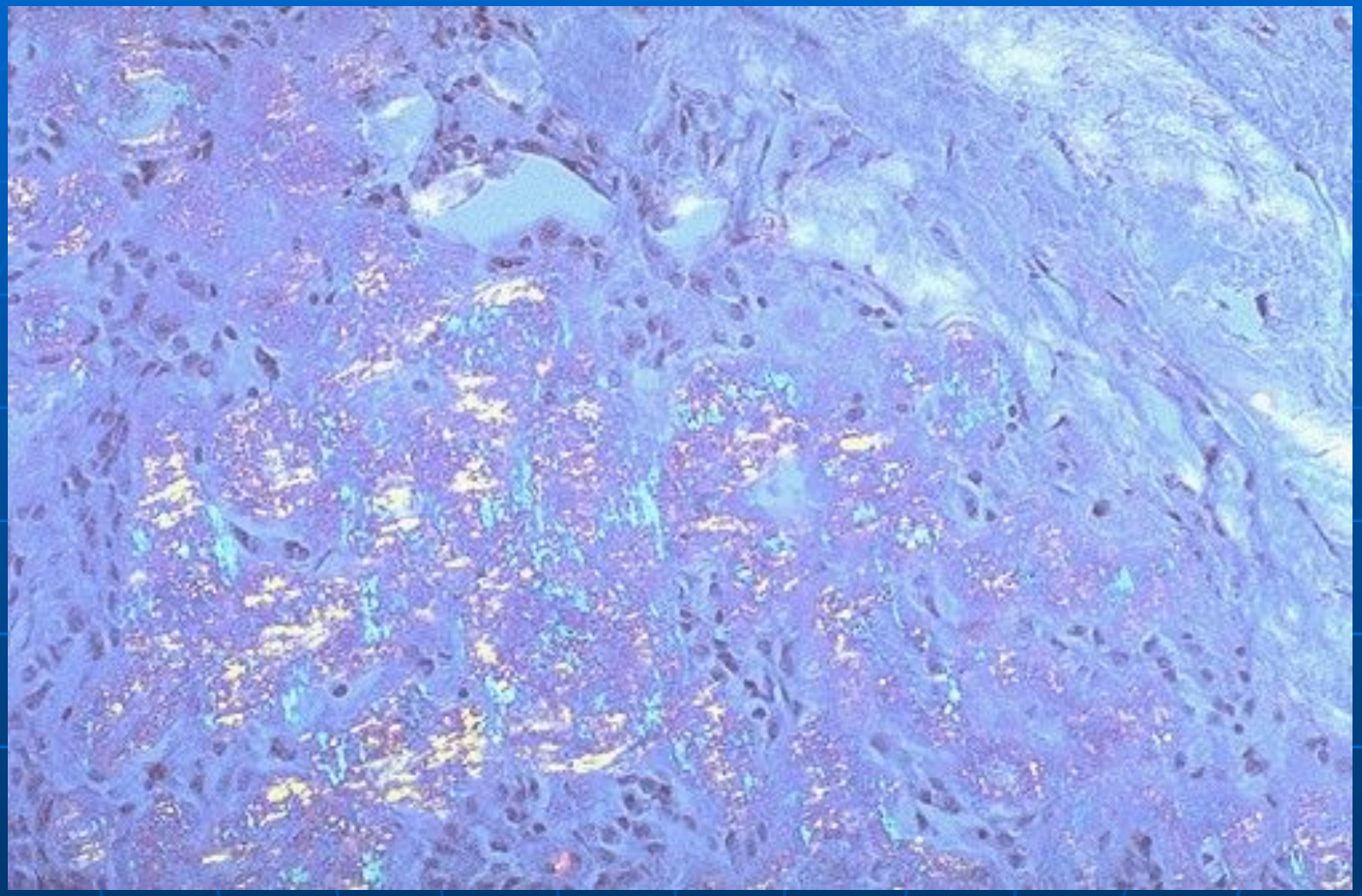




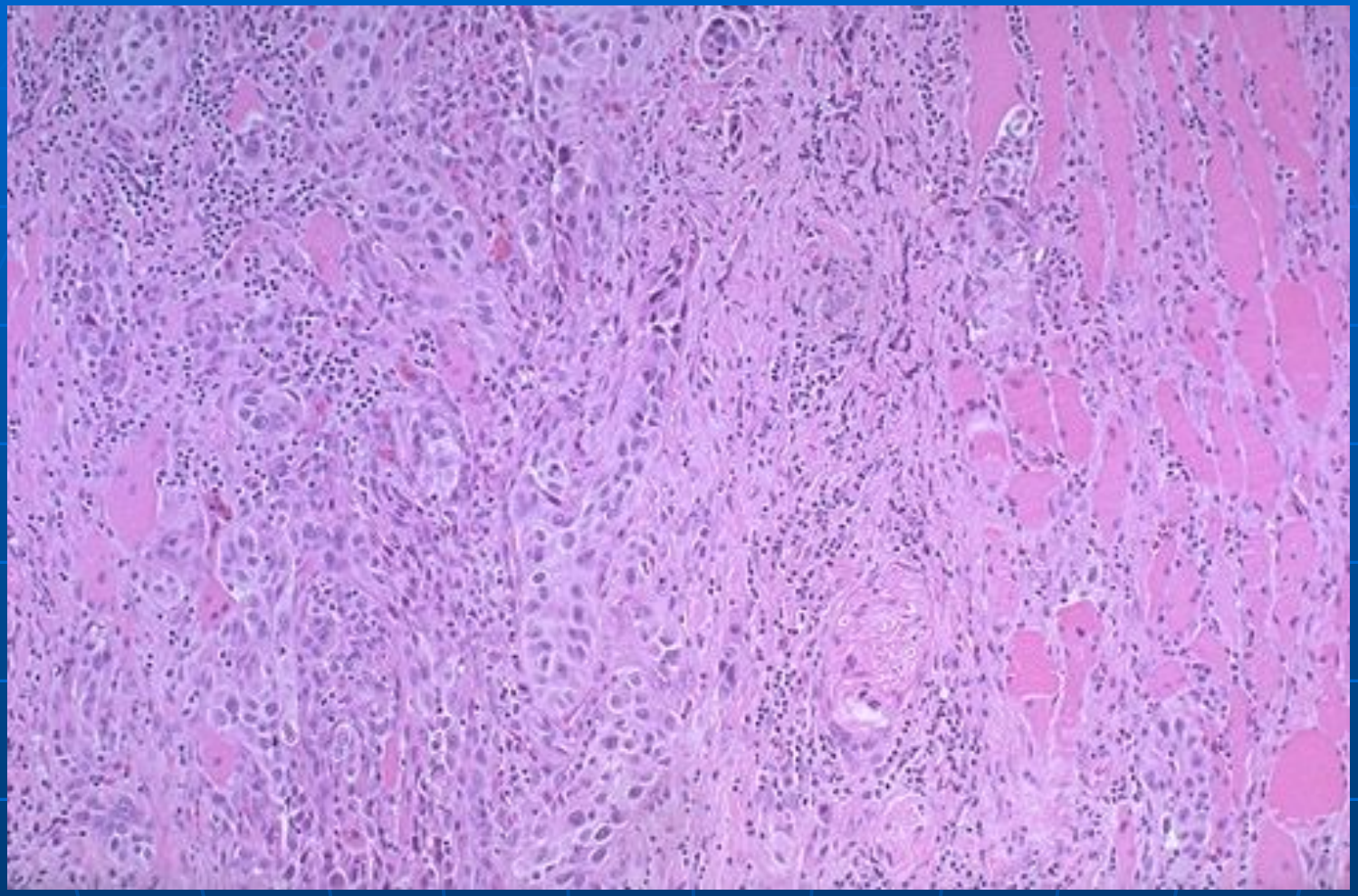
- At the center and to the right is a medullary carcinoma of thyroid. At the far right is pink hyaline material with the appearance of amyloid. These neoplasms are derived from the thyroid "C" cells and, therefore, have neuroendocrine features such as secretion of calcitonin.



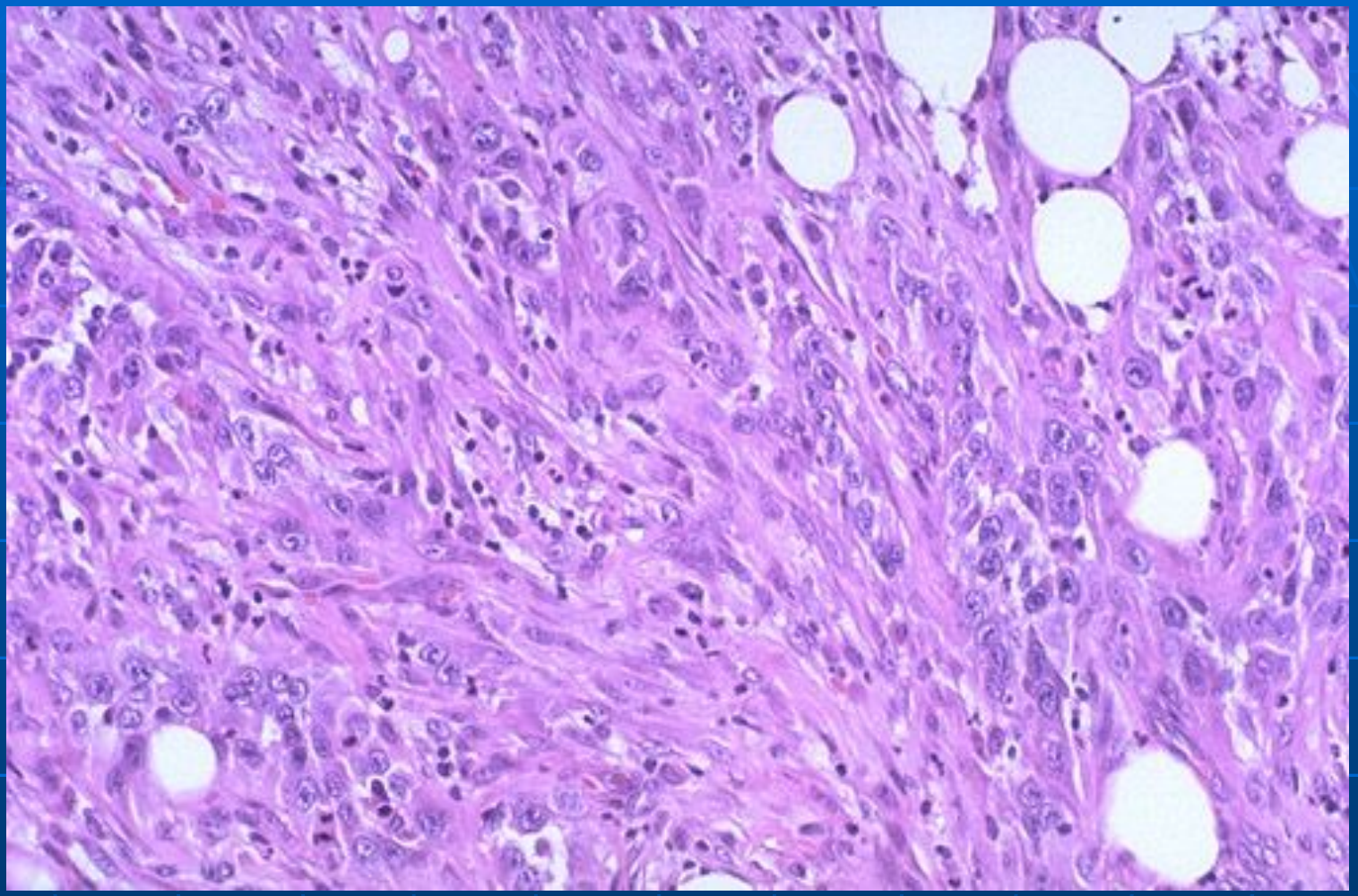
- Here the amyloid stroma of the medullary thyroid carcinoma has been stained with Congo red. Medullary carcinomas can be sporadic or familial. The familial kind are associated with multiple endocrine neoplasia syndrome.



- This is the Congo red stained amyloid stroma of the medullary carcinoma under polarized light, which produces a pale greenish appearance.



- The anaplastic carcinoma shown here is invading into skeletal muscle fibers at the right. This is the most aggressive thyroid cancer, and luckily the least common.

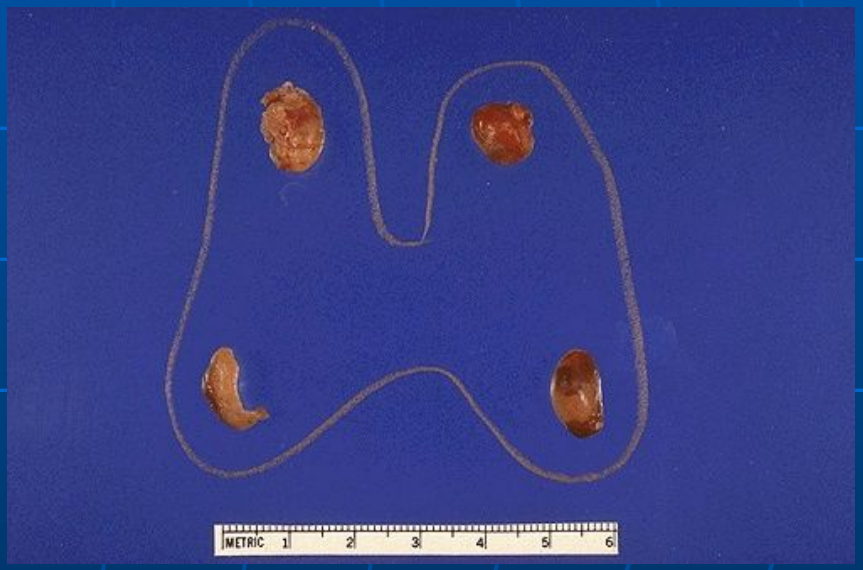


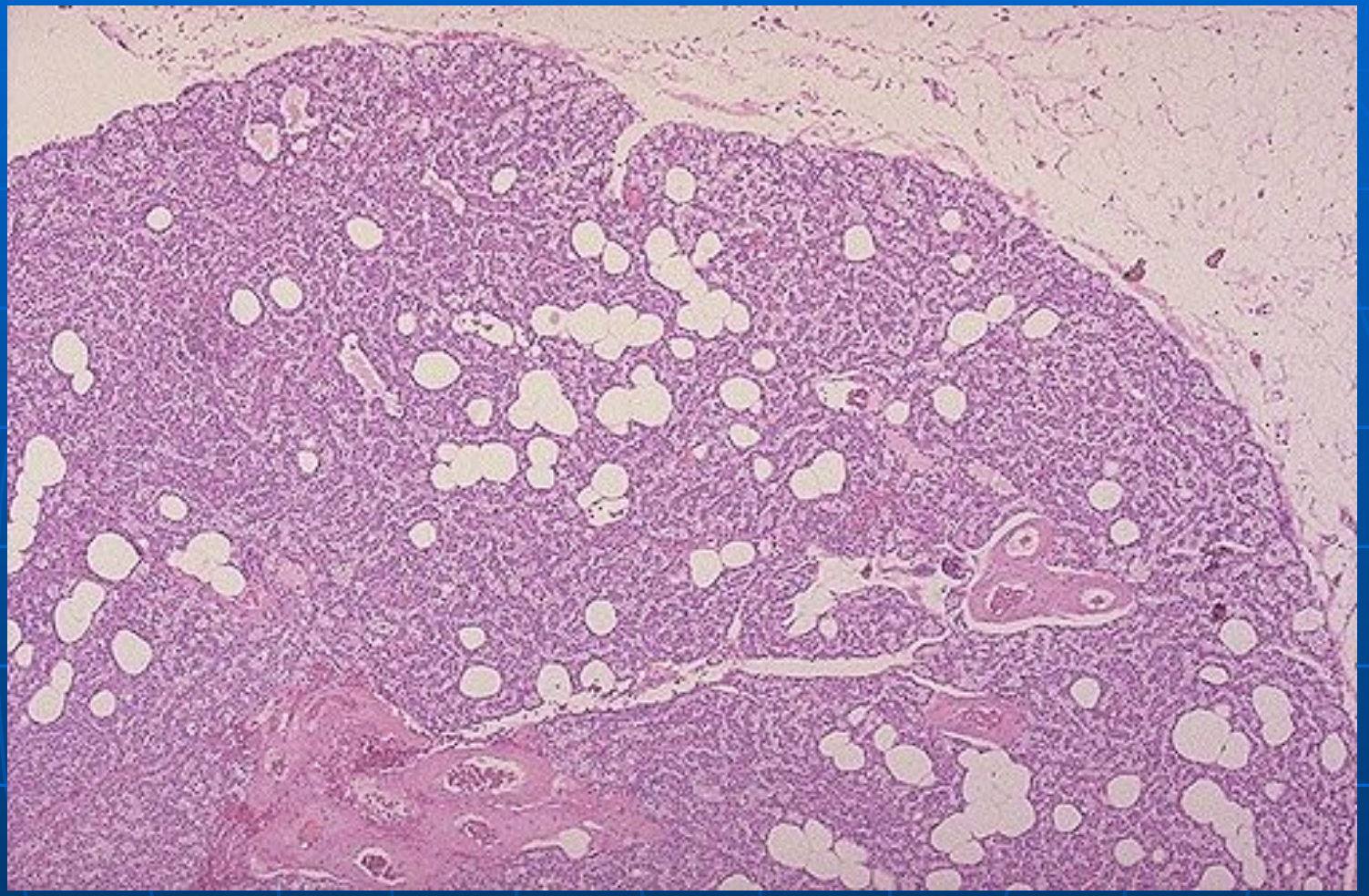
- There is no resemblance to normal thyroid tissue-hence the term "anaplastic" to characterize this thyroid carcinoma. Note the elongated spindle cells.

Parathyroid

- Come from the pharyngeal pouches
- Most of us have 4
- Make PTH
- Mobilizes calcium
- Released by low serum calcium
- High serum phosphate

- Parathyroid hyperplasia is shown here. Three and one-half glands have been removed (only half the gland at the lower left is present). Parathyroid hyperplasia is the second most common form of primary hyperparathyroidism, with parathyroid carcinoma the least common form.

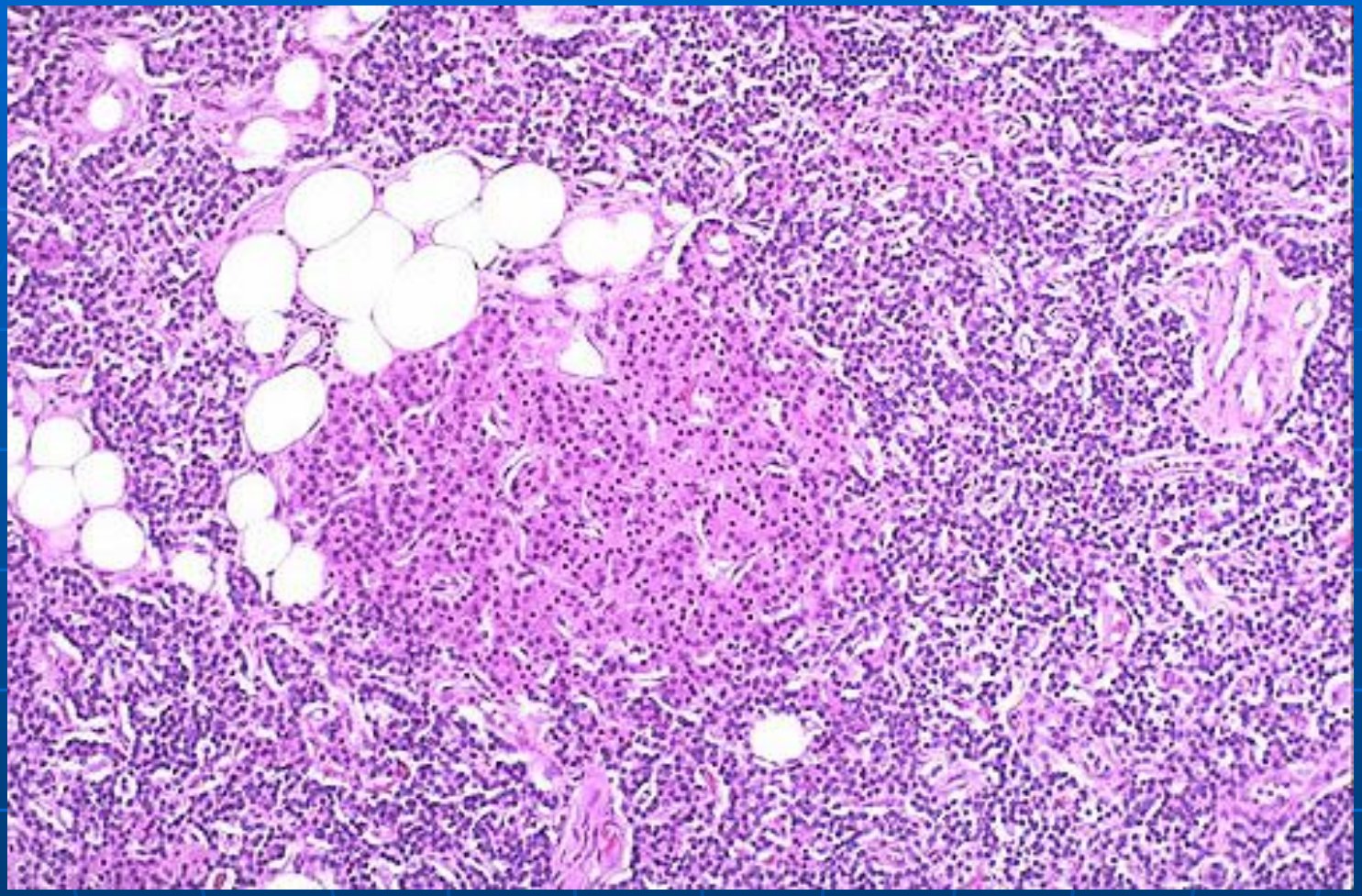




- Here is a normal parathyroid gland. Variable numbers of steatocytes are mixed with the parathyroid tissue. There is a rich vascular supply, as with all endocrine tissues that secrete their hormonal products directly into the bloodstream.

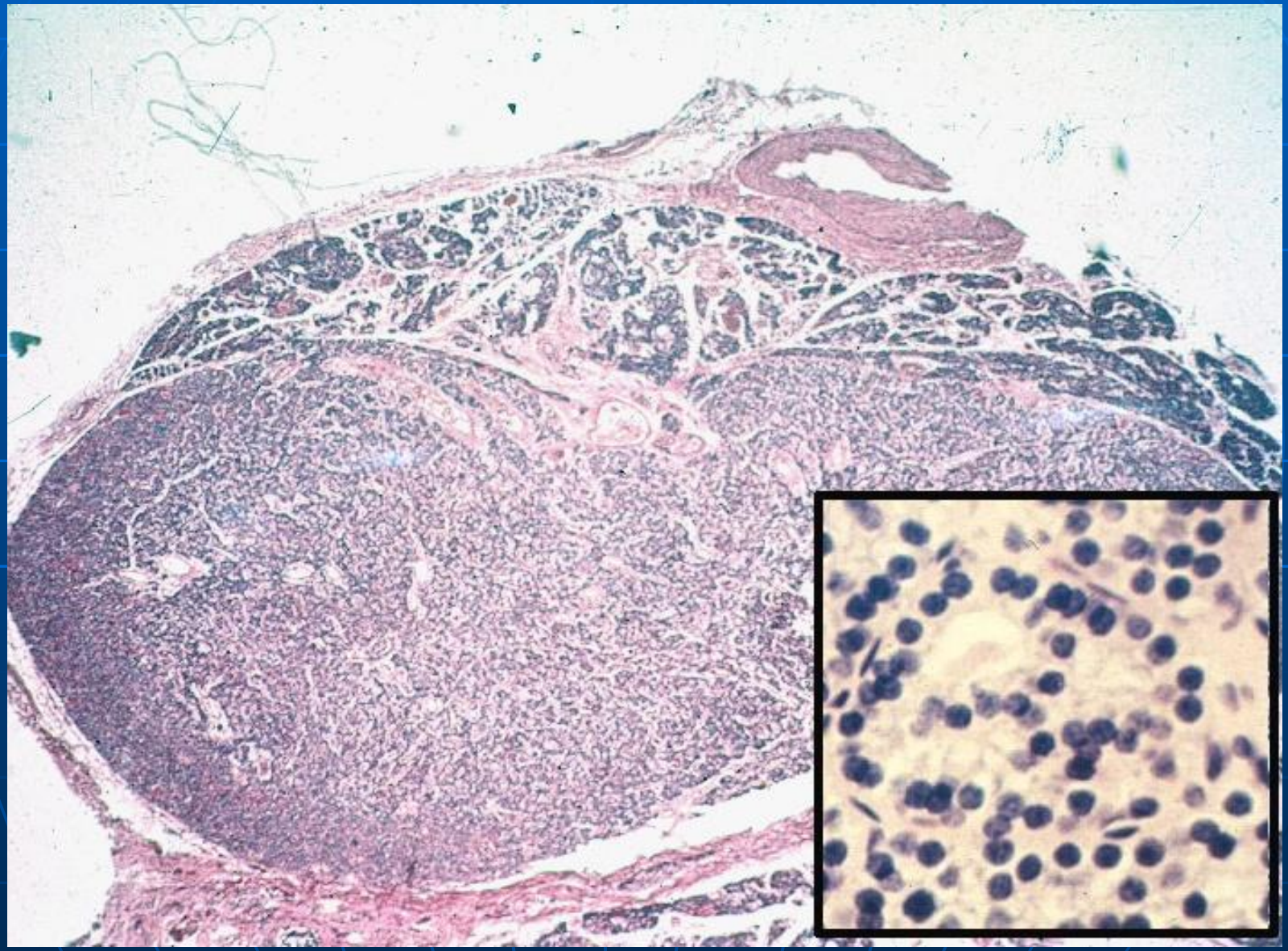
Hyperparathyroidism

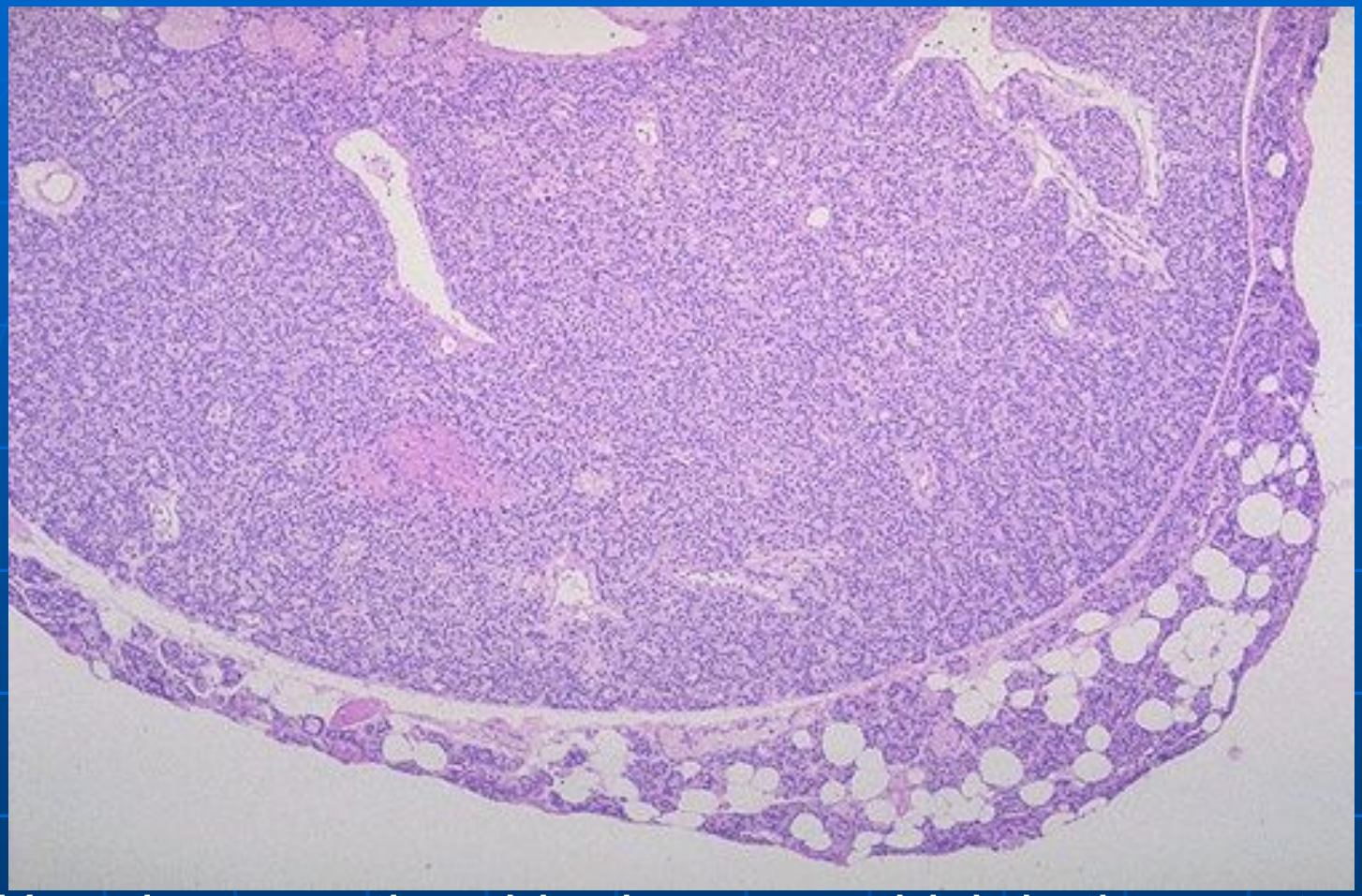
- Primary
  - Parathyroid adenoma 80%
  - Hyperplasia 10-15%
  - Parathyroid ca <5%
- Hypercalcemia
  - Stones, bones, abdominal groans and psychic moans
  - Bone wasting
    - Generalized
    - Osteoitis fibrosa cystica



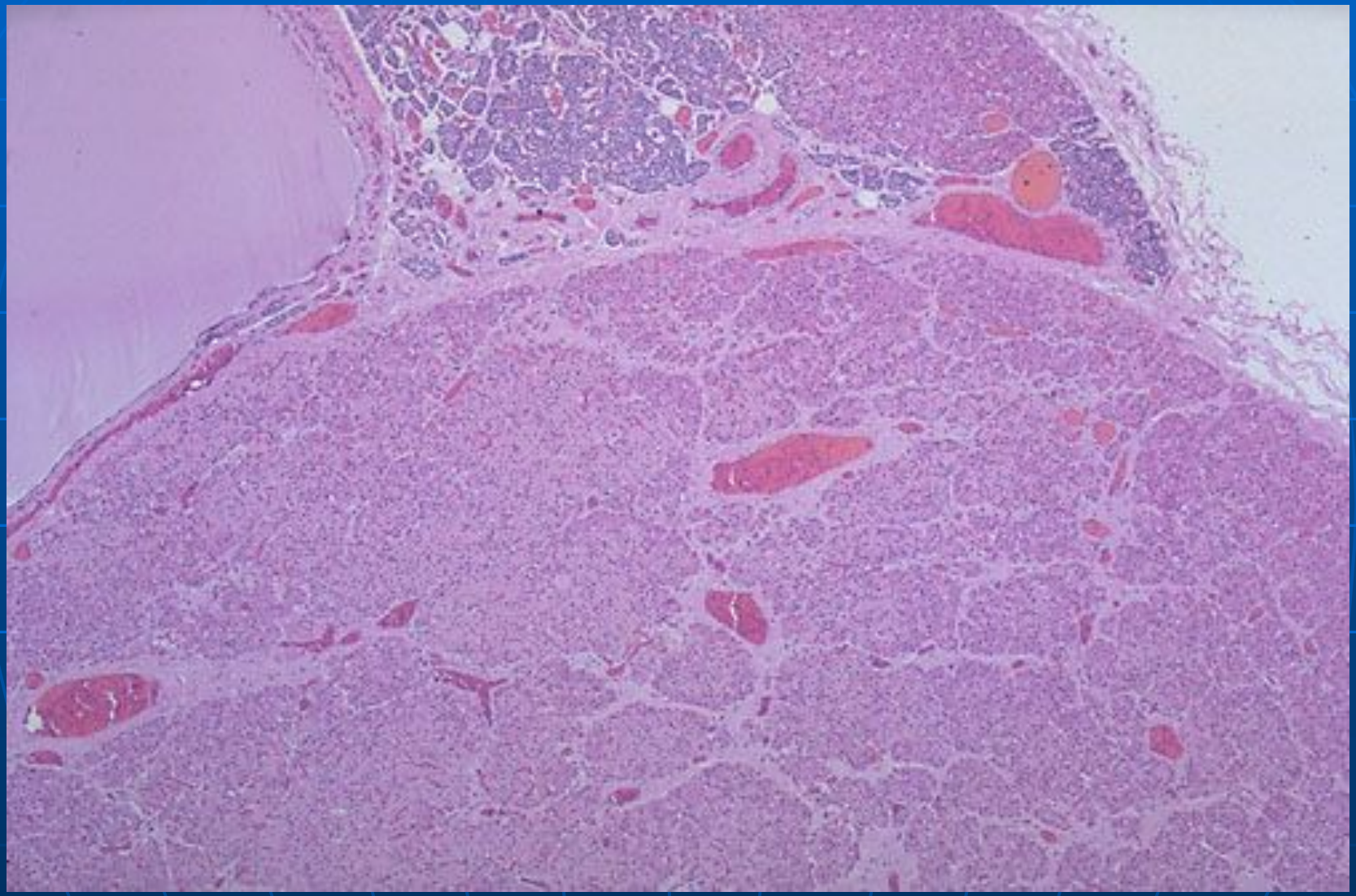
- In parathyroid hyperplasia, there is little or no adipose tissue, but any or all cell types normally found in parathyroid are present. Note the pink oxyphil cells here. This is actually "secondary hyperparathyroidism" with enlarged glands as a consequence of chronic renal failure with impaired phosphate excretion. The increased serum phosphate tends to drive serum calcium down, which in turn drives the parathyroids to secrete more parathormone.

Parathyroid Adenoma





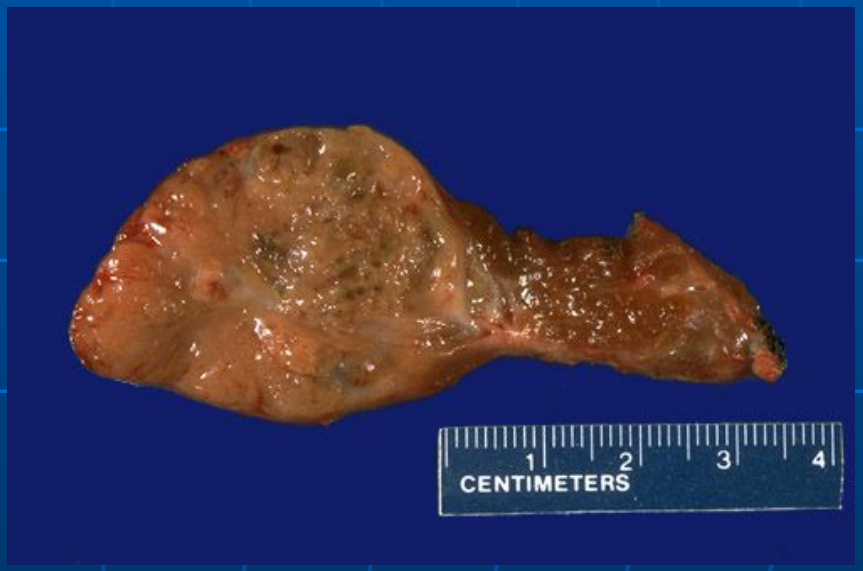
- Here is a parathyroid adenoma, which is the most common cause for primary hyperparathyroidism. A rim of normal parathyroid tissue admixed with adipose tissue cells is seen compressed to the right and lower edge of the adenoma.

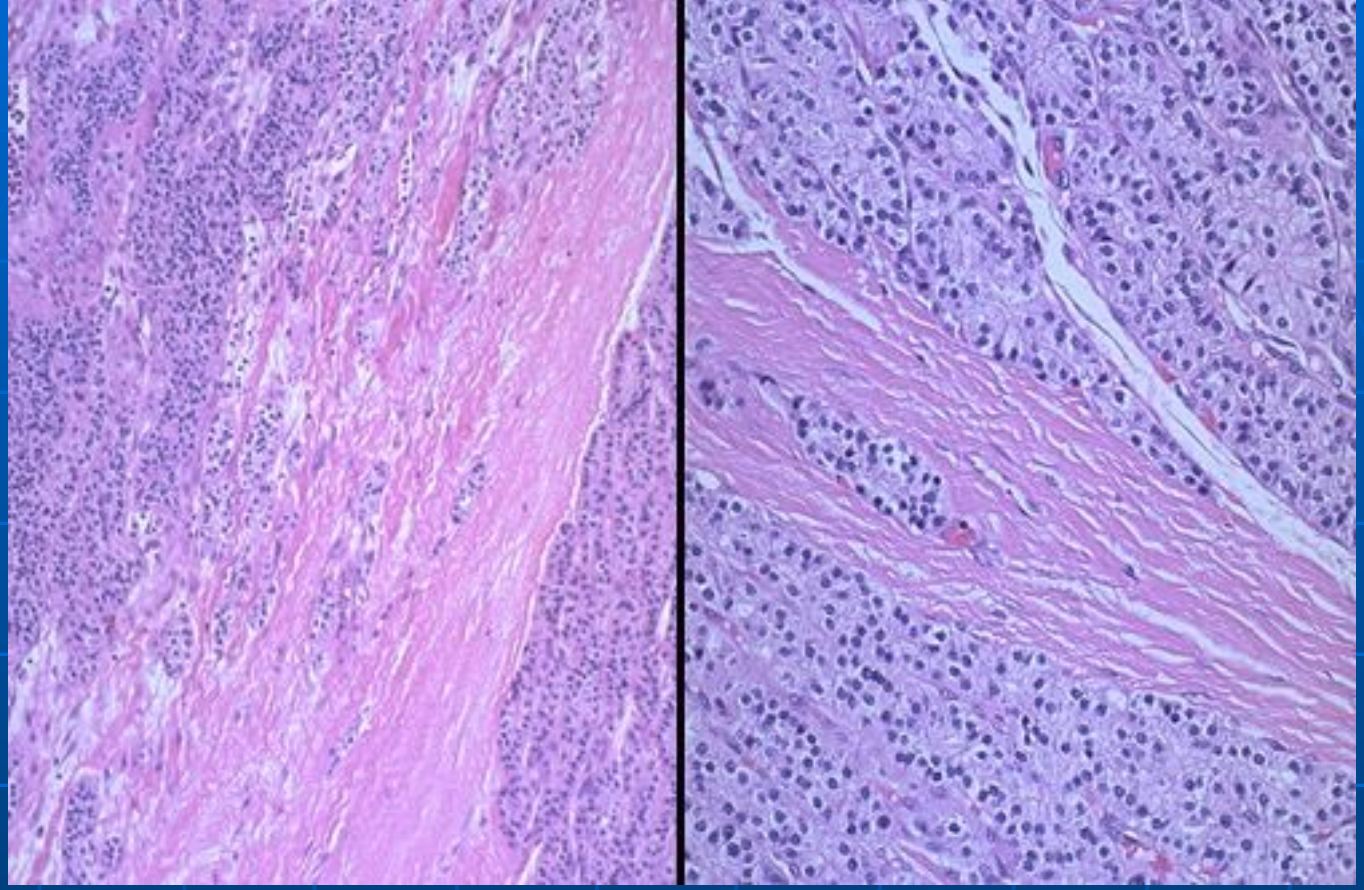


Secondary Hyperparathyroidism

- Renal failure almost always
  - Phosphates build up in the blood.
  - Cause calcium to drop.
    - PTH is made
  - Phosphate itself can cause release of PTH
- Glands begin to function autonomously

- This is the gross appearance of a parathyroid carcinoma. The serum calcium can be quite high. Note the large size and irregular cut surface. These carcinomas have a tendency to invade surrounding tissues in the neck, complicating their removal.





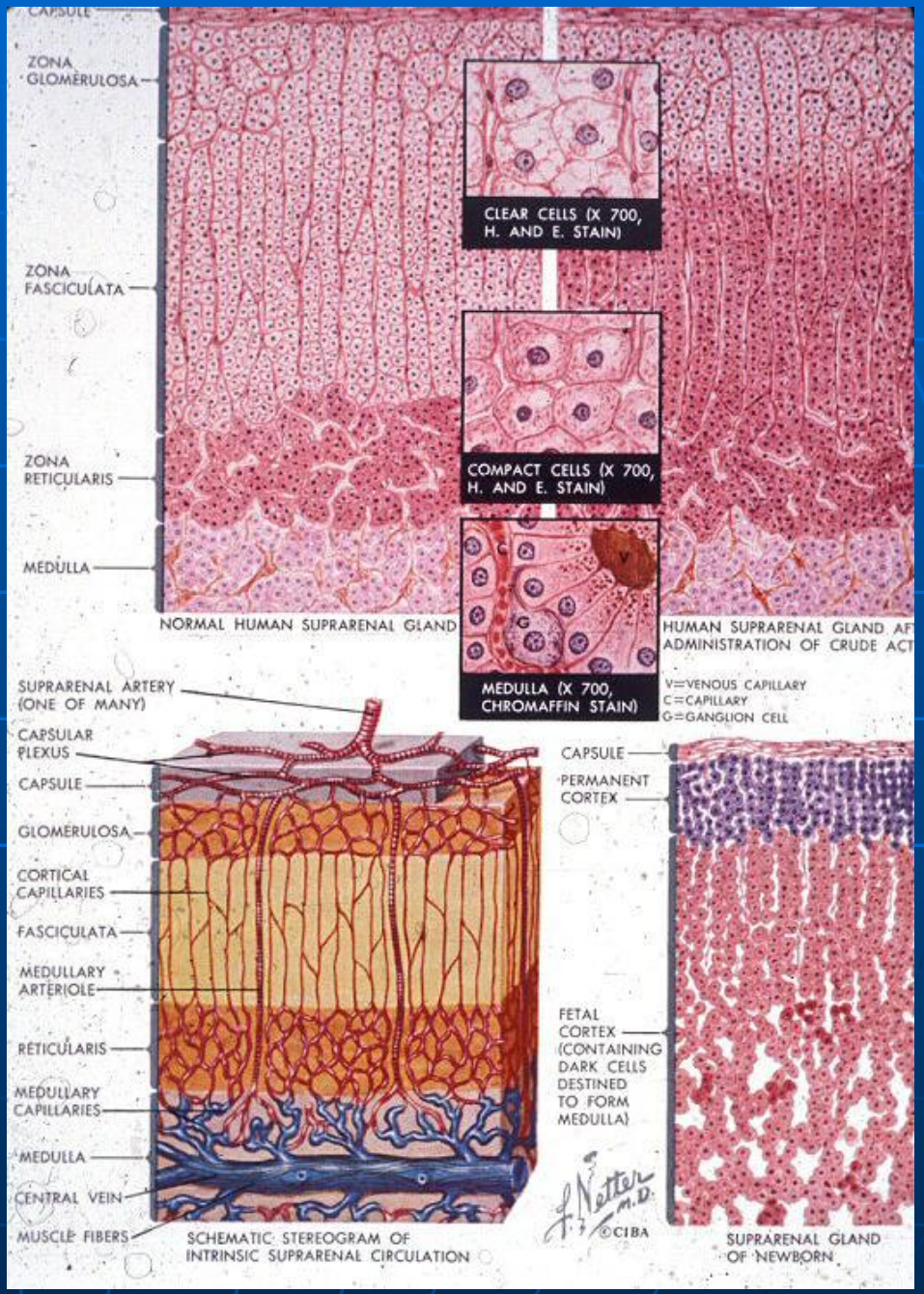
- This is a parathyroid carcinoma seen at medium power on the left and higher power on the right. The nests of neoplastic cells that are not very pleomorphic. Note the bands of fibrous tissue between the nests. Parathyroid carcinomas infiltrate surrounding structures in the neck.

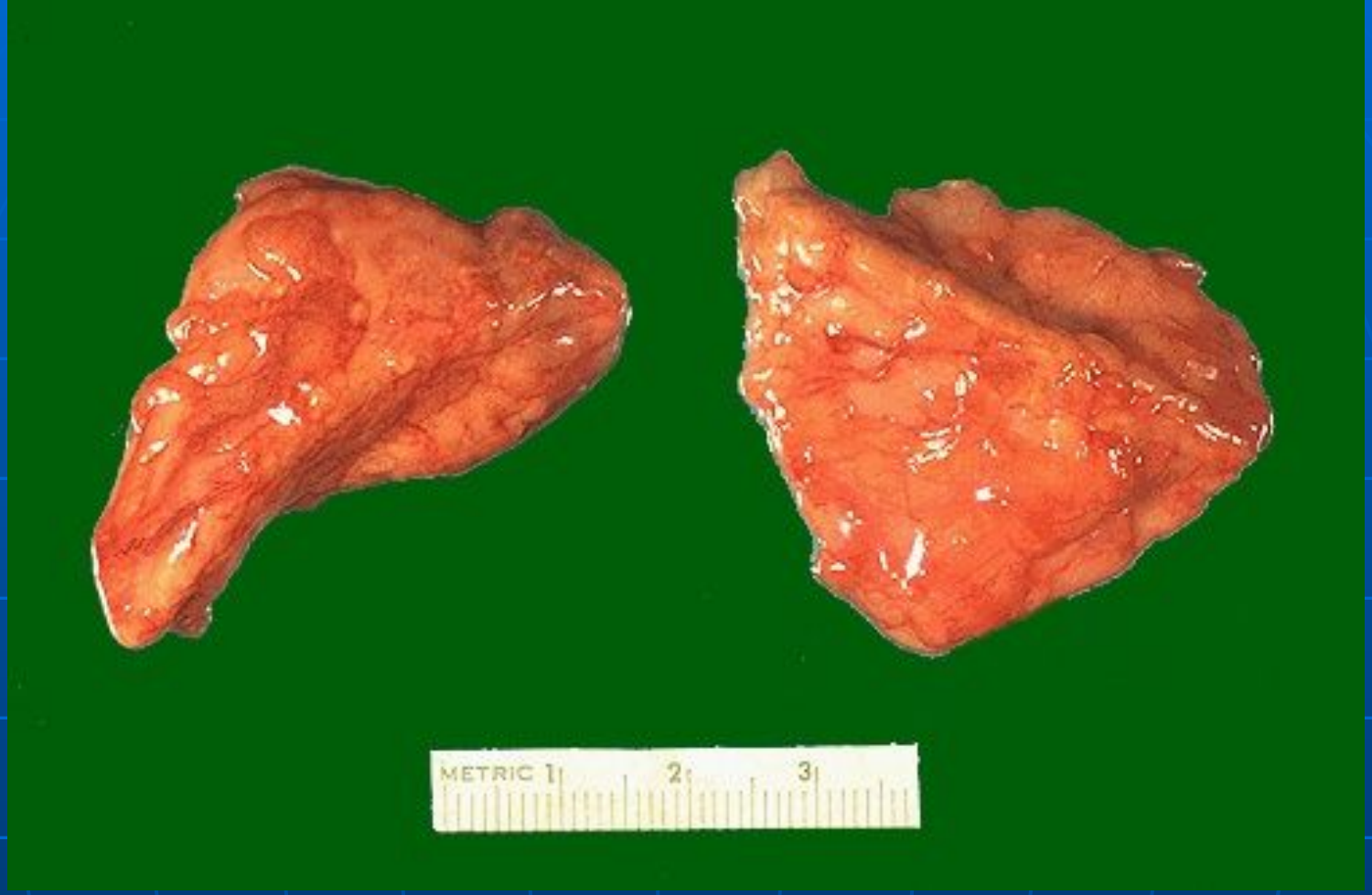
Hypoparathyroidism

- Increased neuromuscular excitability
  - May lead to tetany
- Irritability and possibly even psychosis
- Parkinson-like symptoms
- Cataracts
- Causes
  - Autoimmune destruction
  - Accidental removal with thyroid
  - Congenital absence

Adrenal Gland

- Really two glands in one.
  - Cortex ->
    - Salt
    - Sugar
    - Sex
  - Medulla
    - Epinephrine
    - Norepinephrine





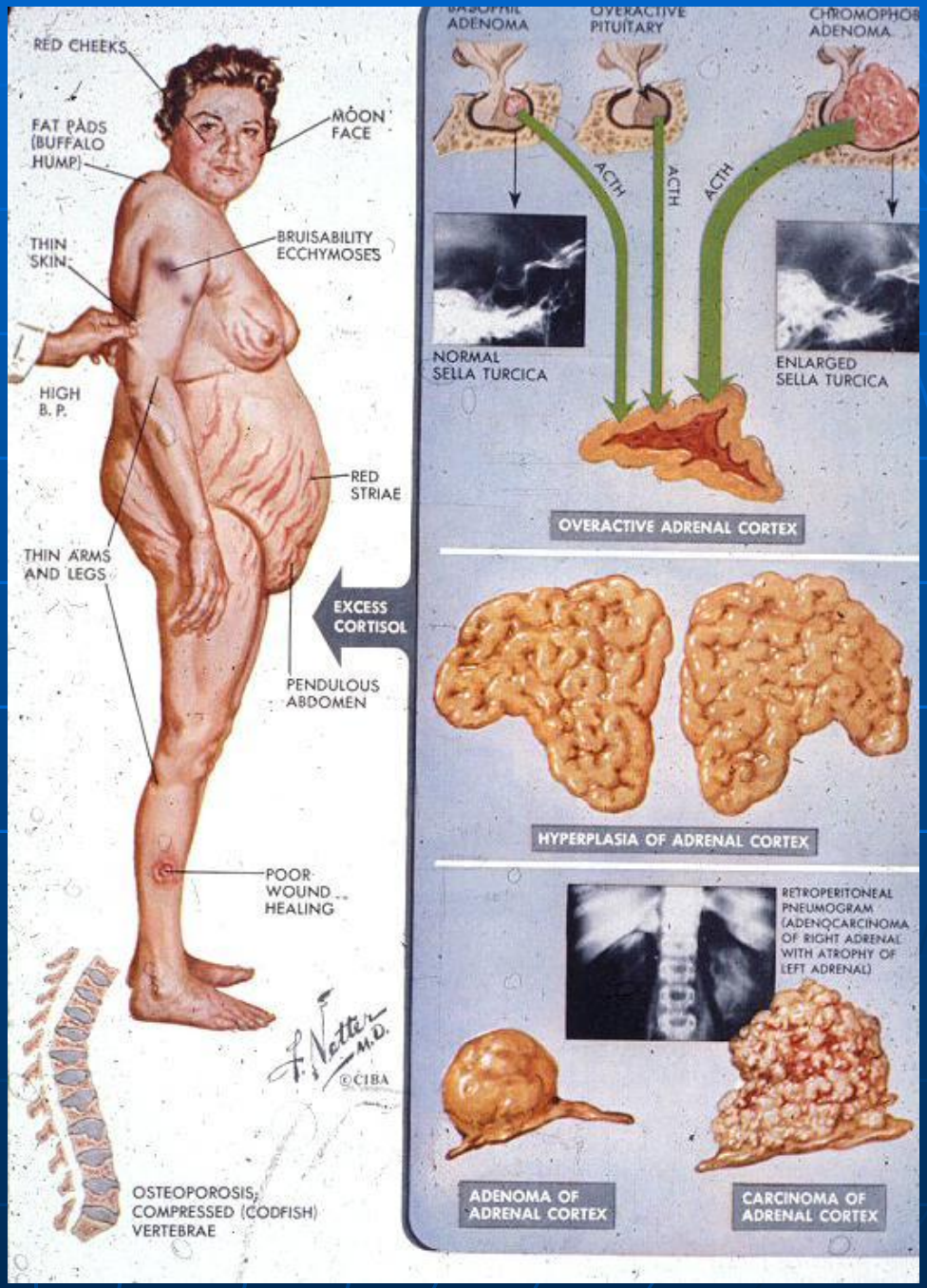
- Here are normal adrenal glands. Each adult adrenal gland weighs from 4 to 6 grams.

- The pair of adrenals in the center are normal. Those at the top come from a patient with adrenal atrophy (with either Addison's disease or long-term corticosteroid therapy). The adrenals at the bottom represent bilateral cortical hyperplasia. This could be due to a pituitary adenoma secreting ACTH (Cushing's disease), or Cushing's syndrome from ectopic ACTH production, or idiopathic adrenal hyperplasia.

- These adrenals are black-red from extensive hemorrhage in a patient with meningococcemia. This produces the Waterhouse-Friderich sen syndrome.

Cushing's Syndrome

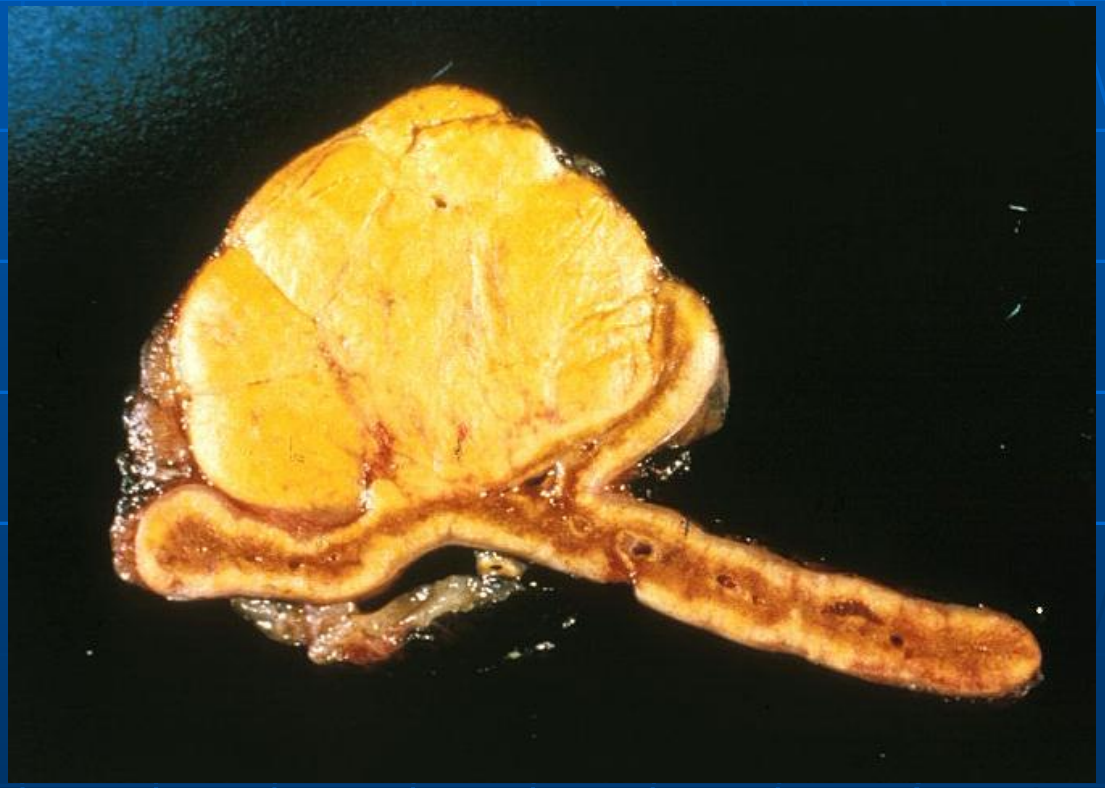
- Effects of too much cortisol
  - Moon face
  - Central obesity
  - Buffalo hump
  - Osteoporosis
    - Fractures
  - Hypertension
  - Weakness



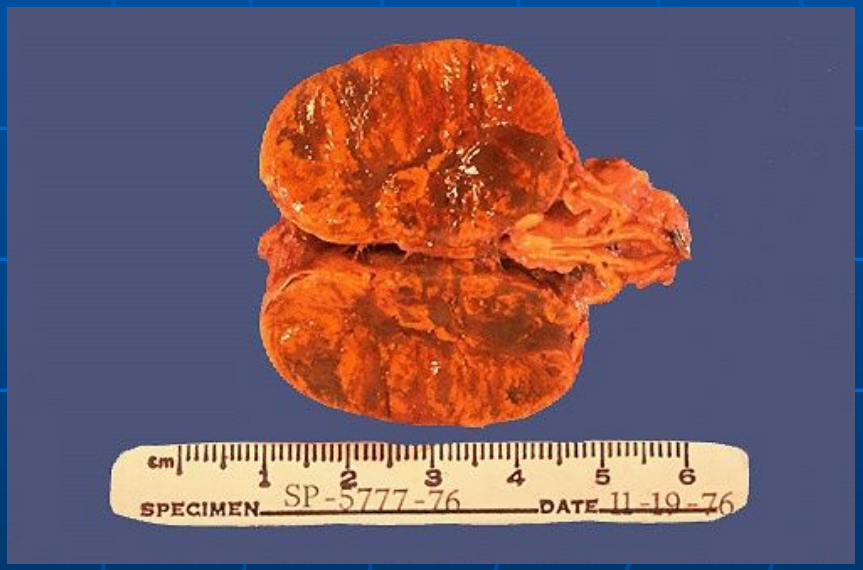
Cushing's Disease

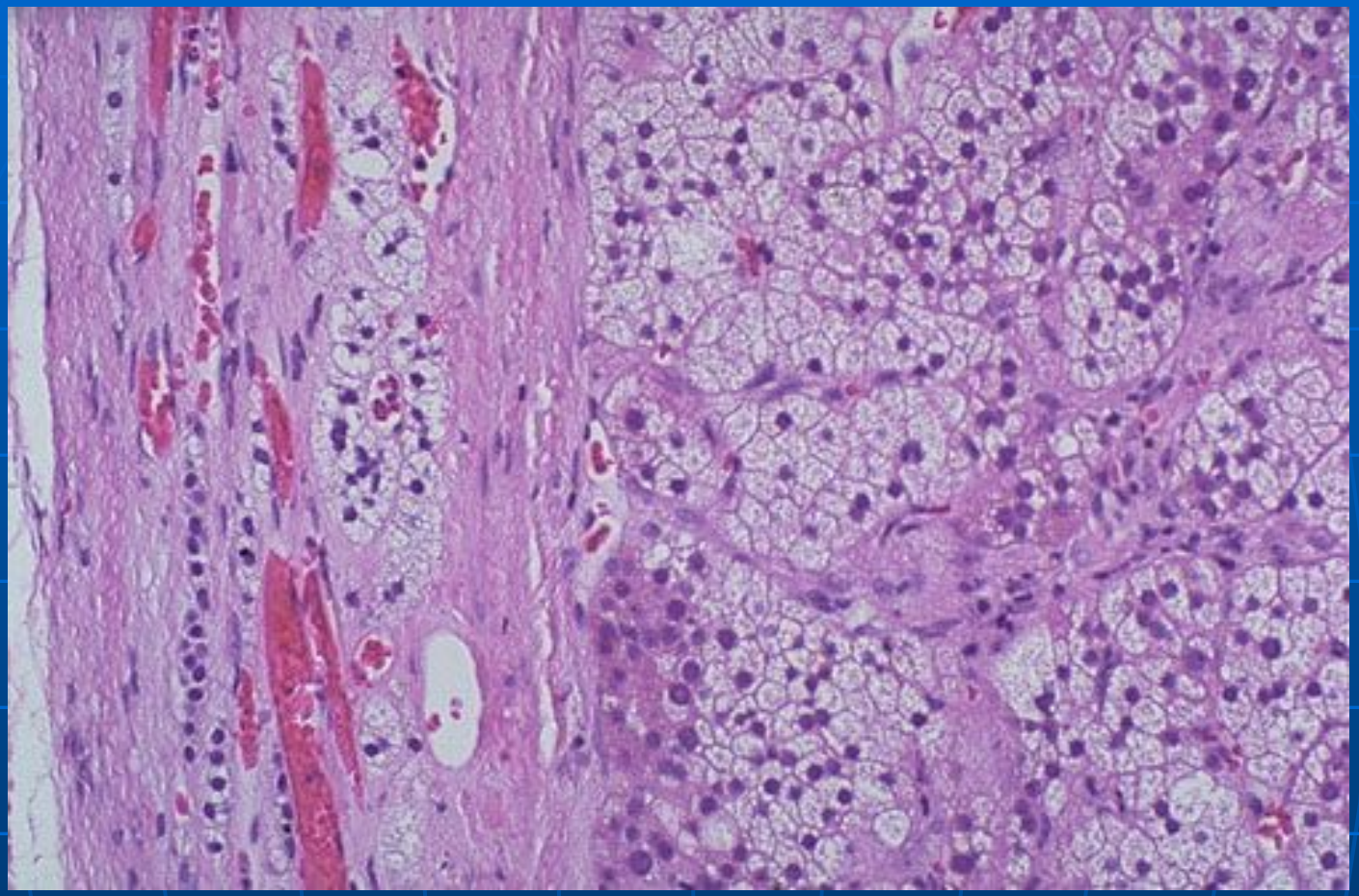
- Altered feedback regulation at level of hypothalmus and pituitary
  - It only takes a small increase in ACTH
  - Loss of cortisol diurnal cycle
- Pituitary adenoma
- Ectopic ACTH
  - Small cell carcinoma of lung
- Adrenal tumors autonomously functioning

Cushing's Disease

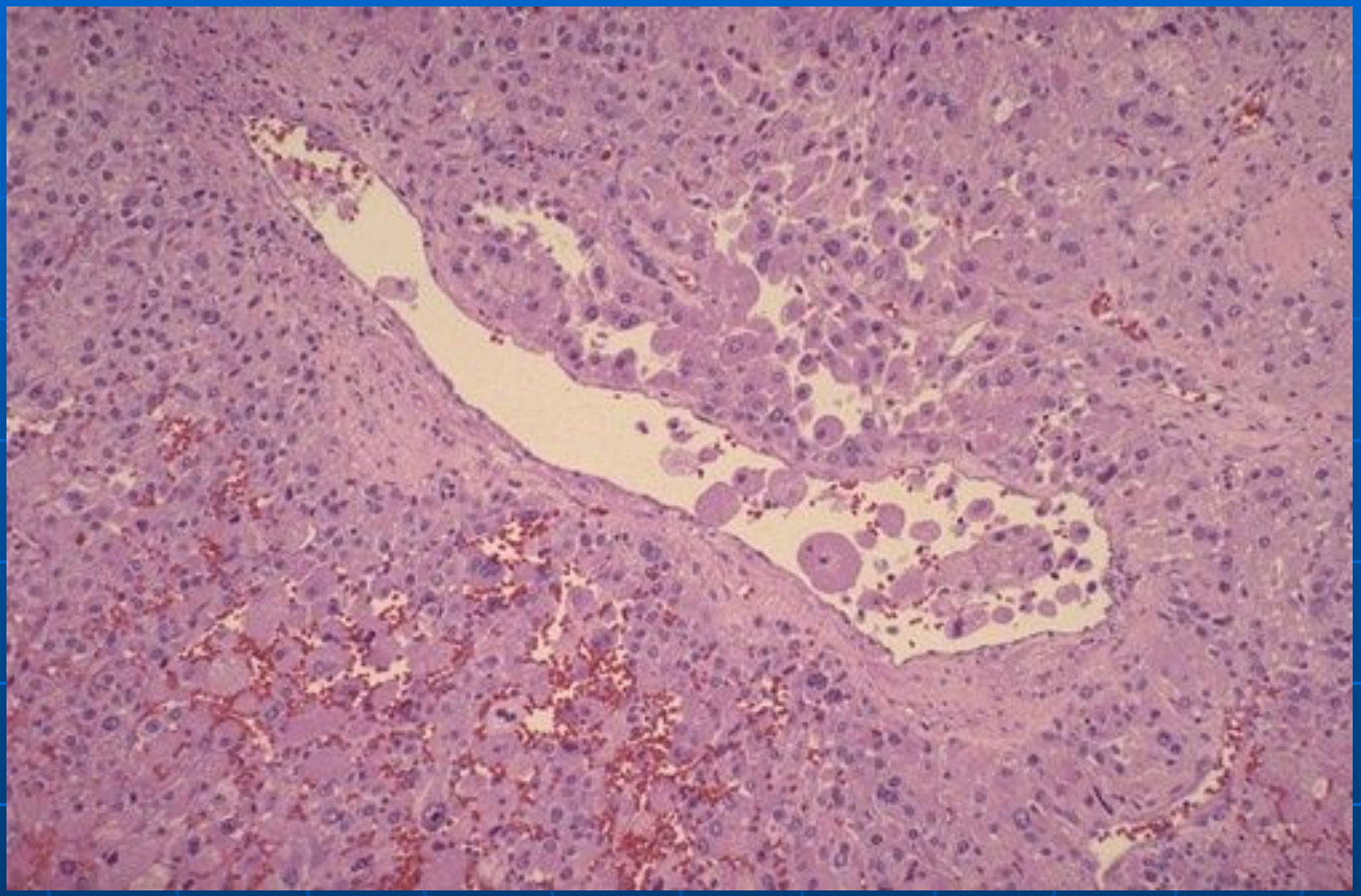


- This adrenal gland removed surgically in a patient with Cushing's syndrome has been sectioned in half to reveal an adenoma. Some remaining atrophic adrenal is seen at the right. The adenoma is composed of yellow firm tissue just like adrenal cortex. This neoplasm is well-circumscribed. Histologically, it is composed of well-differentiated cells resembling cortical fasciculata zone. It is benign.





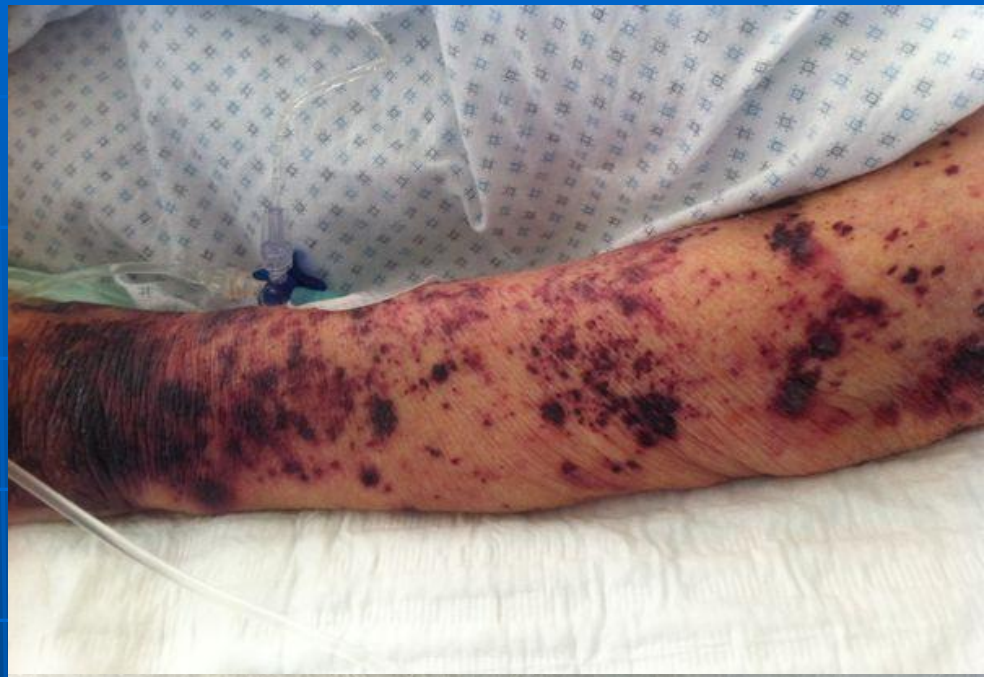
- Microscopically, the adrenal cortical adenoma at the right resembles normal adrenal fasciculata. The capsule is at the left. There may be some cellular pleomorphism.

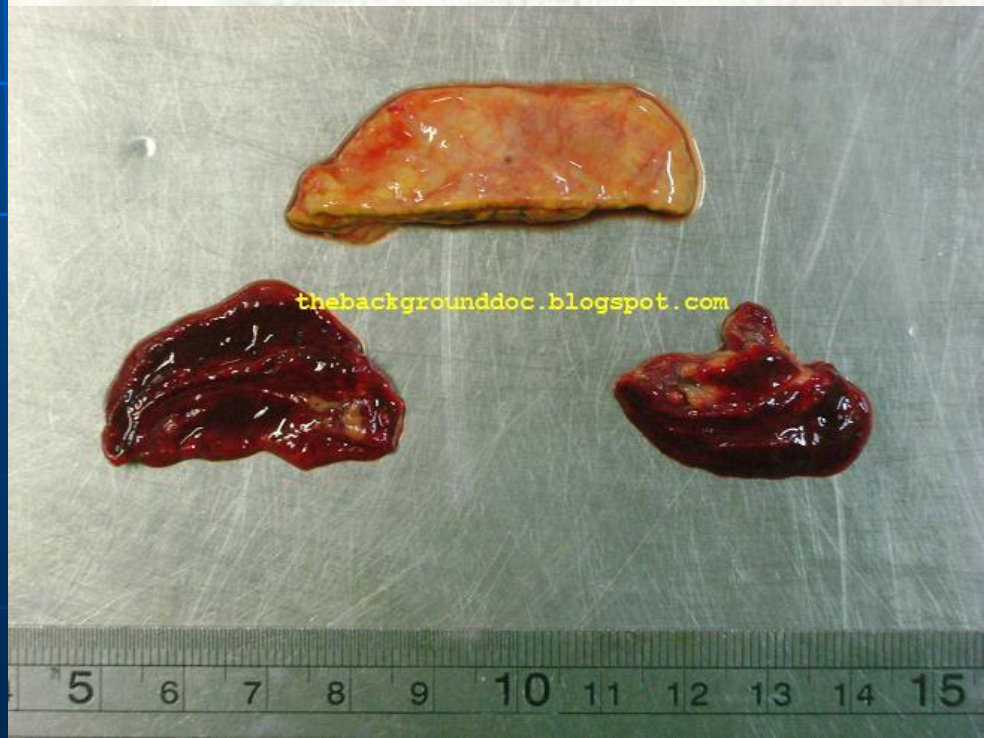


- This high power microscopic appearance of an adrenal cortical carcinoma demonstrates that the neoplasm closely resembles normal adrenal cortex. It is difficult to determine malignancy in endocrine neoplasms based upon cytology alone. Thus, invasion (as seen here in a vein) and metastases are the most reliable indicators. Luckily, most endocrine neoplasms are benign adenomas.

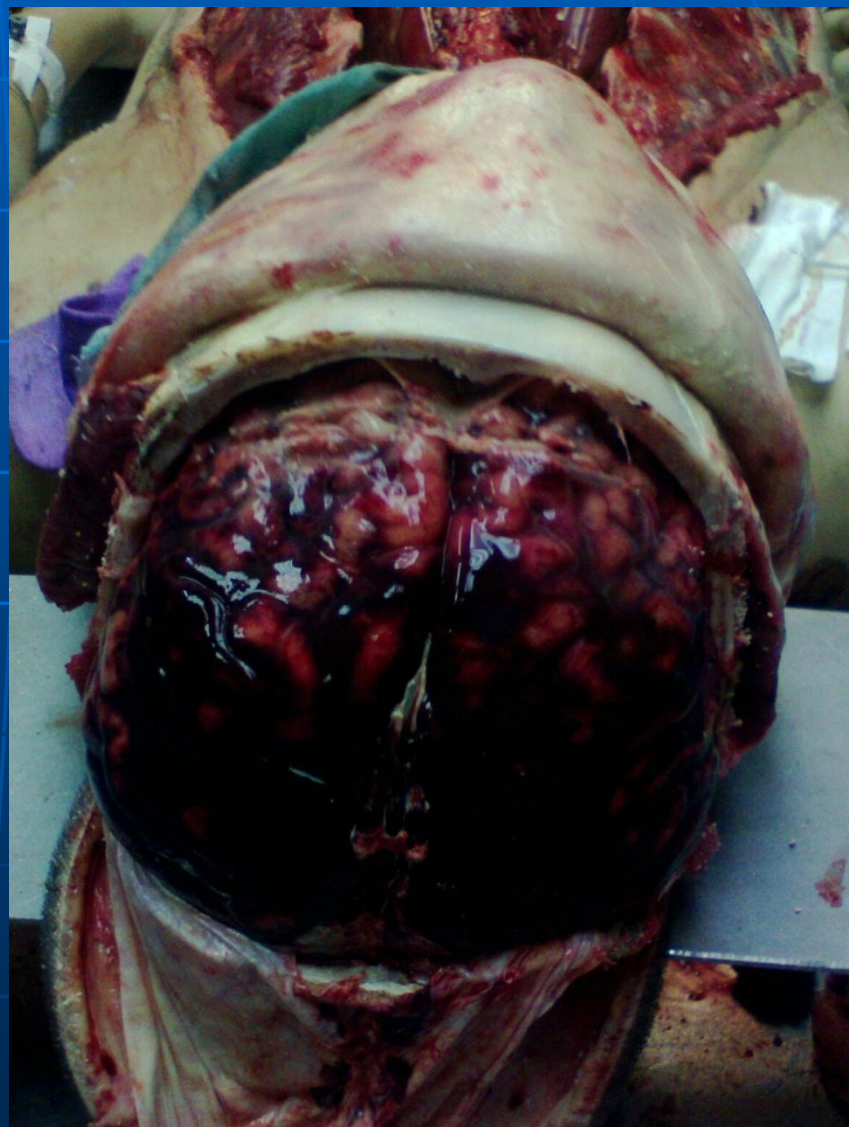
Hypoadrenalism

- Acute loss vs. Chronic
- Pituitary vs. adrenal
- Acute
  - Waterhouse-Fridericshen syndrome ->
  - Overwhelming infection with encapsulated bacteria.
  - Leads to vascular infection.
  - Hemorrhagic destruction of adrenal glands
  - Medical crisis

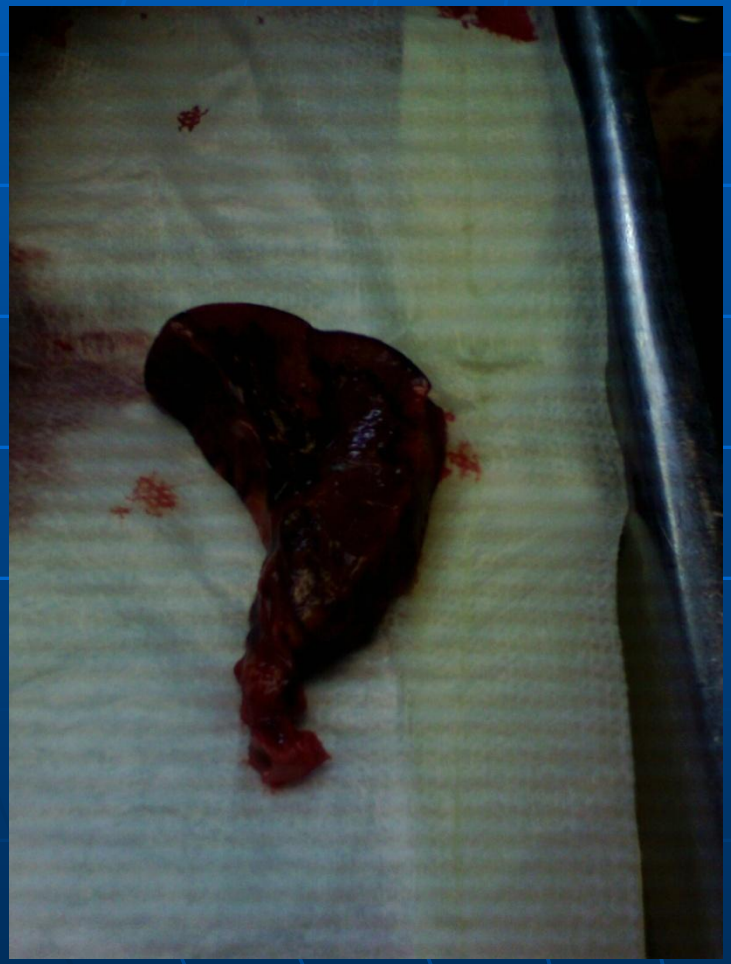


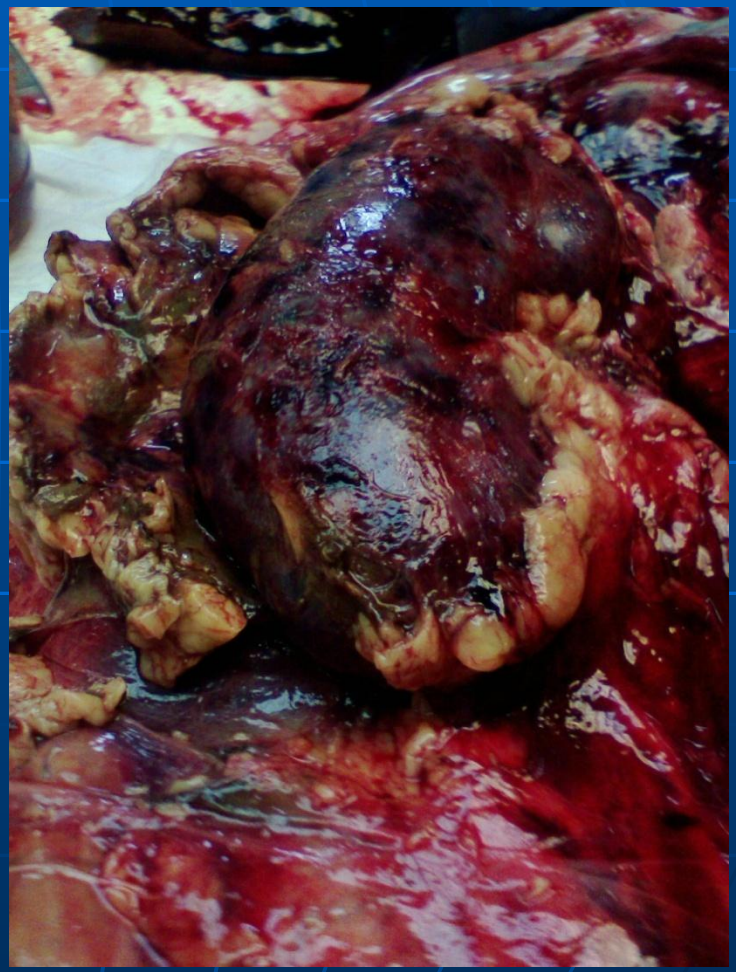


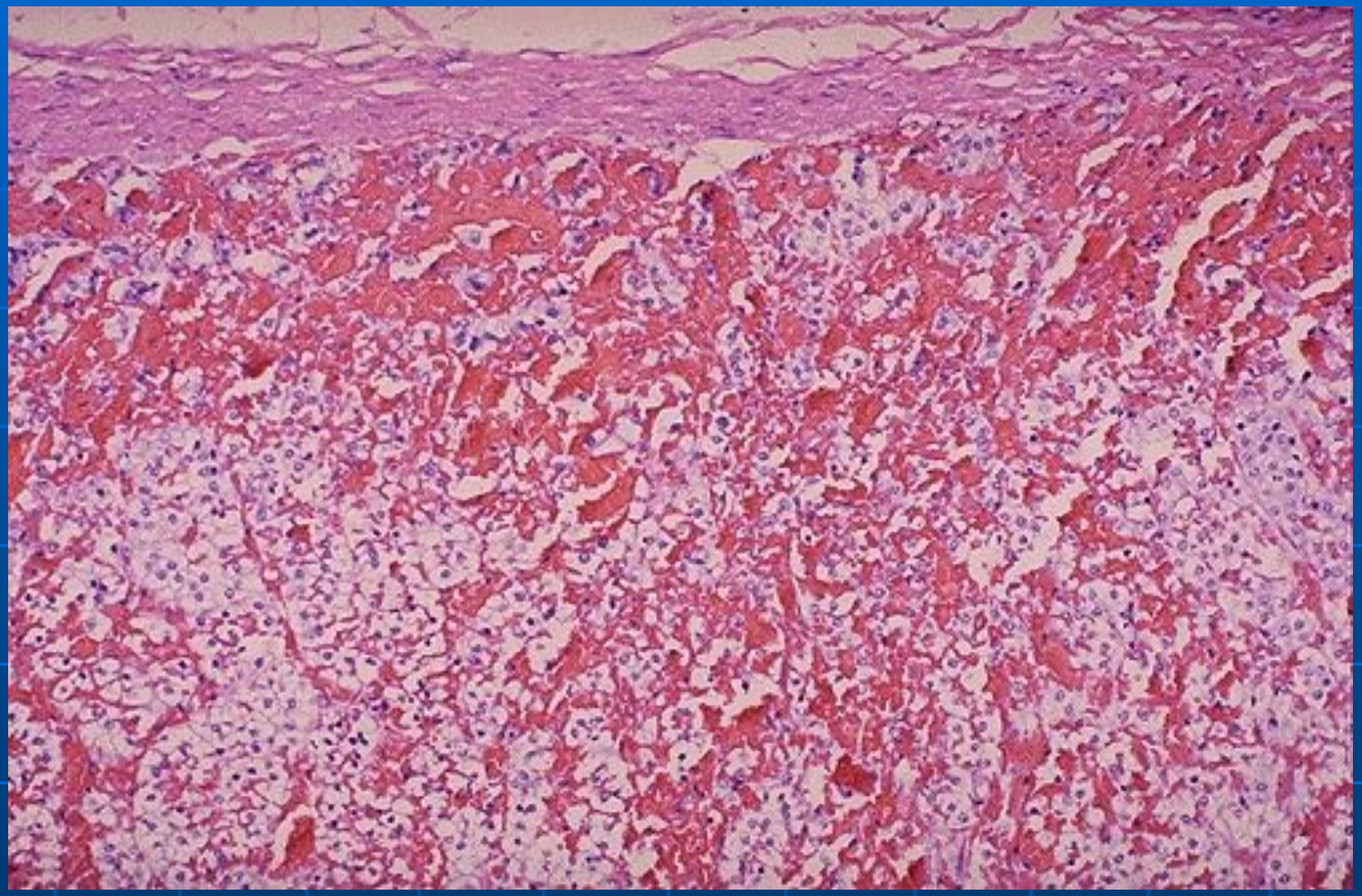
Waterhouse-Fridericshen syndrome



Waterhouse-Fridericshen syndrome



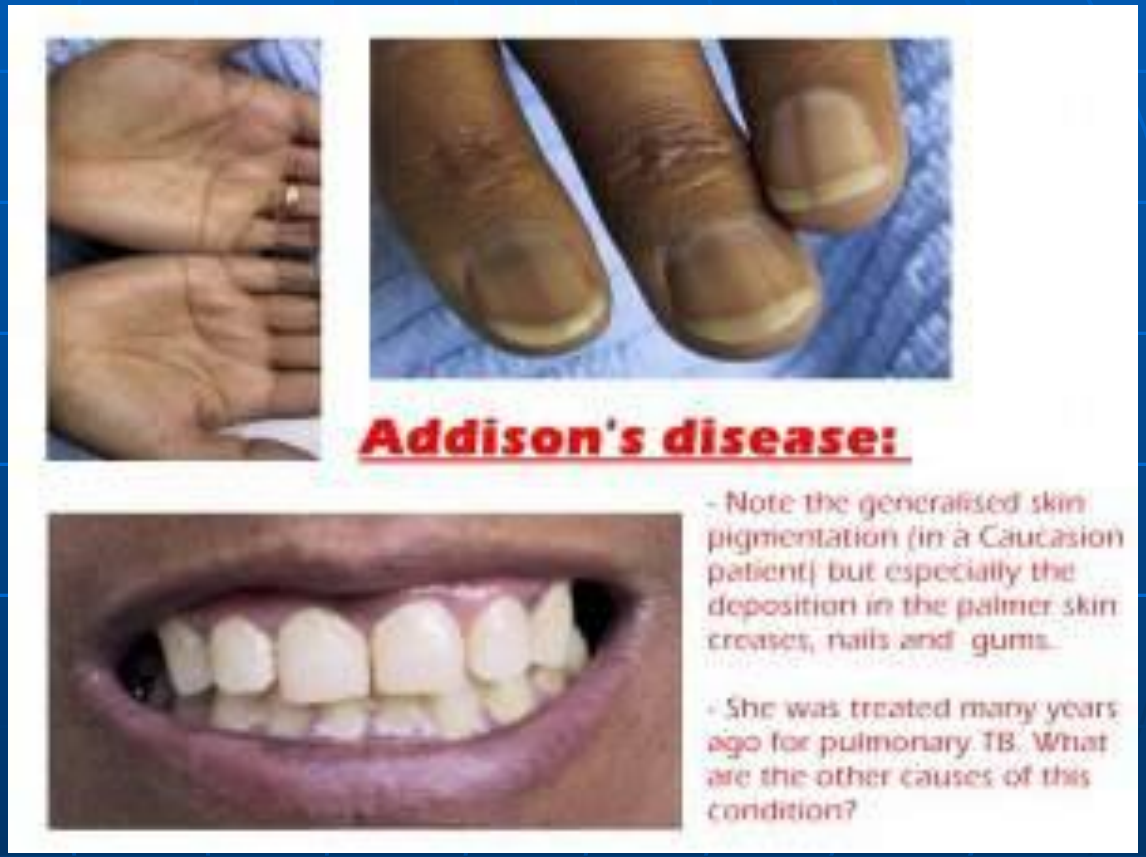




- This is the microscopic appearance of the adrenals with meningococcemia. There is marked hemorrhagic necrosis with acute adrenal insufficiency.

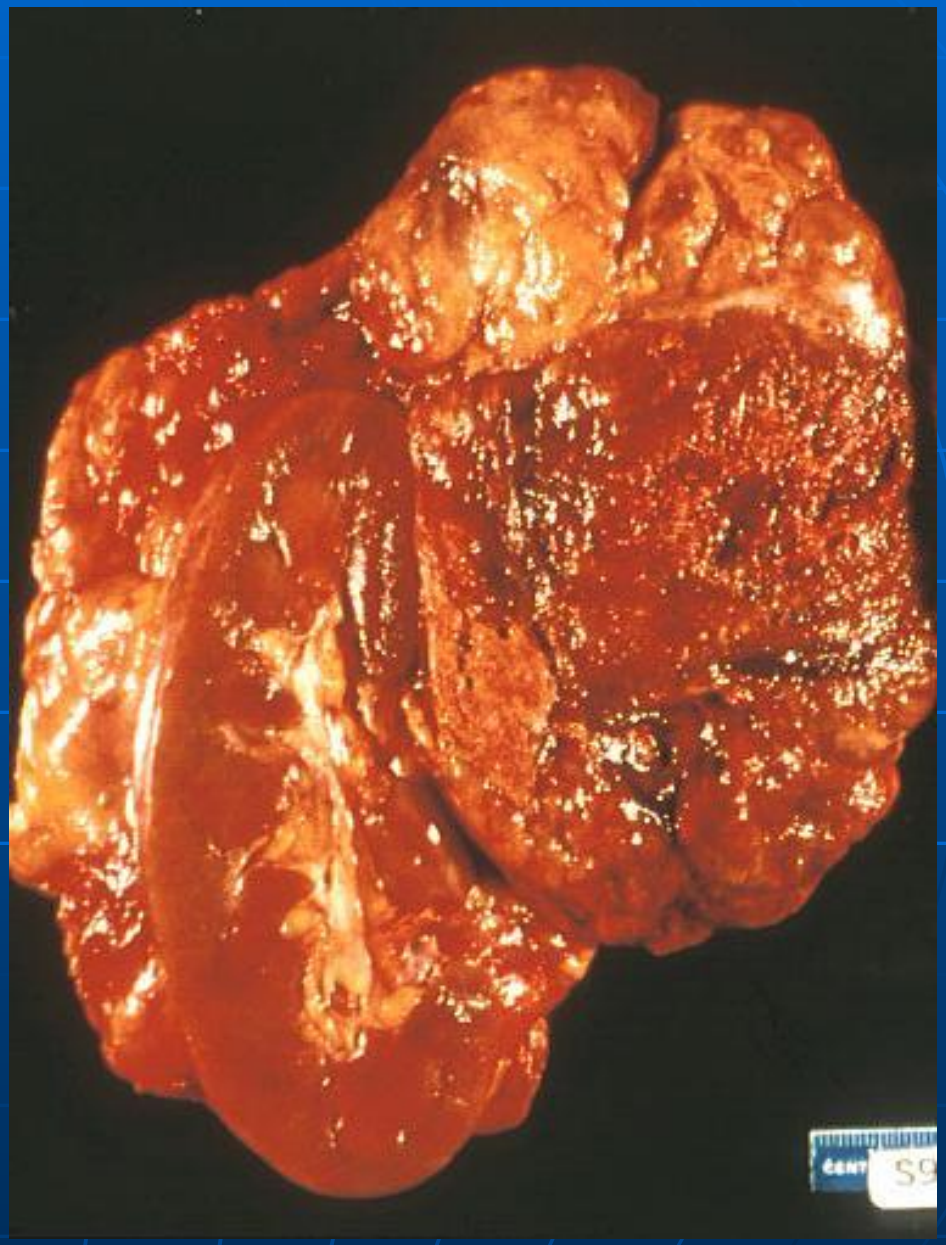
Addison's Disease

- Slowly develops
- Loss of adrenal glands
- Lots of ACTH, but nothing it can do.
- Metastatic tumor
- TB
- Clinical
  - Weight loss
  - Hypotension
  - Hyperpigmentation

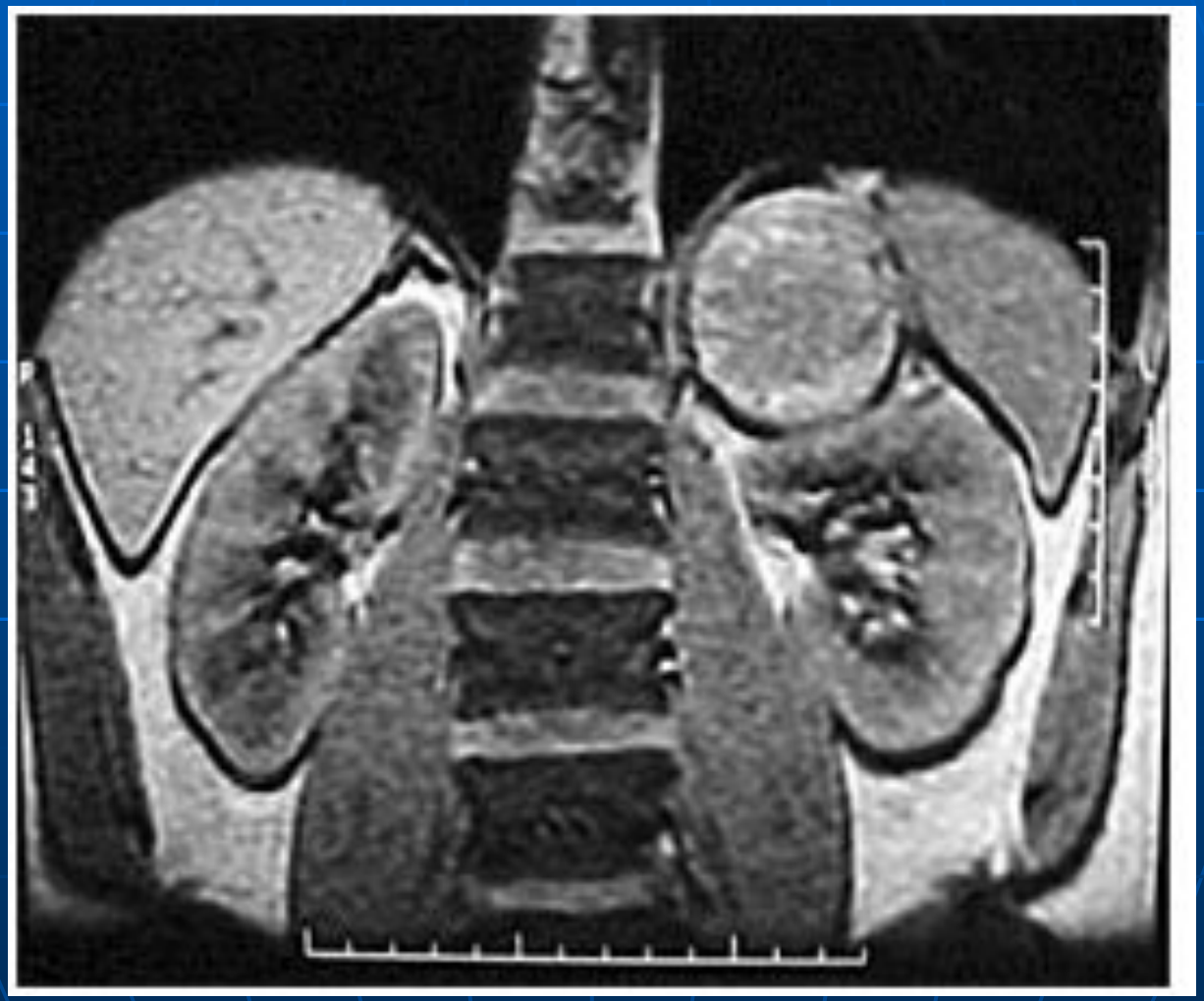


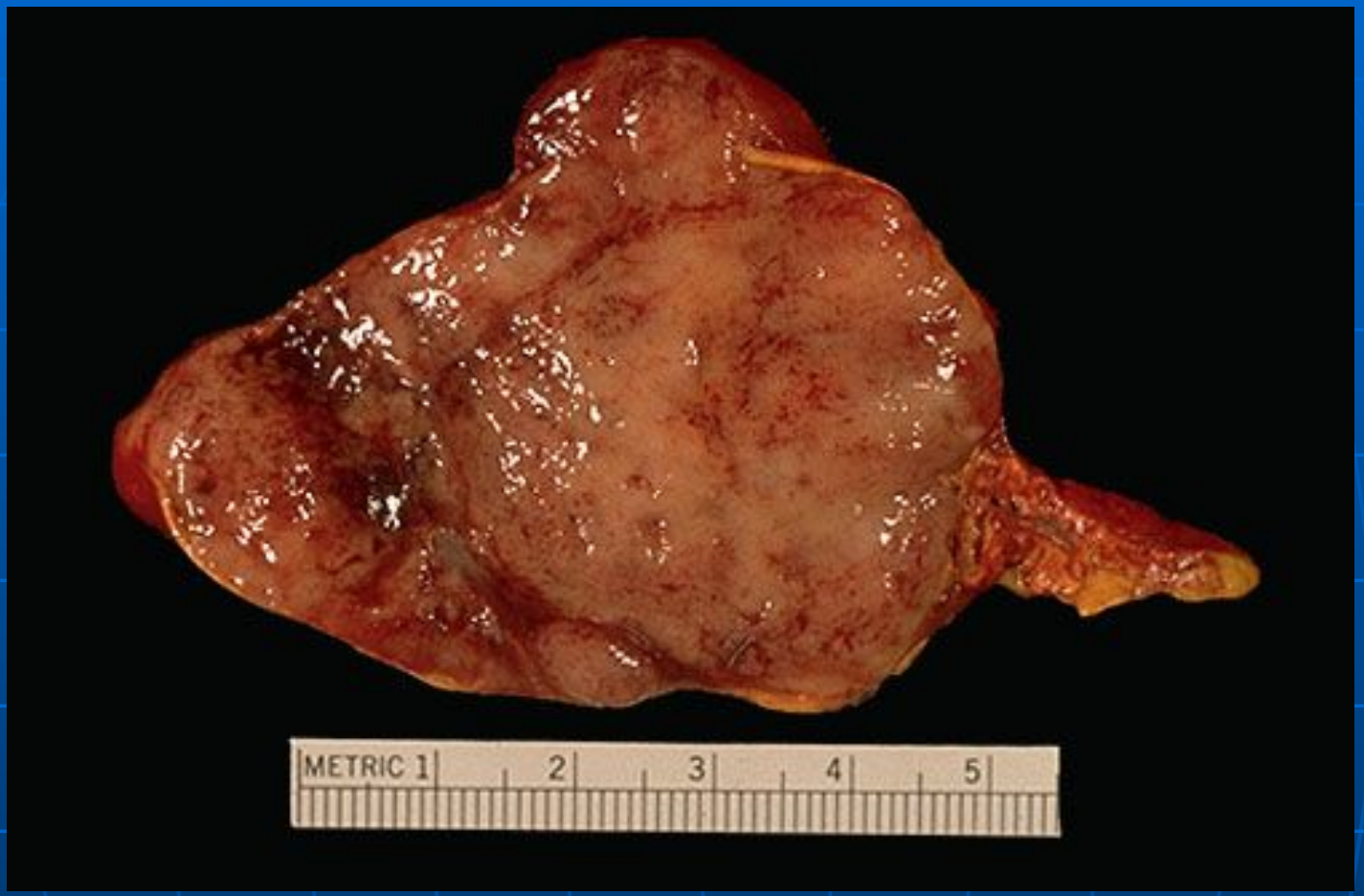
Adrenal Medulla

- Pheochromocytoma
- Catacholamines
- Elevated blood pressure
- Syncopal episodes
- Headaches
- Nose bleeds
- Anxiety
- Maybe an isolated tumor or part of a multiple endocrine tumor syndrome.

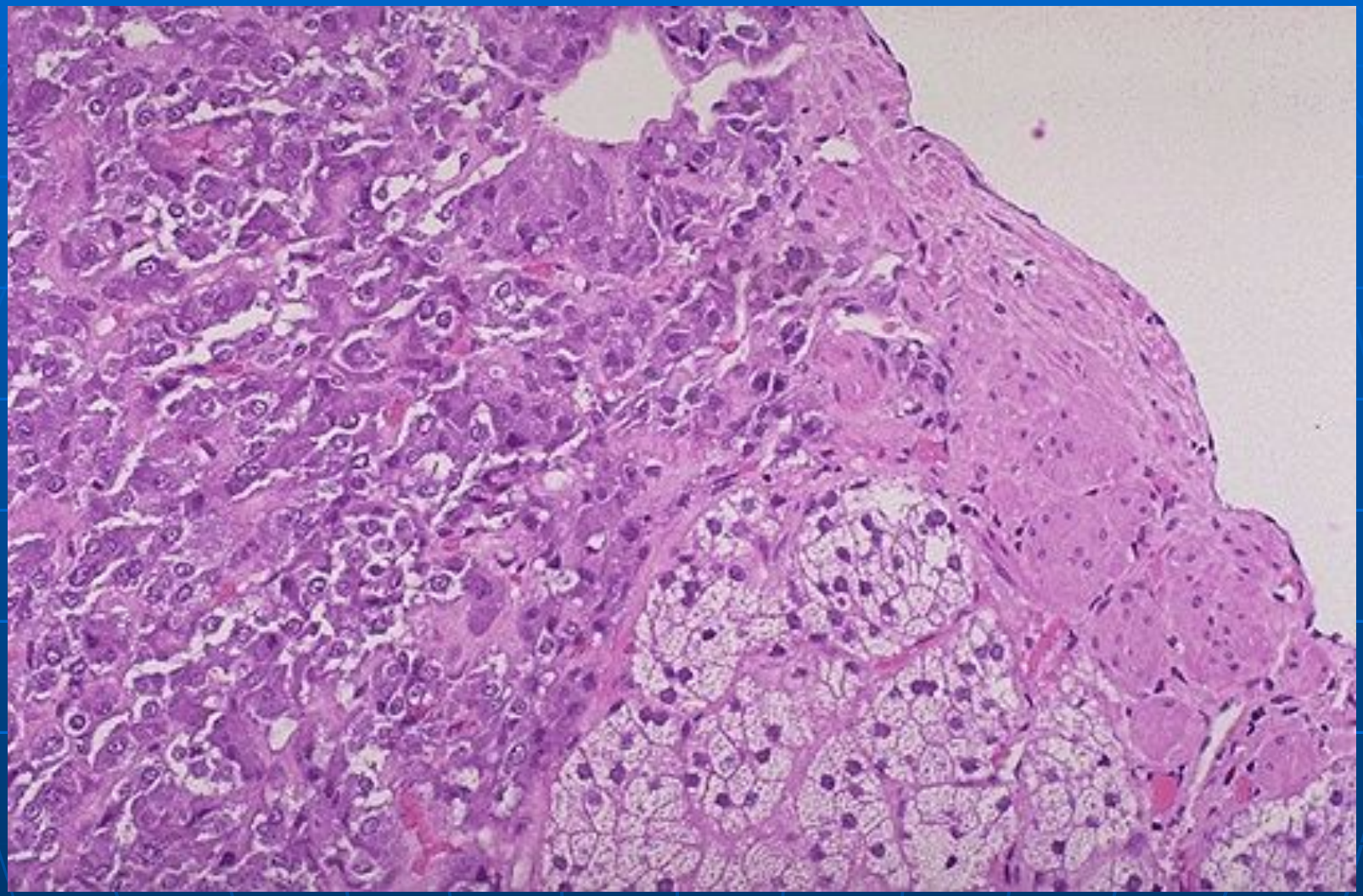


Pheochromocytoma



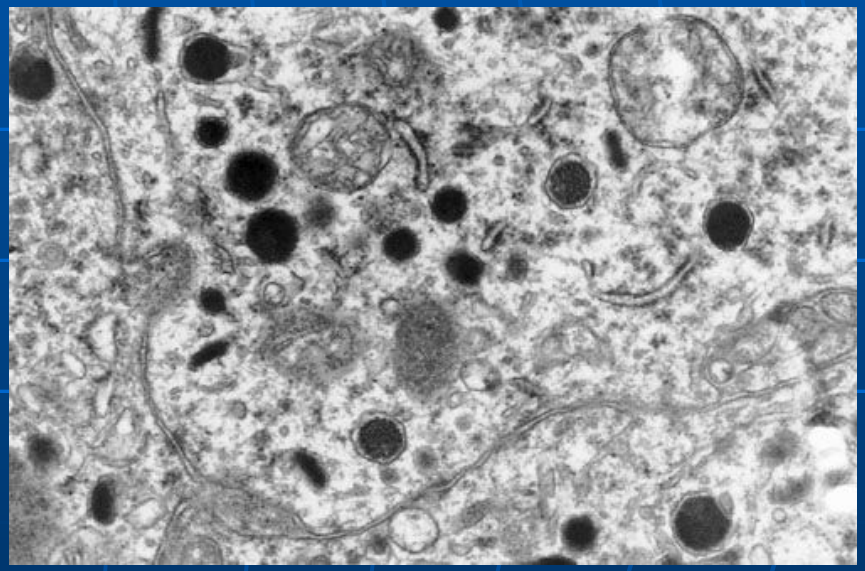


- This large adrenal neoplasm has been sectioned in half. Note the grey-tan color of the tumor compared to the yellow cortex stretched around it and a small remnant of remaining adrenal at the lower right. This patient had episodic hypertension. This is a tumor arising in the adrenal medulla--a pheochromocytoma.



- There is some residual adrenal cortical tissue at the lower center right, with the darker cells of pheochromocytoma seen above and to the left.

- By electron microscopy, the neoplastic cells of the pheochromocytoma contain neurosecretory granules. It is these granules that contain the catecholamines. The granules seen here appear as small black round objects in the cytoplasm of the cell. The cell nucleus is at the upper left.



Diabetes mellitus

Diabetes Mellitus

- General definition: Chronic disorder of glucose metabolism with hyperglycemia, triggered by conditions associated with a relative or absolute insulin deficiency.
- **Primary** diabetes mellitus: Insulin deficiency due to islet damage from autoimmune inflammation (**type I**) or
- — Dysfunction of pancreatic insulin-producing cells (**type II**).

Diabetes Mellitus

- Secondary diabetes mellitus: Insulin deficiency due to islet damage from pancreatic disease such as
- pancreatitis,
- hemochromatosis, or
- cystic fibrosis; or
- Overproduction of insulin antagonist hormones such as cortisone and somatotropic hormone (STH).

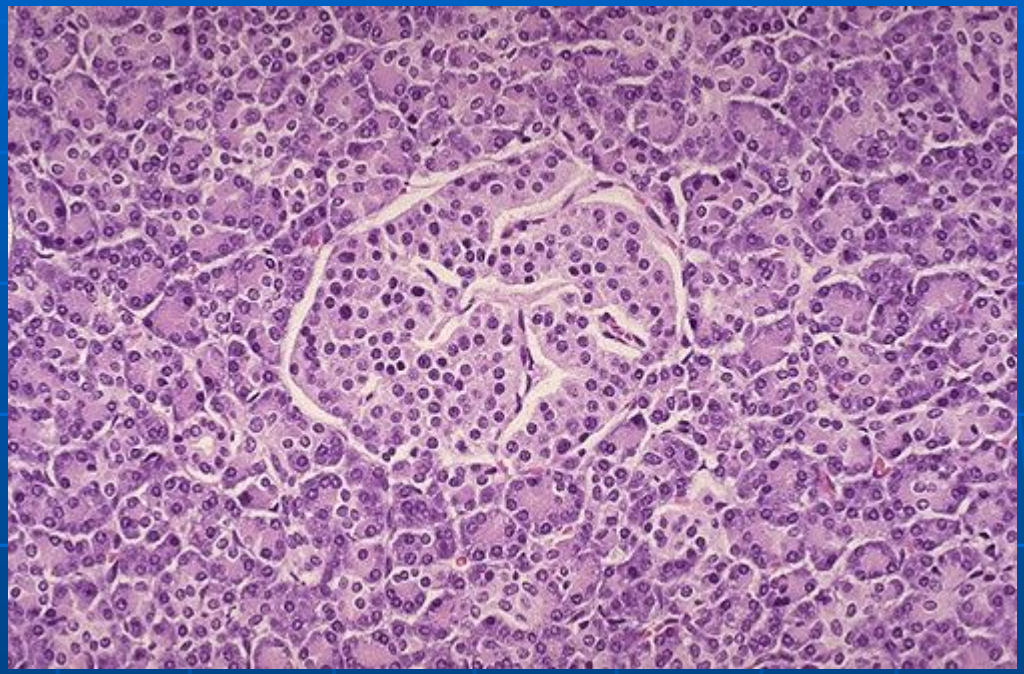
Diabetes Mellitus
Definition

A multisystem disease related to:

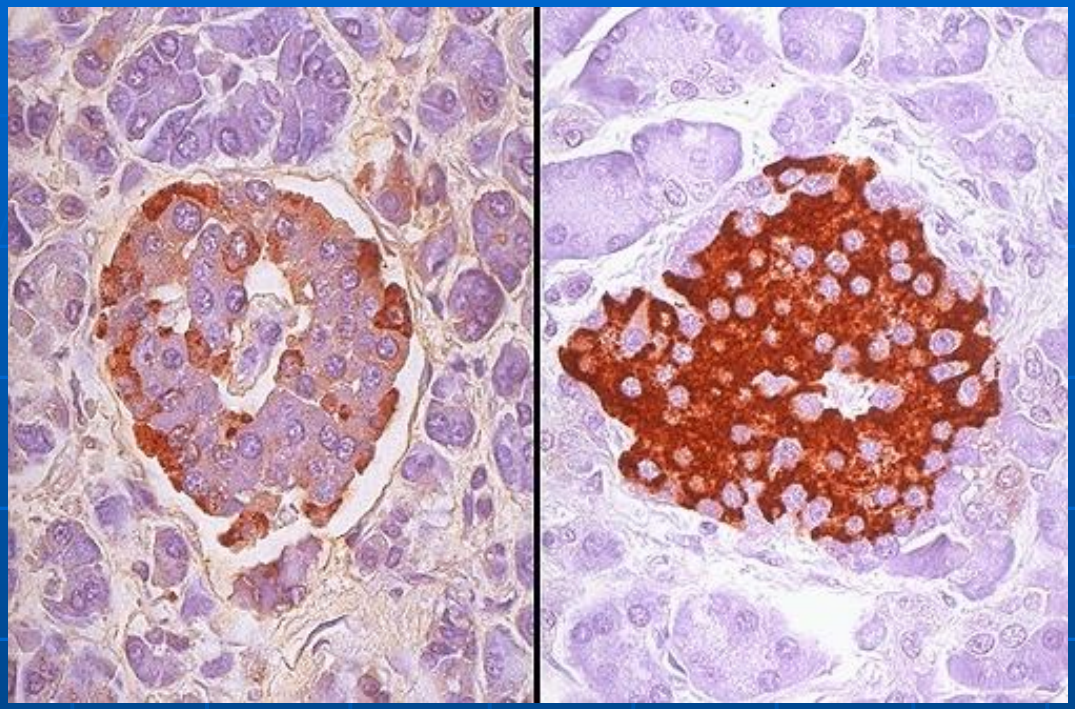
- Chronic disorder
- Abnormal metabolism of fuels glucose and fat
- An endocrine disorder causes Abnormal insulin production
- Impaired insulin utilization
- Both abnormal production and impaired utilization

Diabetes Mellitus
Definition

Leading cause of heart disease, stroke, adult blindness, and nontraumatic lower limb amputations



- Here is a normal pancreatic islet of Langerhans surrounded by normal exocrine pancreatic acinar tissue. The islets contain alpha cells secreting glucagon, beta cells secreting insulin, and delta cells secreting somatostatin



- Immunoperoxidase staining can help identify the nature of the cells present in the islets of Langerhans. On the right, antibody to insulin has been employed to identify the beta cells. On the left, antibody to glucagon identifies the alpha cells.

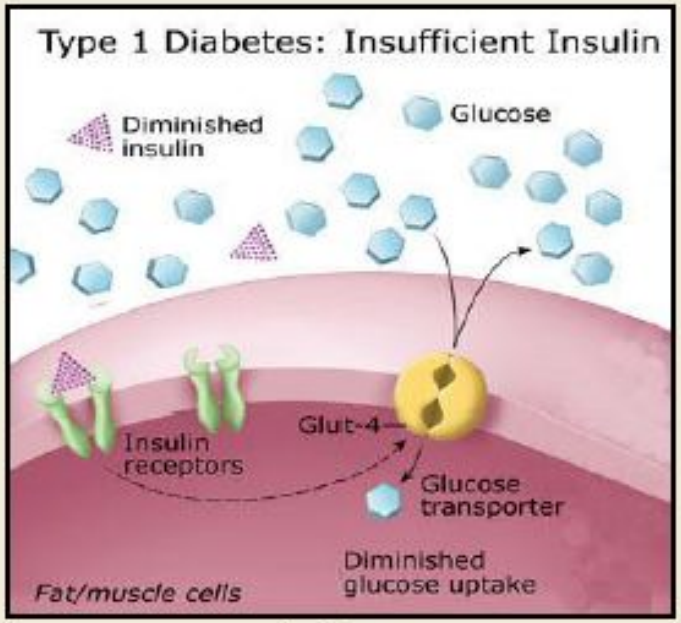
Diabetes Mellitus

Type I diabetes mellitus

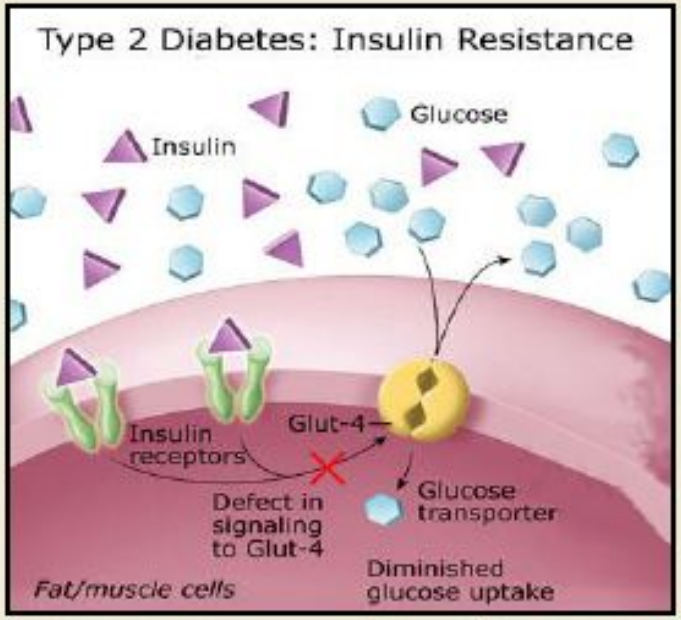
- destruction of beta cells → complete loss of insulin secretion
- insulin-dependent from time of Dx

Type II diabetes mellitus

- characterized by insulin resistance
- over time develop into insulin-dependent DM



healthhype.com

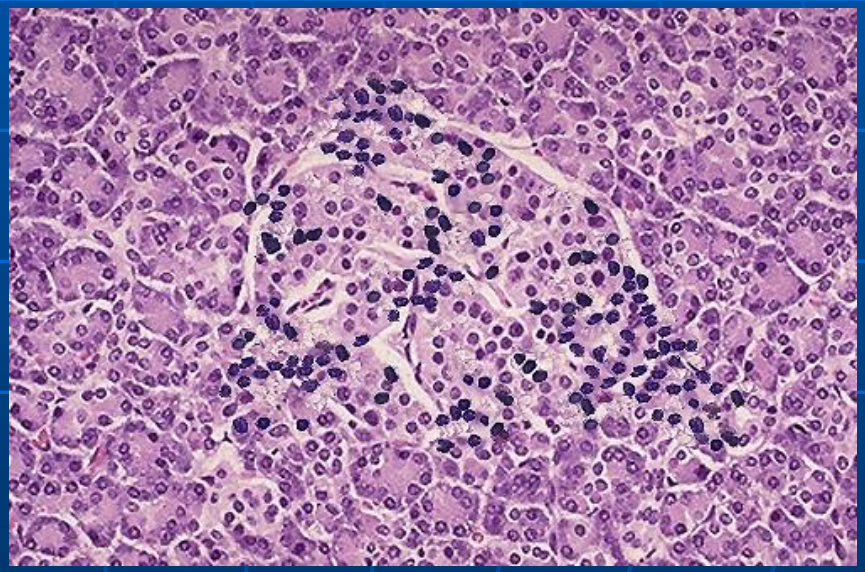


- Type I Diabetes Mellitus
- Synonyms: juvenile-onset diabetes mellitus, insulin-dependent diabetes mellitus (IDDM).
- Autoimmune lymphocytic insulitis in combination with genetic susceptibility (HLA-DR4 and/or DR3) leads to formation of autoimmune T-lymphocytes and islet-cell antibodies.
- They destroy the b cells (A) and leave the glucagon-forming cells intact (B), causing insulin-dependent diabetes mellitus.

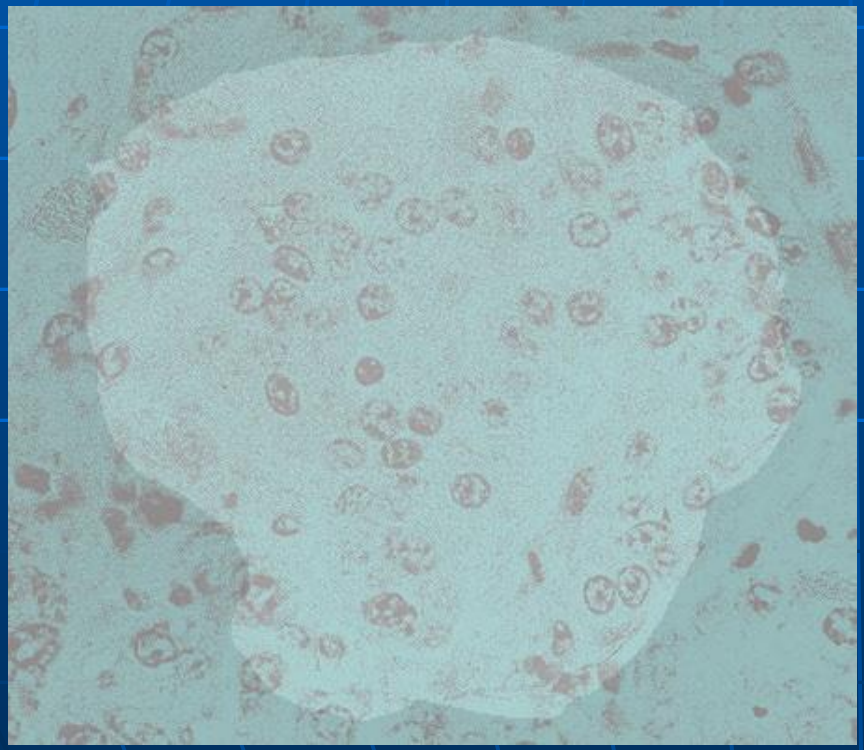
Type 1 Diabetes Mellitus

- Progressive destruction of pancreatic β cells
- Autoantibodies cause a reduction of 80% to 90% of normal β cell function before manifestations occur
- Causes:
  - Genetic predisposition
    - Related to human leukocyte antigens (HLAs)
  - Exposure to a virus

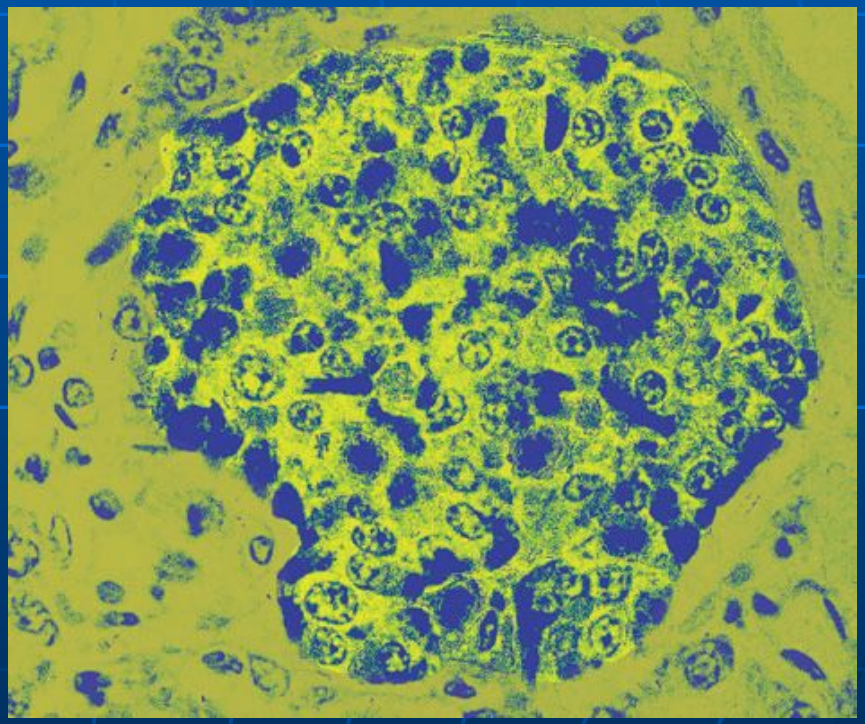
- This is an insulitis of an islet of Langerhans in a patient who will eventually develop type I diabetes mellitus. The presence of the lymphocytic infiltrates in this edematous islet suggests an autoimmune mechanism for this process. The destruction of the islets leads to an absolute lack of insulin that characterizes type I diabetes mellitus.



A Type I diabetes mellitus: loss of βcells (IH; insulin) x 200



B Type I diabetes mellitus: dominance of α cells (IH; glucagon) x 200



Diabetes Mellitus

- Type II Diabetes Mellitus
- Synonyms: adult-onset diabetes mellitus, non-insulindependent diabetes mellitus (NIDDM).
- Type IIa is without obesity; type IIb with obesity. Together with insulin, b cells form amylin (islet amyloid peptide), which condenses to AE amyloid, "smothering" the function of the islets. Peripheral organs and tissues in obese patients also exhibit insulin resistance due to the protein resistin, secreted by fat cells, leading to non-insulin-dependent diabetes mellitus. Immunohistochemical findings reveal normal counts of insulin-producing cells and glucagon-producing cells.

Type 2 Diabetes Mellitus

- Accounts for 90% of patients with diabetes
- Usually occurs in people over 40 years of age
- 80-90% of patients are overweight

- Pancreas continues to produce some endogenous insulin
- Insulin produced is either insufficient or poorly utilized by the tissues
- **Insulin resistance**
  - Body tissues do not respond to insulin
  - Results in hyperglycemia

Type II diabetes mellitus

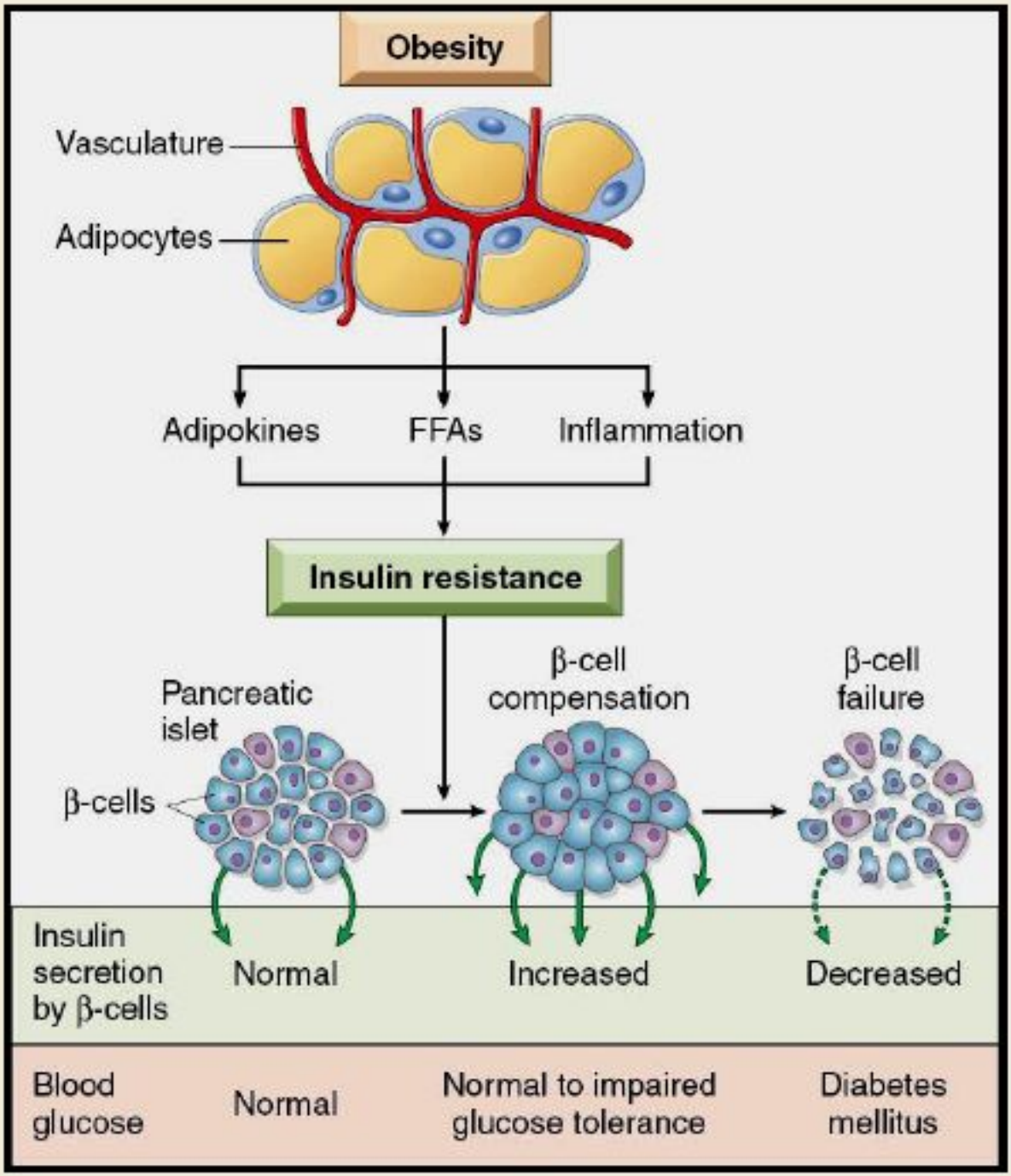
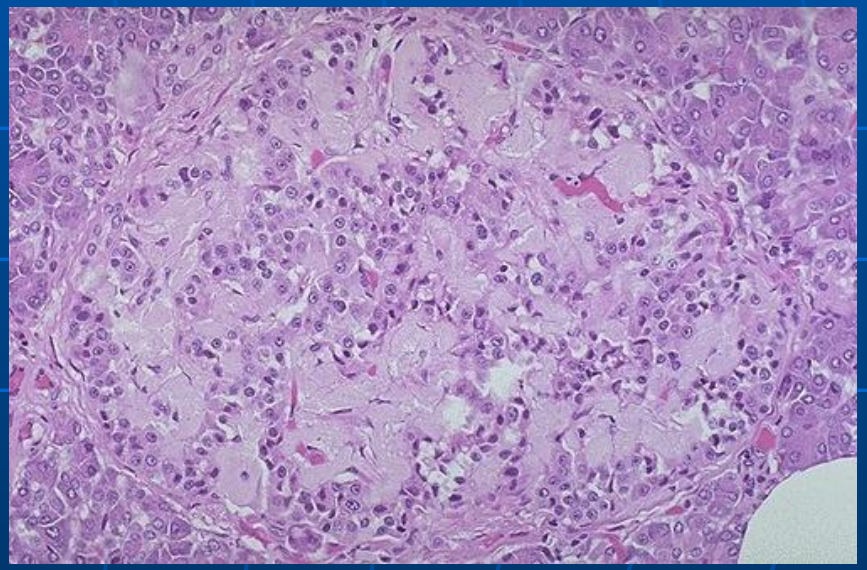
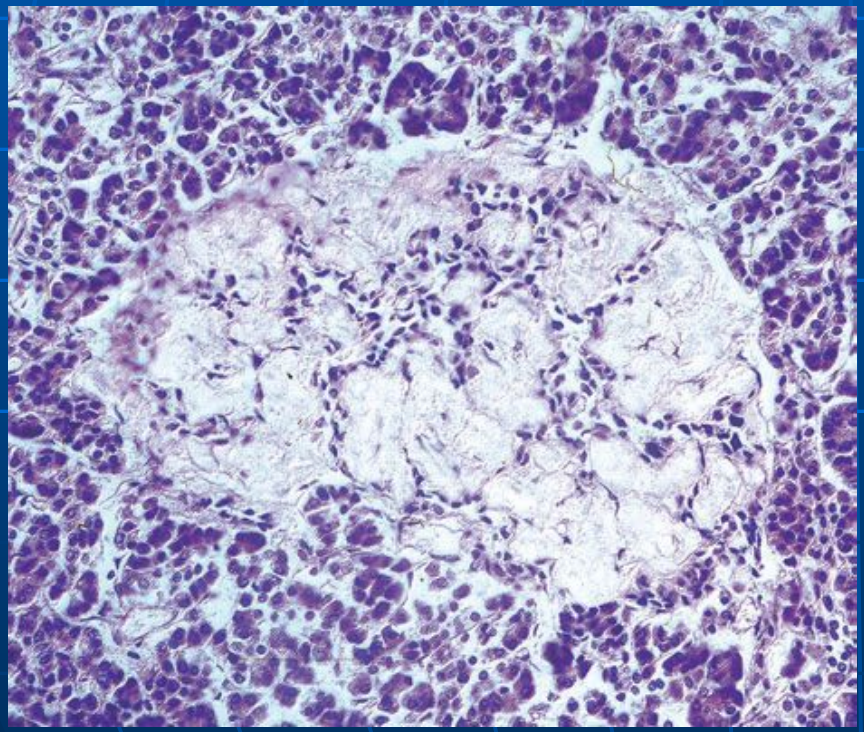


FIGURE 24–31 (Robbin's)
Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β-cell compensation is followed by β-cell failure, and diabetes ensues.

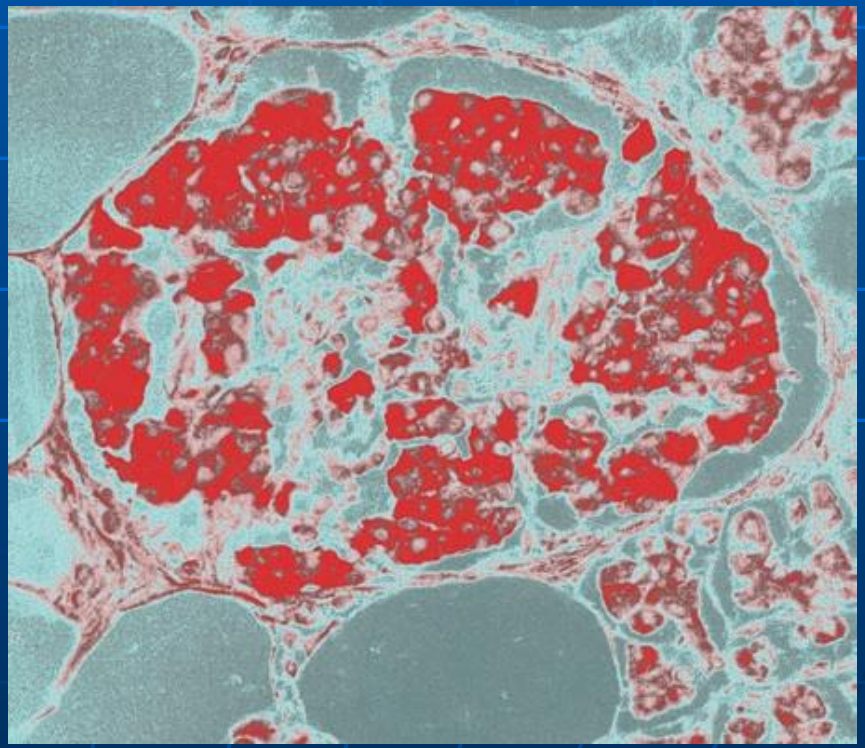
- This islet of Langerhans demonstrates pink hyalinization (with deposition of amyloid) in many of the islet cells. This change is common in the islets of patients with type II diabetes mellitus.



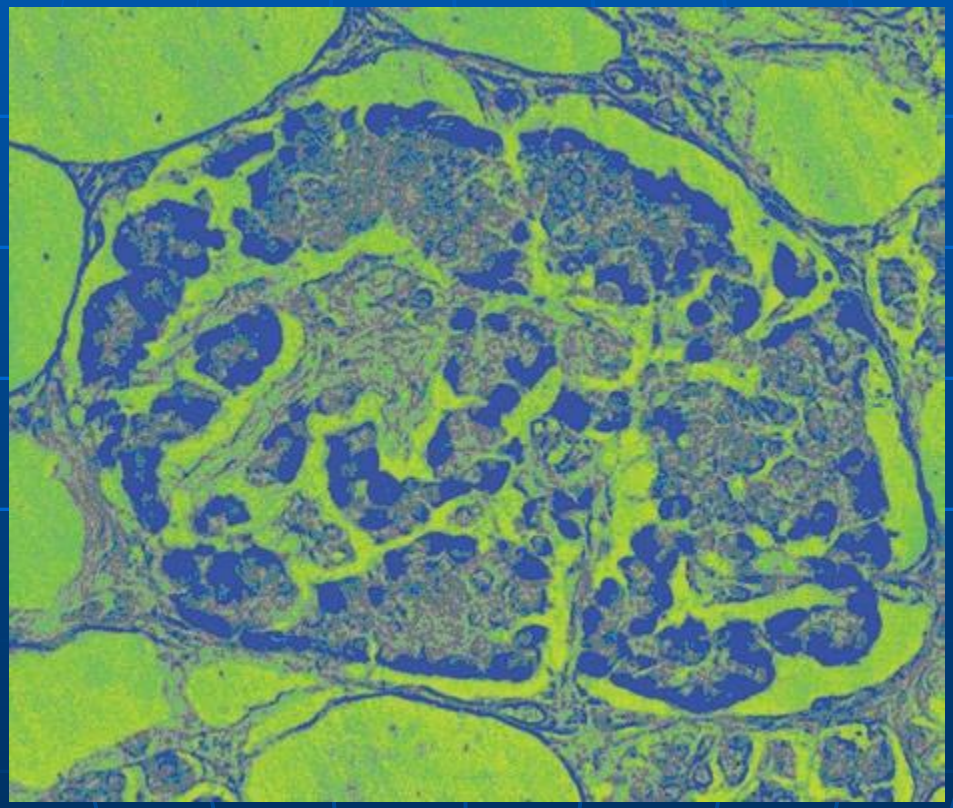
Islet amyloidosis (HE) x 200



Type II diabetes mellitus: B cells (IH; insulin) x 200



E **Type II diabetes mellitus: alpha cells** (IH; glucagon) x 200



Secondary Diabetes

- Results from another medical condition or due to the treatment of a medical condition that causes abnormal blood glucose levels
  - Cushing syndrome
  - Hyperthyroidism
  - Parenteral nutrition

Diabetes Mellitus

Secondary diabetes mellitus

- reflects antagonism in peripheral tissues between insulin and other hormones:

progesterone

glucagon

growth hormone

glucocorticoids

Diabetes Mellitus

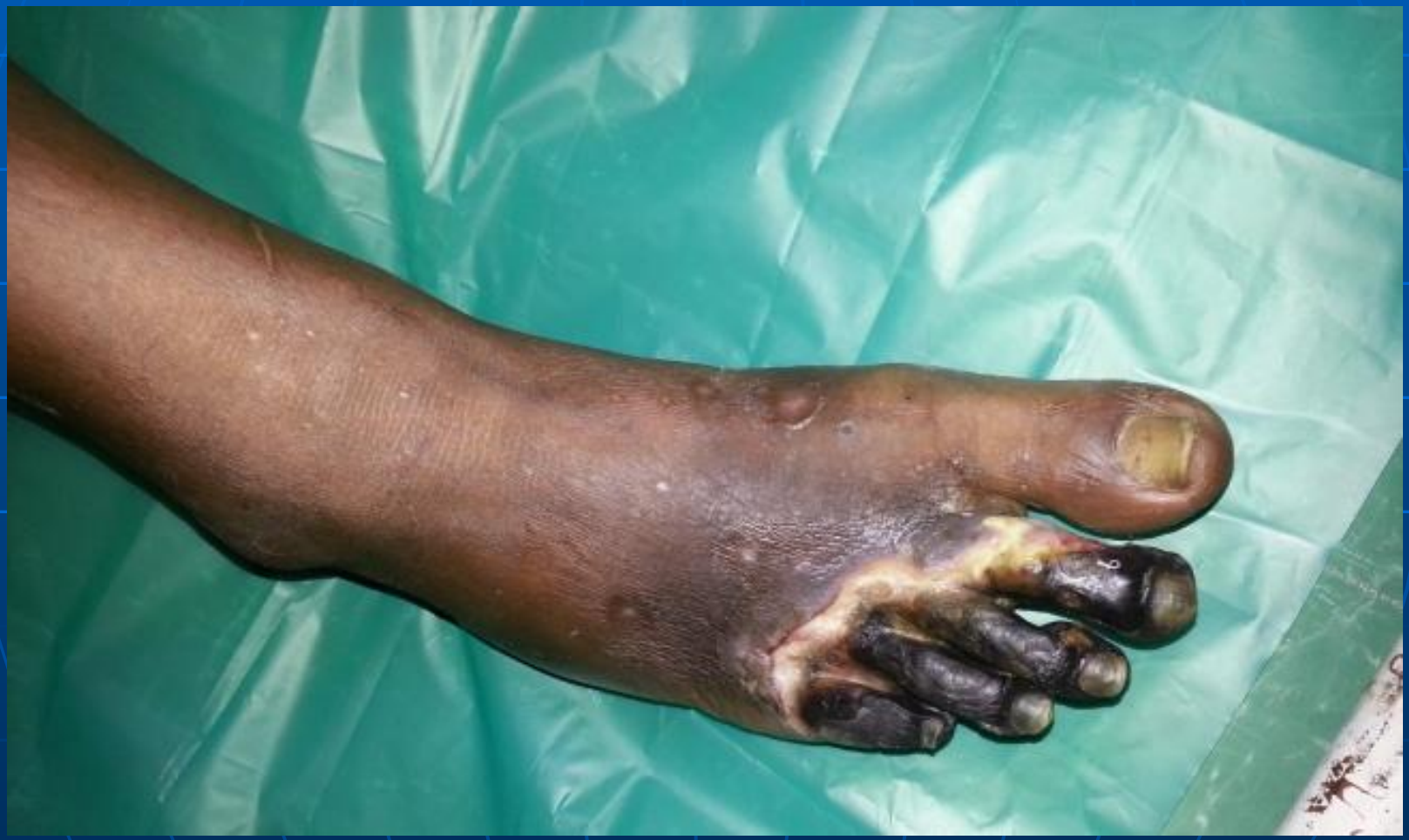
Clinical Signs & Lesions

- **hyperglycaemia and glycosuria -** decreased insulin or insulin resistance
- **polydipsia / polyuria** - glucosuria → osmotic diuresis with compensatory polydypsia
- **polyphagia** - affect on satiety center
- **loss of weight -** glucosuria & generalized ↑ catabolism
- **weakness -** ↓ tissue/muscle glucose, protein catabolism ± polyneuropathy
- **hepatic lipidosis -** increased lipolysis in adipose tissue → excess fatty acids to liver
- **bilateral cataracts -** excess glucose to polyol pathway causing:
  - ↑ osmotic sorbitol → hydropic degeneration of lens fibers
  - glutathione depletion → oxidative damage of lens fibers
- **recurrent infections -** ↓ leukocyte kinetics and ↑ glucose substrate
- **vascular damage -** glomerulo-sclerosis and retinopathy
- **neuropathies -** peripheral demyelinating neuropathies

- Diabetic macroangiopathy follows the pattern of atherosclerosis .
- Complications:

– Coronary sclerosis can lead to myocardial infarction.
– Cerebral sclerosis can lead to cerebral infarction.
– Popliteal sclerosis can lead to gangrene.

Diabetic gangrene



- Diabetic microangiopathy: Chronic increased glucose concentration leads to glycosylation of proteins, altering the structure and permeability of the microvascular basement membranes .
- Complications:

– Diabetic retinopathy (a late complication):

Capillary microaneurysms and arteriosclerosis cause microinfarctions (punctate hemorrhages).

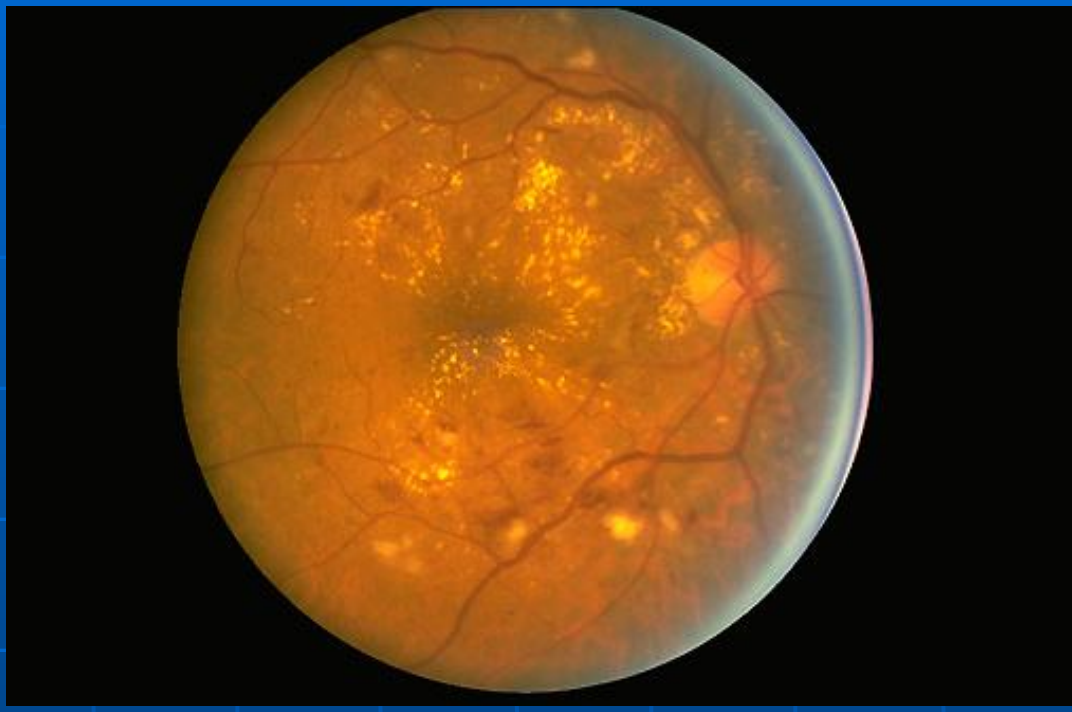
- Proliferative retinitis leads to shrinkage of the vitreous body and retinal detachment.
- – Diabetic glomerulosclerosis (Kimmelstiel-Wilson lesion): Deranged synthesis and breakdown of the glomerular basement membrane cause thickening of the membrane . This causes diffuse and, later, nodular deposition of PAS-positive material in the mesangium and between the glomerular podocytes and basement membrane, leading to proteinuria and renal insufficiency.

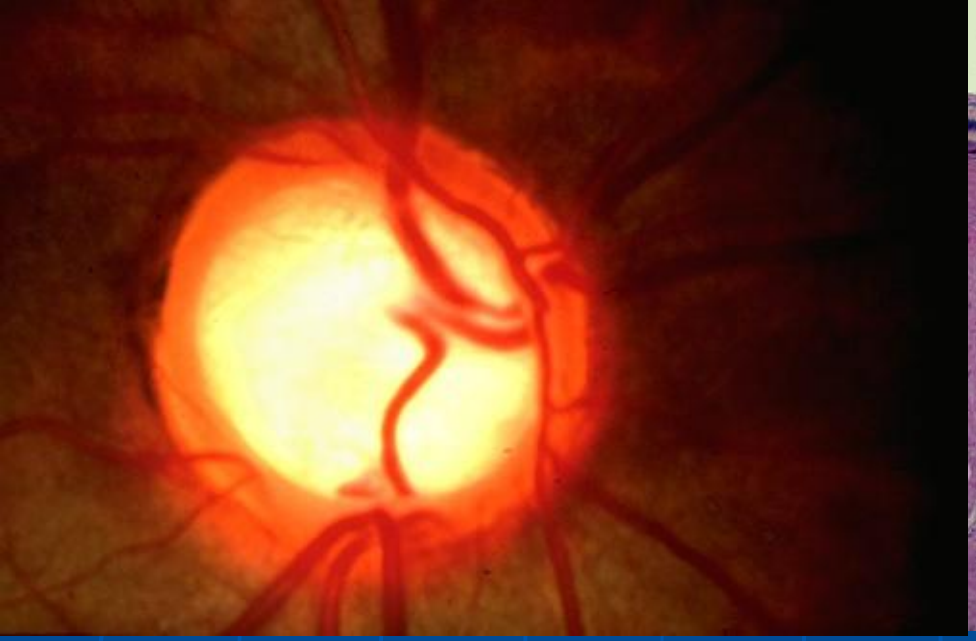
- Diabetic cataract: Osmotic vacuolar degeneration of the epithelium of the lens creates lens opacities.
- Diabetic liver: Secondary glycogenosis (glycogen-induced nuclear defects) occurs in relation to the level of blood glucose; simultaneous fatty degeneration correlates with obesity in type IIb diabetes.
- Diabetic neuropathy: After approximately 25 years of diabetes, 50% of patients exhibit axonal and/or myelin degeneration leading to hyporeflexia and decreased deep sensation.
- Complications: diabetic microangiopathy and diabetic neuropathy lead to gangrene in the toes.

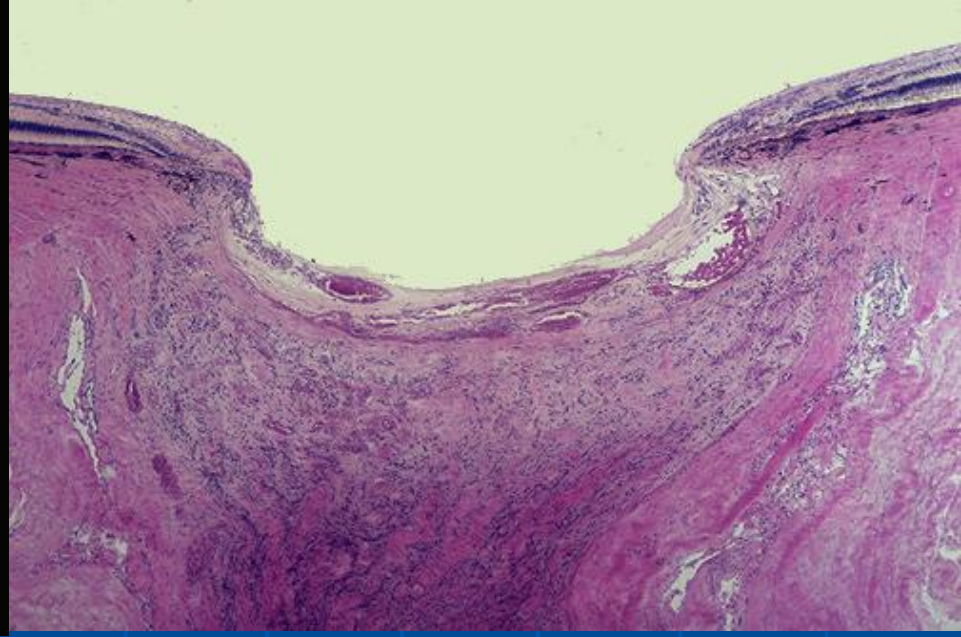
Gestational Diabetes

- Develops during pregnancy
- Detected at 24 to 28 weeks of gestation
- ↑ Risk for cesarean delivery, perinatal death, and neonatal complications

Diabetic retinopathy

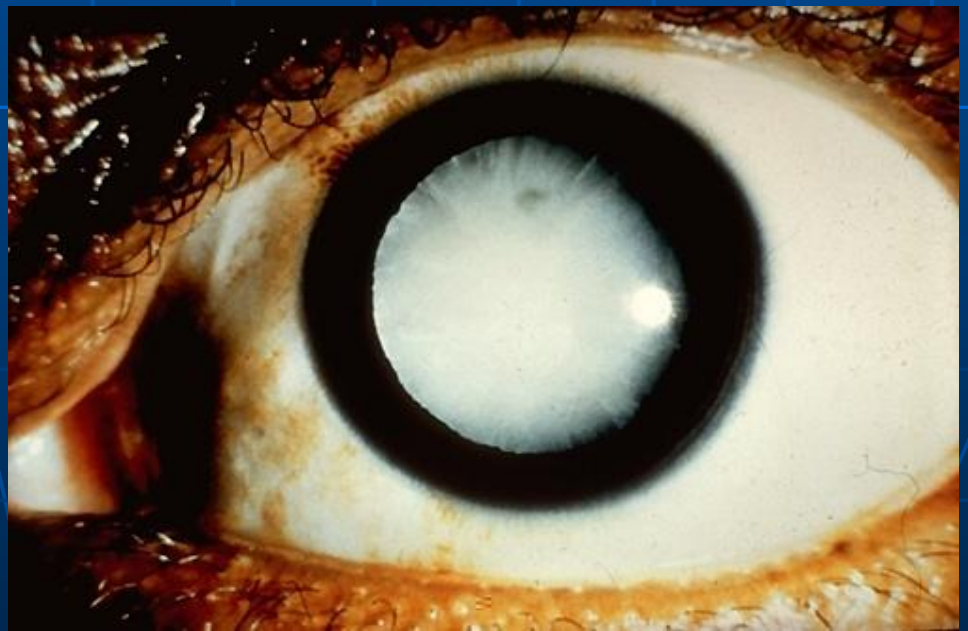




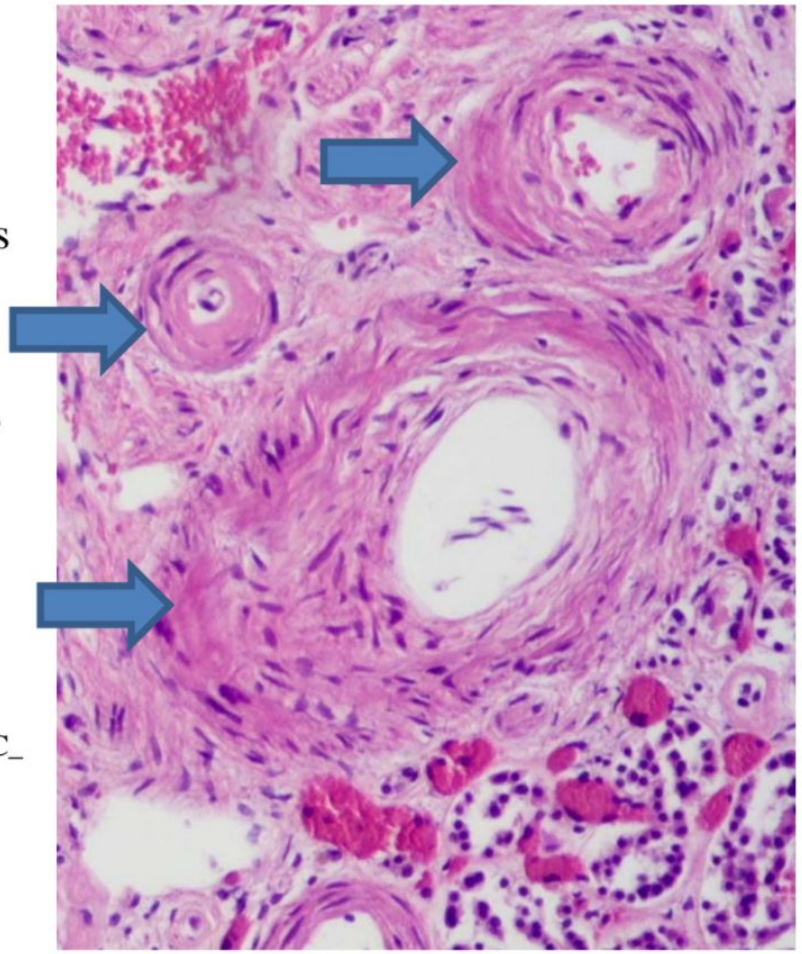


Diabetic retinopathy

Diabetic cataract

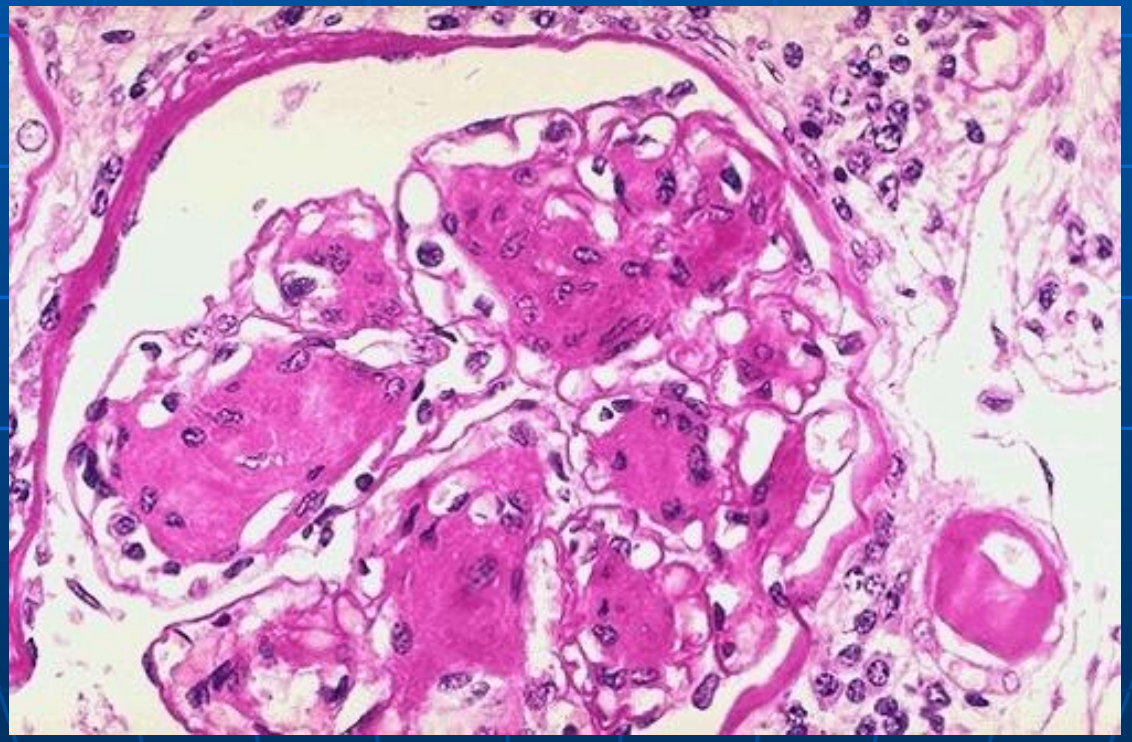


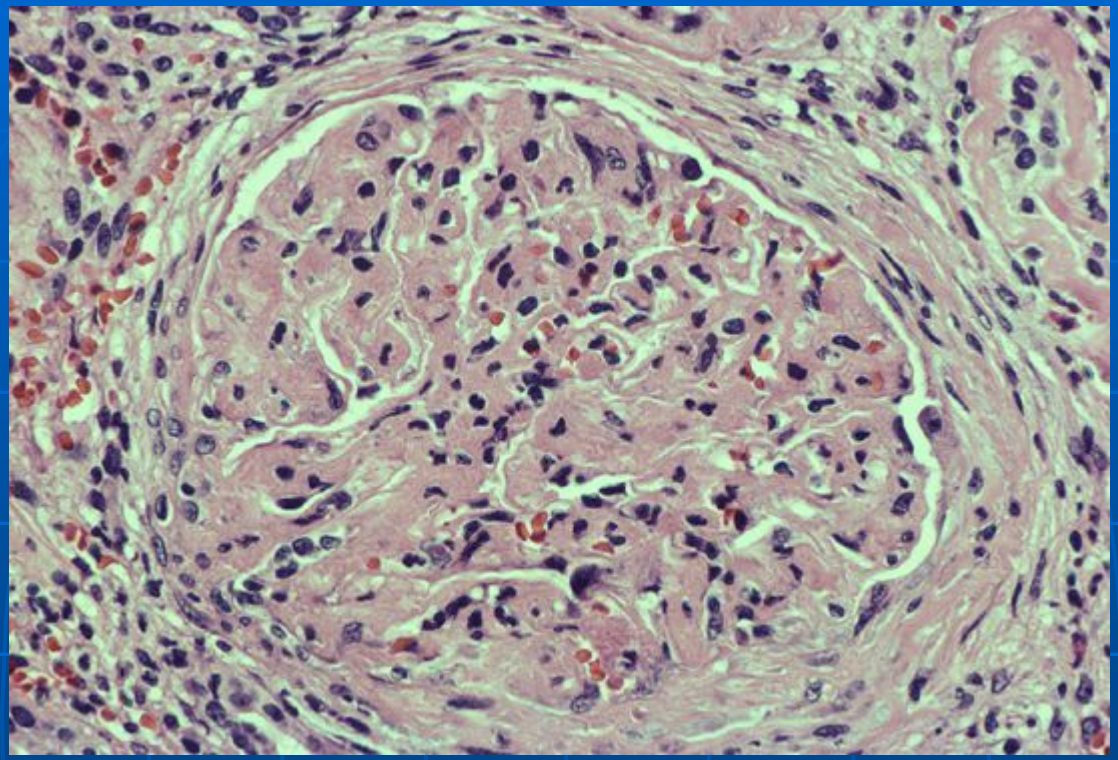
- **Hyaline arteriolosclerosis** is associated with **mild hypertension** and diabetic microangiopathy; medial and intimal thickening that appears very homogenous and pink ('hyalinosis'), consisting of plasma protein deposition with some smooth muscle proliferation
    - **Fibrinoid necrosis** can appear to be a pinker, more 'advanced' lesion of hyalinosis; they both share an etiology of intimal injury with leakage of plasma proteins in the wall



https://upload.wikimedia.org/wikipedia/commons/1/18/Arteriolosclerosis%2C_kidney%2C_HE_4.JPG

Diabetes mellitus

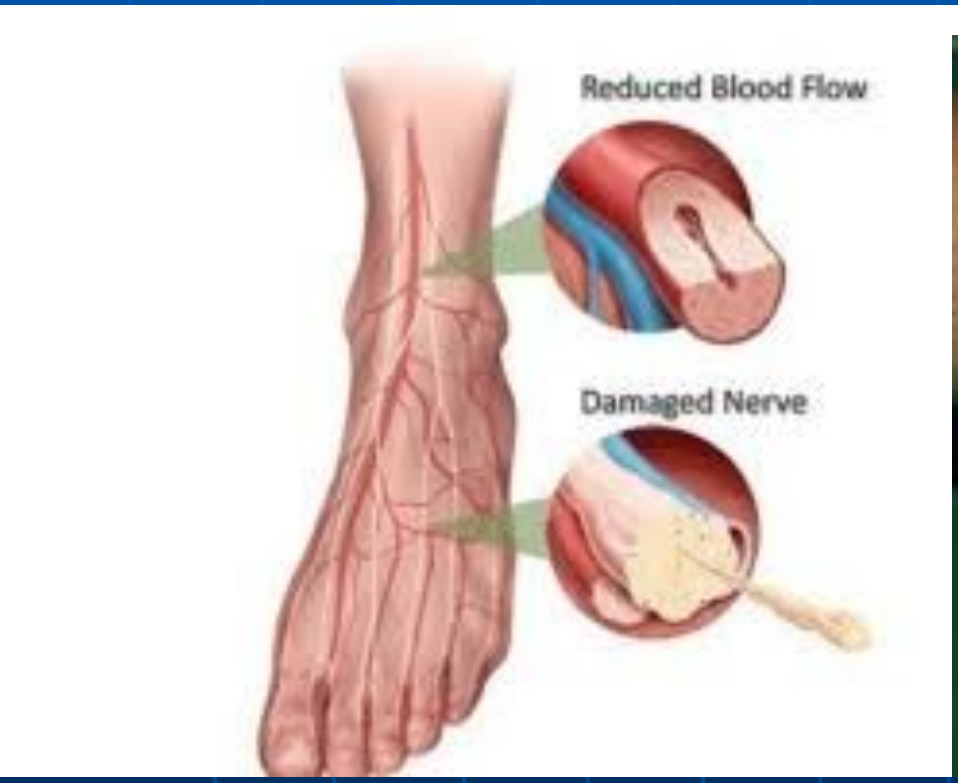


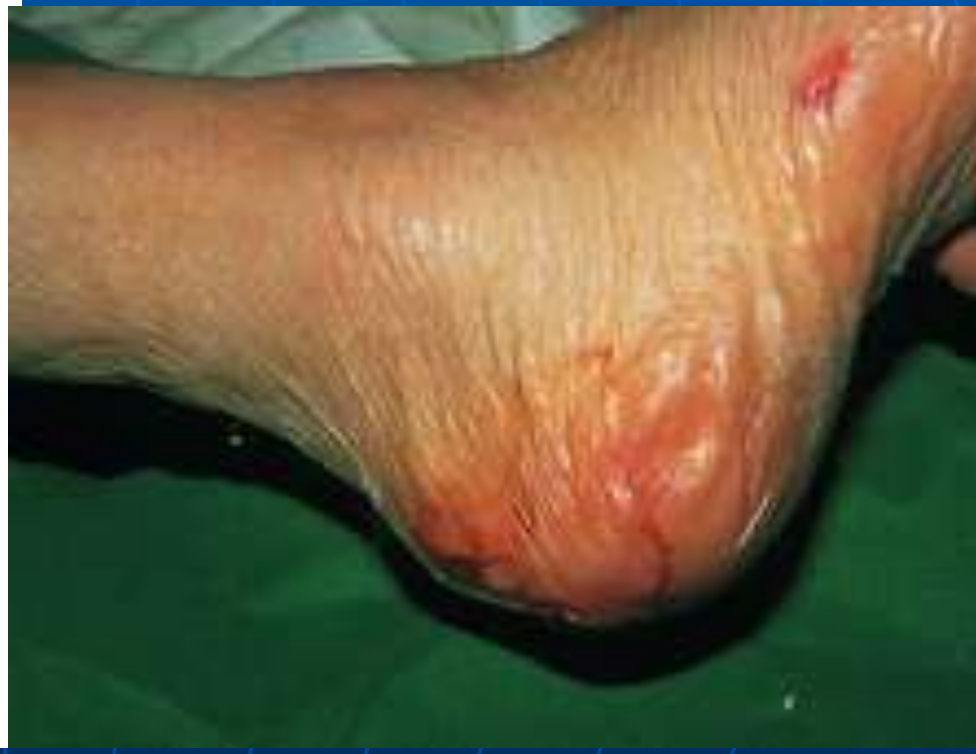


Diffuse glomerulosclerosis

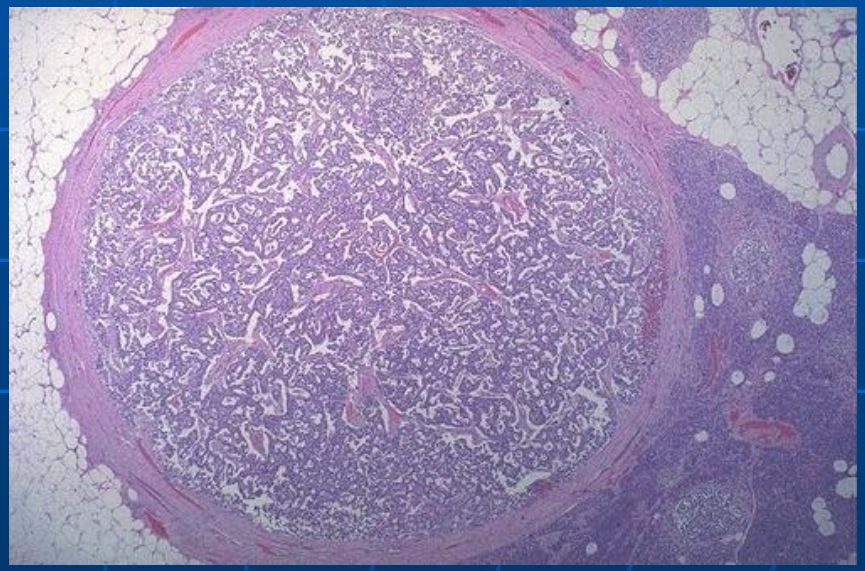
Characterized by diffuse thickening of glomerular capillary basement membranes and increased amount of mesangial matrix with mild mesangial cell proliferation. Glomerular changes always begin in the vascular stalk. The affected glomeruli eventually develop obliterative diabetic glomerulosclerosis. These changes are seen in at least 40% of diabetic patients after more than 10 to 20 years.

Diabetic microangiopathy, Diabetic neuropathy

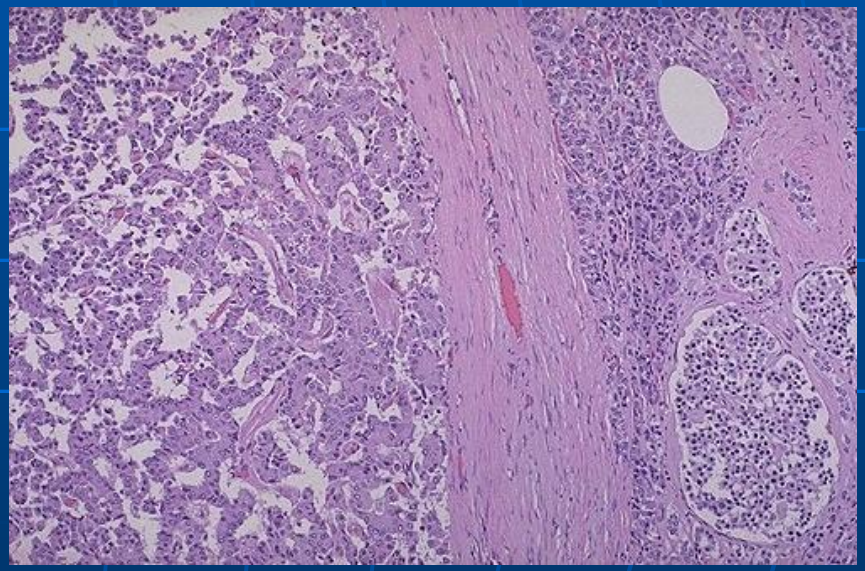




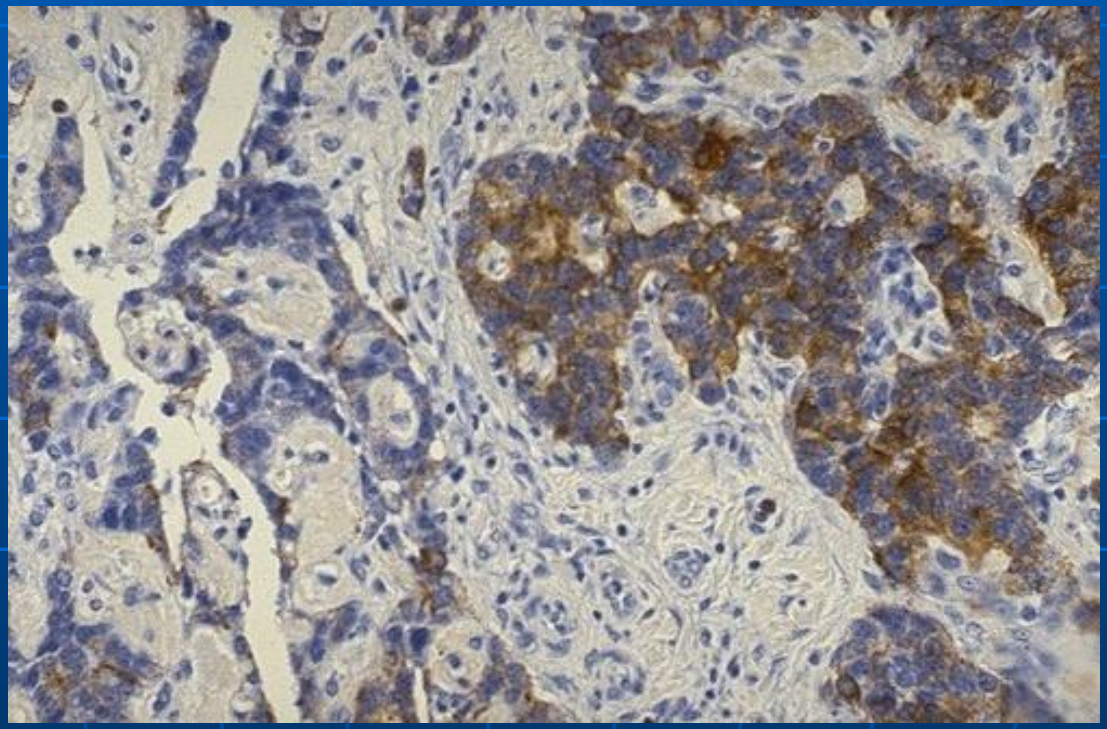
- An islet cell adenoma is seen here, separated from the pancreas by a thin collagenous capsule. A few normal islets are seen in the pancreas at the right for comparison.



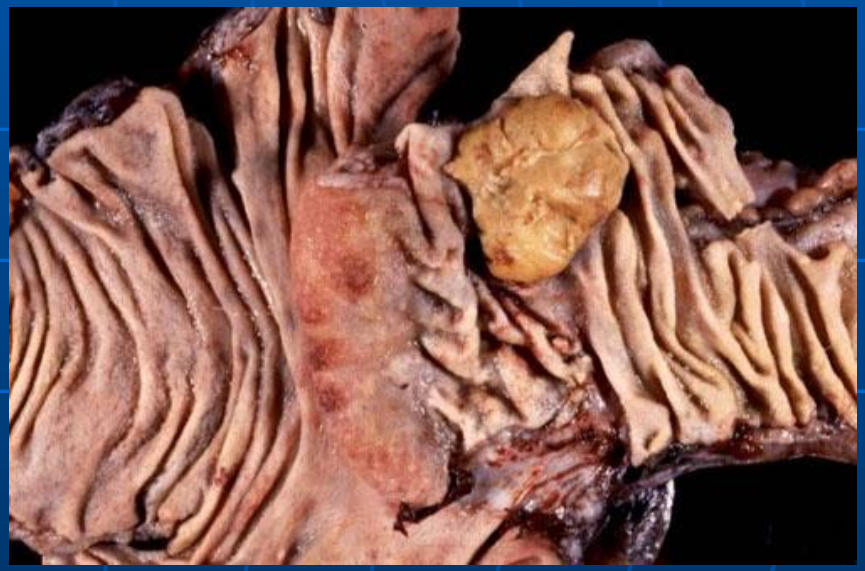
- The islet cell adenoma at the left contrasts with the normal pancreas with islets at the right. Some of these adenomas function. Those that produce insulin may lead to hypoglycemia. Those that produce gastrin may lead to multiple gastric and duodenal ulcerations (Zollinger-Ellison syndrome).



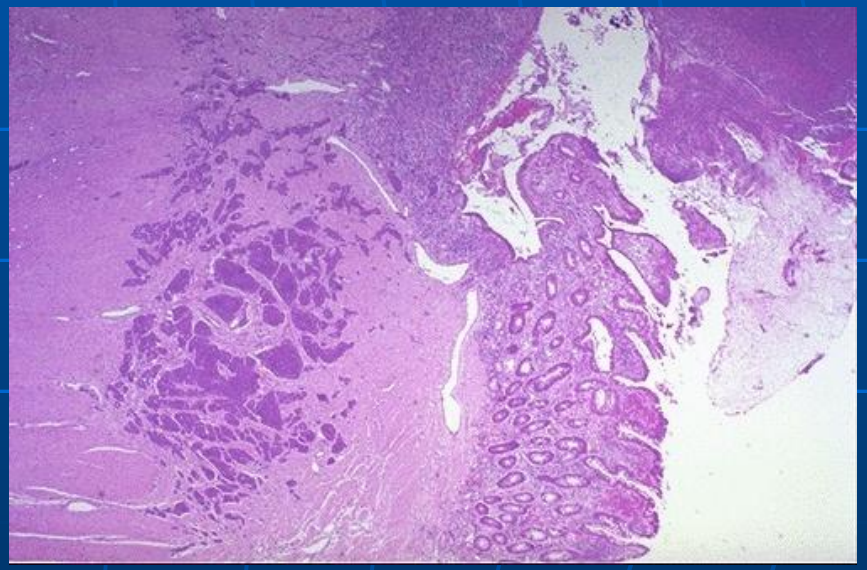
- This is an immunohistochemical stain for insulin in the islet cell adenoma. Thus, it is an insulinoma.



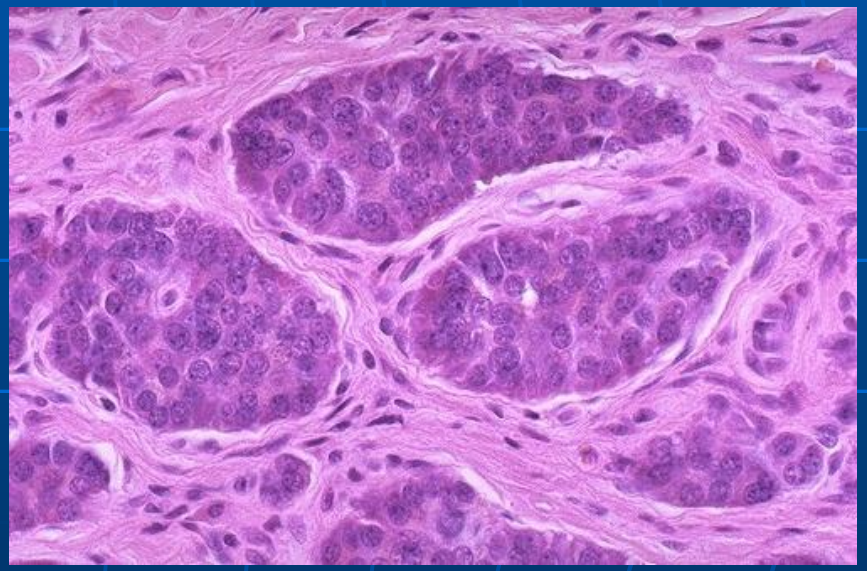
- Here is a carcinoid tumor seen on the mucosal surface at the ileocecal valve. Note that it is a small, well-circumscribed mass that has a yellowish tint to it. Such neoplasms are typically benign, even though they may be multiple. Most do not secrete a detectable hormone.



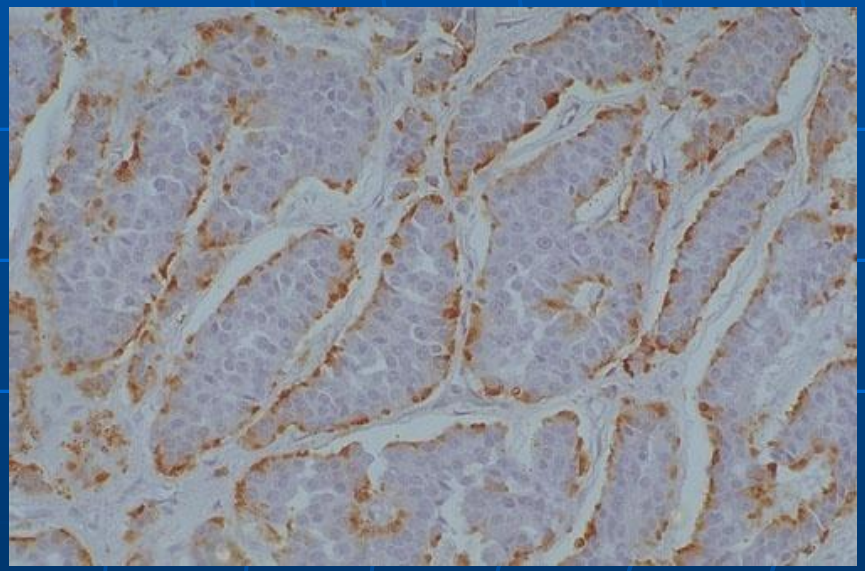
- At low magnification, the small blue nests of tumor cells in this carcinoid tumor are grouped together beneath the mucosa, but are not encapsulated and appear to "infiltrate" in the muscularis, though this is not strictly invasion. It is rare for a carcinoid <1 cm to behave in a malignant fashion, while the majority >2 cm are malignant. Most carcinoids are <1 cm.



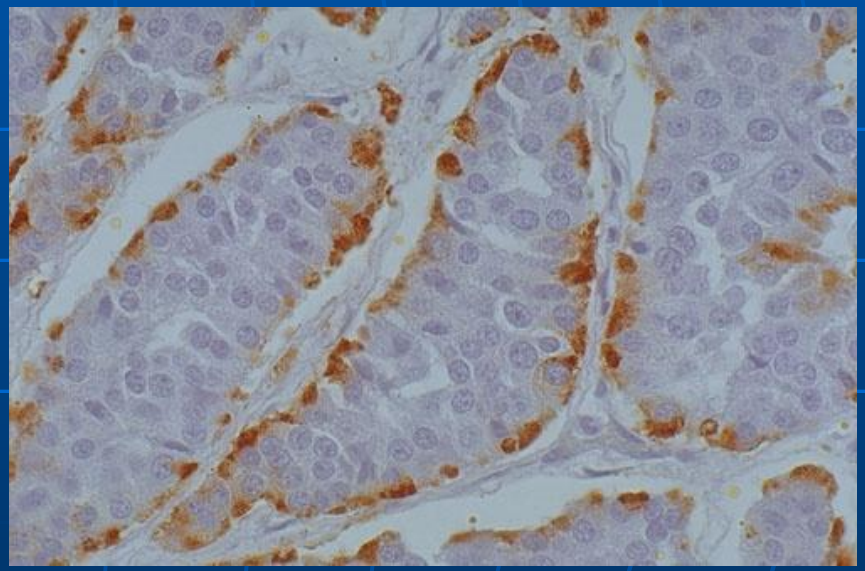
- At high magnification, the small nests of tumor cells in this carcinoid contain round cells with round nuclei. Carcinoids can be found anywhere in the gastrointestinal tract, though they are most common in ileum, appendix, and colon. Carcinoids may rarely be found arising in bronchi of the lung.



- This immunoperoxidase stain with antibody to ACTH demonstrates staining of the cells in this carcinoid tumor. This patient had Cushing's syndrome due to ectopic ACTH production from the carcinoid.



- At higher power, the immunoperoxidase staining pattern with antibody to ACTH is shown in this carcinoid tumor. Carcinoids are capable of secreting a variety of hormones. Gastrin secretion can lead to the Zollinger-Ellison syndrome (multiple gastric ulcers). The "carcinoid syndrome" (quite rare) from serotonin secretion is typically a result of a malignant carcinoid that has metastasized to the liver.



Thank You!